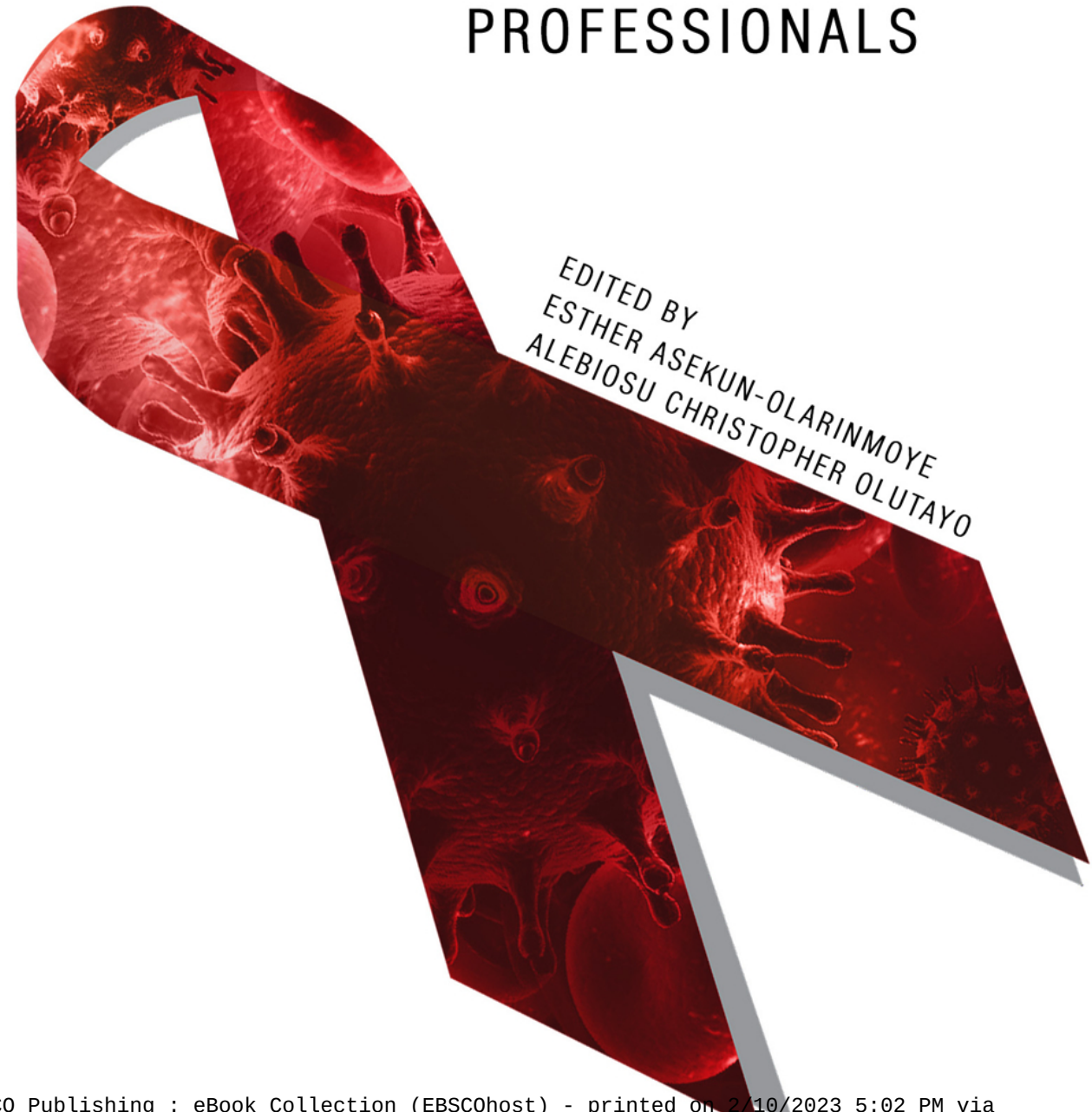
NEW INSIGHTS INTO HIV/AIDS FOR STUDENTS AND HEALTHCARE PROFESSIONALS



EDITED BY
ESTHER ASEKUN-OLARINMOYE
ALEBIOSU CHRISTOPHER OLUTAYO

New Insights into HIV/AIDS for Students and Healthcare Professionals

New Insights into HIV/AIDS for Students and Healthcare Professionals

Edited by

Esther Olufunmilayo Asekun-Olarinmoye
and Olutayo Christopher Alebiosu

Cambridge
Scholars
Publishing

New Insights into HIV/AIDS for Students and Healthcare Professionals

Edited by Esther Olufunmilayo Asekun-Olarinmoye
and Olutayo Christopher Alebiosu

This book first published 2019

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-2196-6
ISBN (13): 978-1-5275-2196-4

This book is dedicated to stakeholders in HIV care

TABLE OF CONTENTS

PREFACE

Human Immunodeficiency Virus (HIV) infection with its attendant Acquired Immune Deficiency Syndrome (AIDS) is a pandemic that has been ravaging different countries of the world despite the colossal resources channelled towards its containment. It is estimated that about 36.7 million people are currently living with HIV/AIDS in the world and the brunt of the infection is mostly felt in Africa. Presently, Nigeria is the second most endemic country in the world after South Africa and about 3.2 million people are living with HIV/AIDS. The infection is more prevalent among the youths (18-49 years) and over 160,000 people die due to the infection and its complications annually. This is indeed, worrisome.

So far, all efforts to find a cure for the HIV/AIDS infection globally have not yielded appreciable results. The containment of the infection has centred on chemotherapeutic management, public health education on the aetiology and transmission of the infection and the enactment of policies to guide Local and National Ministries of Health and other caregivers to stem the tide of the infection.

It is therefore, heart-warming to note that biomedical researchers and medical practitioners from diverse backgrounds have come together to produce a textbook on HIV/AIDS for the utilization of the students and health caregivers involved in the management of HIV/AIDS. The textbook has chapters which cover a broad spectrum of topics in HIV/AIDS such as history, epidemiology, complications, laboratory diagnosis, chemotherapeutic case management, policies and advocacy.

While commending the College of Health Sciences, Osun State University for championing and chatting pathways for the diffusion of knowledge and the containment of the HIV/AIDS pandemic through this effort, it is my fervent hope that this textbook will not only find its relevance in Nigeria but in the entire globe. I recommend it to all and sundry.

Labode POPOOLA, Ph.D, *FFAN*
Vice-Chancellor
Osun State University, Osogbo

FOREWORD

Since the first case of HIV was diagnosed in 1981, several efforts have gone into its prevention and control. Yet HIV remains the leading scourge of our times with its attendant deaths and sickness. There is no cure for HIV as of today despite the international attention and publicity received by the disease. It is one of the few diseases specifically given attention in the Millennium Development Goals (MDG) and now the Sustainable Development Goals (SDGs). There has been little effort by academia in developing countries towards contributing to in-depth knowledge of HIV, as well as stimulating the interest of students at both undergraduate level and in carrying out research on HIV. As the search for a cure continues, the writing of this book is a timely concept, discussing the changing epidemiology of HIV and presenting from the angle of both academics and public health programming. The authors are not only academicians but seasoned programmers who have worked or are currently working in the realm of HIV comprehensive care. HIV has been looked into from multi-disciplinary and multisystem angles including pregnancy, the bodily organs and systems, cancers, and its effects on the general population.

This book presents the current perspective of HIV care. Because recommendations for care are bound to change with time, the authors and reviewers of this book have accurately showcased the present concepts, and shall not be liable for any errors or omissions in information or any perceived inaccuracies to the users of this book as recommendations and guidelines change with time. I am confident that this will just be the first of the books to be written by a team of erudite scholars presented by the College of Health Sciences of Osun State University and their collaborators in other Universities within Nigeria. Thus, students, programme planners, programme managers and policy makers among other stakeholders in HIV care would benefit immensely from this book.

The book would also assist the Nigerian Government in making policy decisions that would further crash the current prevalence of HIV. All the chapters were double-blinded peer reviewed and subjected to plagiarism assessments. With the high level of research interest that this book will

stimulate, there is no doubt that Nigeria is gradually moving towards a pattern of zero prevalence and an HIV-free generation.

Professor Alebiosu C.O.
Visiting Professor of Medicine
Office of Global Health
Department of Internal Medicine
Yale University School of Medicine

ACKNOWLEDGEMENT

Having an idea and turning it into a book is as hard as it sounds. The experience is both challenging and rewarding.

This book was prepared under the auspices of the College of Health Sciences, Osun State University and collaborators in other Universities within Nigeria. Expert reviews, feedbacks and comments were contributed by numerous experts. Outstanding amongst these reviewers are the Special Editors / Editorial Consultants, Professor Adesegun Fatusi and Professor L. Salawu, of the Obafemi Awolowo University, who reviewed and edited every chapter. We appreciate the fact that you are able to create time out of your ever busy schedule to carry out this assignment.

A very sincere note of acknowledgement to all the authors whose works were cited; their contributions have indeed been a source of enrichment with regard to the existing body of knowledge pertaining to the subject.

Writing a book is harder than we thought, our gratitude also goes to the publishers of this book - Cambridge Scholars Publishing.

List of Abbreviations

AAN:	American Academy of Neurology
ABC:	Abacavir
ACE:	Angiotensin-Converting Enzyme
AD:	Alzheimer's disease
ADRs:	Adverse Drug Reactions
AIDP:	Acute Inflammatory Demyelinating Polyneuropathy
AIDS:	Acquired Immune Deficiency Syndrome
AJOL:	African Journals Online
AKI:	Acute Kidney Injury
ANC:	Antenatal Care
ANI:	Asymptomatic Neurocognitive Impairment
ANUG:	Acute Necrotizing Ulcerative Gingivitis
ART:	Antiretroviral therapy
ARVs:	Antiretrovirals
ATN:	Acute tubular necrosis
AZT:	Azidothymidine
Aβ:	Beta-amyloid
BBB:	Blood–Brain Barrier
BCC:	Behavioural Change Communication

cART:	combination antiretroviral therapy
CCF:	Congestive Cardiac Failure
CD:	Cluster of differentiation
CDC:	Center for Disease Control and Prevention
CEDAW:	Convention on the Elimination of All Forms of Discrimination against Women
CHAI:	Clinton Health Access Initiative
CHER:	Children with HIV Early Antiretroviral Therapy
CIDP:	Chronic Inflammatory Demyelinating Polyneuropathy
CKD:	Chronic kidney diseases
CKD-EPI:	Chronic Kidney Disease Epidemiology Consortium
CMI:	Cell-Mediated Immunity
CMV:	Cytomegalovirus
CPT:	Co-trimoxazole Preventive Therapy
CRA:	Child Rights Act
CRFs:	Circulating recombinant forms
CSF:	Cerebrospinal fluid
CT:	Computerised Tomography
CVD:	Cardiovascular diseases
DBS:	Dried blood spot
DILS:	Diffuse Infiltrative Lymphocytosis Syndrome
DM:	Diabetes Mellitus
DSP:	Distal Sensory Polyneuropathy

DTG: Dolutegravir

EBV: Epstein-Barr virus

EID: Early Infant Diagnosis

ELISA: Enzyme-linked immunosorbent assay

ENT: Ear-Nose-Throat

ESRD: End-stage renal disease

FDA: Federal Drug Agency

FGC: Female genital cutting

FP: Family Planning

FSW: Female Sex Workers

GFR: Glomerular filtration rate

GIT: Gastrointestinal tract

HAART: Highly Active Antiretroviral Therapy

HAD: HIV-associated dementia

HAND: HIV-associated neurocognitive disorders

HCT: HIV Counselling and Testing

HCV: Hepatitis C virus

HHV8: Human herpes virus 8

HIV DNA-PCR: HIV DNA-Polymerase Chain Reaction

HIV: Human Immunodeficiency Virus

HIV-1: HIV type 1

HIV-2: HIV type 2

HIVAN: HIV associated nephropathy

HIVICK: HIV-immune complex mediated kidney disease

HIV-SGD: HIV salivary gland disease

HPV: Human Papilloma Virus

HSV: Herpes Simplex Virus

HTC: HIV Testing and Counselling

HTLV-III: Human T-cell Lymphotropic Virus III

HZ: Herpes Zoster

HZO: Herpes Zoster Ophthalmicus

HZV: Herpes Zoster Virus

IDUs: Injection drug users

IDUs: Intravenous Drug Users

IFN-α: interferon α

IgA: Immunoglobulin A

IPT: Isoniazid Preventive Therapy

IUGR: Intrauterine growth Restriction

IVIg: Intravenous immunoglobulin

JC: John Cunningham

KS: Kaposi's sarcoma

LD: Liposomal doxorubicin

LGE: Linear gingival erythema

LTRs: Long terminal repeats

MAC: M avium-intracellulare complex

MALT: Mucosa-associated lymphoid tissue

MDG: Millennium Development Goal

MDRD: Modification of diet in renal disease

MI: Myocardial infarction

MMSE: Mini-mental status examination

MNCH/FP: maternal, child health and family planning

MND: Mild neurocognitive disorder

MRI: Magnetic Resonance Imaging

MRSA: Methicillin-resistant *S aureus*

MSM: Men having sex with men

MTCT: Mother-to-child transmission

NACA: National Agency for Control of AIDS

nef: negative regulatory factor

NF-κB: Nuclear factor kappa B

NGOs: Non-governmental Organizations

NHL: non-Hodgkin lymphoma

NMDA: *N*-Methyl-D-aspartate

NNRTIs: Non-nucleoside Reverse Transcriptase Inhibitors

NRTI: Nucleoside Reverse Transcriptase Inhibitors

NUG: Necrotizing ulcerative gingivitis

NUP: Necrotizing ulcerative periodontitis

NVP:	Nevirapine
OHL:	Oral Hairy Leukoplakia
PBMC:	Peripheral blood mononuclear cell
PCNSL:	Primary CNS lymphoma
PCR:	Polymerase Chain Reaction
PEP:	Post-exposure prophylaxis
PHC:	Primary Health Care
PIs:	Protease inhibitors
PITC:	Provider initiated testing and counselling
PLHIV:	People living with HIV
PML:	Progressive Multifocal Leukoencephalopathy
PMTCT:	Prevention of mother to child transmission
PORN:	Progressive outer retinal necrosis
PPAR:	Peroxisomal proliferator-activated receptor
PPD:	Purified protein derivative
PPE:	Pruritic papular eruption
PRN:	Progressive retinal necrosis
pTAU:	hyperphosphorylated tau
RDTs:	Rapid Diagnostic Tests
rev:	Regulator of viral protein expression
RH:	Reproductive Health
RTI:	Reverse Transcriptase Inhibitor

RUQ:	Right upper quadrant
SDGs:	Sustainable Development Goals
SIVs:	Simian immunodeficiency viruses
SPECT:	Single-photon emission computed tomography
STDs:	Sexually transmitted diseases
STIs:	Sexually transmitted infections
tat:	trans-activator of transcription
TBAs:	Traditional Birth Attendants
TDR:	Tenofovir
T_H Cells:	T Helper cells
TWGs:	Technical Working Groups
UNAIDS:	United Nations Agency for AIDS
VCT:	Voluntary Counselling and Testing
vif:	Viral infectivity protein
VL:	viral load
VMMC:	Voluntary male medical circumcision
vpr:	Viral protein R
vpu:	Viral protein U
vpx:	Viral protein X
VZV:	Varicella-Zoster Virus
WBC:	White Blood Cell
WHO:	World Health Organization

ZDV: Zidovudine

LIST OF ILLUSTRATIONS

12. Endoscopic findings, revealing reddish, elevated lesions in the greater curvature of the proximal body. Adapted from Silver *et al.,* 2016.
13. Haematoxylin and eosin stain showing spindle cell proliferation in the submucosa. Adapted from Silver *et al.,* 2016.
14. Immunohistochemical stain for human herpes virus 8. Adapted from Silver *et al.,* 2016.
15. Steps for the screening and initial management of Kidney Diseases. Adapted from New York State Department of Health AIDS Institute. www.hivguidelines.org.
16. Reproductive choices for HIV-positive women. Adapted from Wilcher *et al.,* 2009.
17. Linkage between Sexual and Reproductive Health Services and HIV/AIDS. UNAIDS, 2005.
18. Dull red, bluish-purple, maculopapular lesions on the upper part of the trunk (back) in a 49-year-old man with primary HIV-1 infection. Adapted from Schwartz, R A. *Cutaneous Manifestations of HIV*. Available at www.medscape.com.
19. AIDS patient with pruritic popular eruption – PPE. Adapted from *World J Life Sci. and Medical Research* 2013.
20. Genital wart in an HIV positive patient. Adapted from *World J Life Sci. and Medical Research* 2013.
21. Molluscum contagiosum. Adapted from Ansary et al. *A Colour Atlas of AIDS in the Tropics.* London, Wolfe Medical Publications, 1989.
22. Scabies. Adapted from *The Prn Notebook*™ • 2(4), 1997.
23. Herpes zoster: lesions are dermatomal. Adapted from *The Prn Notebook*™ • 2(4), 1997.
24. Group Pmtct Counselling in the Ante Natal Clinic. Adapted from SIDCAIN (www.sidcain.org) GDM project © 2016.
25. T2 MRI showing cerebral atrophy. Adapted from: https://radiopaedia.org/articles/hiv-associated-dementia [Accessed on March 7, 2018].
26. T2 MRI showing hyperintense multiple white mater lesions and evidence of cerebral atrophy. Adapted from: https://radiopaedia.org/articles/progressive-multifocal-leukoencephalopathy [Accessed on March 7, 2018].
27. T1 MRI post-contrast axial view of the brain. Adapted from: https://radiopaedia.org/articles/toxoplasmosis-vs-lymphoma [Accessed on March 7, 2018].
28. MRI T1 post-contrast axial view of the brain. Adapted from: http://neuroradiologyteachingfiles.com/bfa.html [Accessed on March 7].

LIST OF TABLES

Chapter Twenty-Six

HISTORY OF HIV

IBUKUN PETER OYEYIPO, PHD

Human immunodeficiency virus (HIV) originated from the non-human primates in Central and West Africa. HIV type 1 and 2 (HIV-1 and HIV-2) which are lentiviruses are causative agents of Acquired Immune Deficiency Syndrome (AIDS). M, N, O and P are the distinct lineages of HIV-1 with M classified into nine subtypes. On the other hand, HIV-2 has at least eight distinct lineages. The greatest morbidity and mortality of HIV/AIDS have been experienced in the developing countries with young adults in sub-Saharan Africa most vulnerable. Consequently, this has impacted adversely on the working-class raising fundamental issues which are related to unemployment, work rehabilitation, and stigmatization among others.

Human immunodeficiency virus (HIV) is established as the causative agent of Acquired Immune Deficiency Syndrome (AIDS) and it originated from the non-human primates in Central and West Africa. This disease of humans is caused by two lentiviruses; human immunodeficiency viruses types 1 and 2 (HIV-1 and HIV-2). AIDS is an infectious disease which was first recognized in 1981 (1, 2) and ever since then, it has become one of the most challenging diseases to be discovered in recent history (3). Ever since the identification of this virus over three decades ago, the pandemic form of HIV-1 which is also referred to as the main (M) group has caused over 25 million deaths and 60 million infections (4). Thus, AIDS will continue to pose a significant public health threat for decades to come. In 1986, the first clue to the reason for the epidemic's spread and sudden emergence and the unique pathogenicity of HIV-1 was discovered when an antigenically distinct but morphologically similar virus was found to cause AIDS in western African patients. Interestingly, this virus called human immunodeficiency virus type 2 was closely related to a simian virus that caused immunodeficiency in captive macaques (5). Thereafter, other collected viruses termed simian immunodeficiency viruses (SIVs), usually differentiated with a suffix denoting the species of origin, were identified in various primates such as Chimpanzees, sooty mangabeys,

mandrills, African green monkeys and others from sub-Saharan Africa. It was amazing to discover that close simian relatives of HIV-1 were found in Chimpanzees (6) while those of HIV-2 were found in sooty mangabeys (7) therefore this association provides evidence that AIDS had emerged in both macaques and humans as a result of cross-species infections with lentiviruses from different primate species; thus the origin of HIV-1 and HIV-2 has been associated with zoonotic transfer of the viruses from primates to man in Africa. Demographic data also indicate that the HIV-1 pandemic started when there was an expansion of urban populations in west and central Africa (8). At that time, Leopoldville in the Belgian Congo (now Kinshasa in the Democratic Republic of the Congo) was the largest city in the region and thus a likely destination for a newly emerging infection. Moreover, rivers were the major routes for travelling and commercial activity at the time, which might have provided a link between the chimpanzee reservoir of HIV-1 group M in southeastern Cameroon and Leopoldville on the banks of the Congo (9). Thus, all current evidence points to Leopoldville/Kinshasa as the cradle of the AIDS pandemic.

HIV-1 comprises four distinct lineages, termed groups M, O, N, and P, each of these groups is as a result of independent cross-species activities. The first group; M was the first to be discovered, it represents the pandemic form of HIV-1 infecting several millions of people in the world and found in almost all countries (10). It is also currently classified into nine subtypes (A, B, C, D, F, G, H, J and K) as well as over 40 different circulating recombinant forms (11). The origin of Subtypes A and D was central Africa which established epidemics in eastern Africa, while Subtype B, which accounts for most of the HIV-1 infections in America and Europe, was from a single African strain that appears to have first spread to Haiti in the 1960s and then onward to the US and other western countries (12). Subtype C was from Southern Africa from where it spread to India and other Asian countries.

In 1990, Group O was discovered with lesser prevalence, representing less than 1% of global HIV-1 infections with restrictions to a few African countries (13). Group N with a lesser prevalence than O was identified in 1998 with only 13 cases documented in Cameroon (14), while Group P was discovered in France in 2009 in a Cameroonian woman (15) and after that in one other person also from Cameroon (14). Groups M and N of HIV-1 were shown to be closely related to SIV of Chimpanzee origin. HIV-1 group N appears to have originated in the vicinity of the Dja forest in South-Central Cameroon while group M is likely to have emerged in an area near Boumba, Ngoko and Sangha River in the southeastern corner of

Cameroon (16). Phylogenetic data have supported that Group P has a gorilla origin of HIV-1. However, very few SIV of the gorilla strain have been characterized to ascertain the region where transmission occurred. The immediate source of HIV-1 group O is still debatable since to date, no ape viruses are similar to this group. Therefore, HIV-1 group O could either be of Gorilla or Chimpanzee origin.

The mode of transmission through which humans acquired ape precursors of the HIV-1 groups is still unclear but it is most likely that transmission occurred through mucous and cutaneous membrane exposure to infected ape blood and/or fluid from the body such as during bushmeat hunting (16).

HIV-2 is largely restricted to West Africa, with Senegal and Guinea-Bissau having the highest prevalence rates recorded (17). However, HIV-1 is increasingly replacing HIV-2, thus, there is a decline in the overall prevalence of HIV-2 (18). The lower transmission rate and the near complete absence of mother-to-infant infection of HIV-2 could be associated with a lower viral load in infected persons (19). Interestingly, most people infected with HIV-2 do not have AIDS but have clinical symptoms indistinguishable from HIV-1 (20). These facts are all indications that the natural history of HIV-2 infection is different from HIV-1. Since the first isolation of HIV-2, at least eight distinct lineages have been identified, with each representing an independent host transfer. These are groups A–H, and Group A and B have been found to spread to humans. Group A has been isolated in West Africa (21), while group B has been isolated in Cote d'Ivoire (22). Groups C, G, and H have also been associated with Cote d'Ivoire, group D with Liberia and groups E and F with Sierra Leone (23, 24, 25).

The spread of HIV-1 is primarily through sexual intercourse (26), however, perinatal and percutaneous routes have been implicated in the spread (26). The greatest morbidity and mortality of HIV/AIDS have been experienced in developing countries with young adults in sub-Saharan Africa being the most vulnerable. From an epidemiologic point of view, Southern Africa has recorded prevalence rates higher than 10% of the HIV pandemic and it is thus the region of the world that is hardest hit. Surveys across the Southern Africa region indicate that Zambia recorded an HIV prevalence of 15.6% in the Zambia Demographic and Health Survey in the period 2000–2001 (27), Namibia (individuals aged 15–49 years) recorded 10% in 2005, 4.5% in the Democratic Republic of Congo are infected (28), and 14.4% in the Malawi Demographic and Health Survey in 2004

(29). HIV/AIDS was ranked the 5th largest cause of death in Southern sub-Saharan Africa in 1990, whereas in 2010, it was the top cause of death (30). Braveman *et al.* (31) reported that in the United States, 850 000 to 950 000 persons are estimated to be living with HIV and with an increased incidence rate each year and since a large population of the working-class is affected, issues of employment, work rehabilitation, and AIDS are major causes of concern in the workplace.

References

1. CDC. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men – New York City and California. *MMWR Morb Mortal Wkly Rep.* 1981; 30: 305–308.
2. Greene WC. A history of AIDS: Looking back to see ahead. *Eur J Immunol*. 2007; 37 (Suppl. 1): S94–S102.
3. Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science*. 1984; 224: 497–500.
4. Merson MH, O'Malley J, Serwadda D, Apisuk C. The history and challenge of HIV prevention. *Lancet*. 2008; 372: 475–488.
5. Guyader M, Emerman M, Sonigo P, Clavel F, Montagnier L, Alizon M. Genome organization and transactivation of the human immunodeficiency virus type 2. *Nature* 1987; 326: 662–669.
6. Huet T, Cheynier R, Meyerhans A, Roelants G, Wain-Hobson S. Genetic organization of a chimpanzee lentivirus related to HIV-1. *Nature* 1990; 345: 356–359.
7. Hirsch VM, Olmsted RA, Murphey-Corb M, Purcell RH, Johnson PR. An African primate lentivirus (SIVsm) closely related to HIV-2. *Nature* 1989; 339: 389–392.
8. Worobey M, Gemmel M, Teuwen DE, Haselkorn T, Kunstman K, Bunce M, Muyembe JJ, Kabongo JM, Kalengayi RM, Van Marck E. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. *Nature* 2008; 455: 661–664.
9. Sharp PM, Hahn BH. AIDS: Prehistory of HIV-1. *Nature* 2008; 455: 605–606.
10. Gurtler LG, Hauser PH, Eberle J, von Brunn A, Knapp S, Zekeng L, Tsague JM, Kaptue L. A new subtype of human immunodeficiency virus type 1 (MVP-5180) from Cameroon. *J Virol*. 1994; 68: 1581–1585.

11. Taylor BS, Sobieszczyk ME, McCutchan FE, Hammer SM. The challenge of HIV-1 subtype diversity. *N Engl J Med*. 2008; 358: 1590–1602.
12. Gilbert MT, Rambaut A, Wlasiuk G, Spira TJ, Pitchenik AE, Worobey M. The emergence of HIV/AIDS in the Americas and beyond. *Proc Natl Acad Sci.* 2007; 104: 18566–18570.
13. Mauclere P, Loussert-Ajaka I, Damond F, Fagot P, Souquieres S, Monny Lobe M, Mbopi Keou FX, Barre-Sinoussi F, Saragosti S, Brun-Vezinet F. Serological and virological characterization of HIV-1 group O infection in Cameroon. *AIDS* 1997; 11: 445–453.
14. Vallari A, Holzmayer V, Harris B, Yamaguchi J, Ngansop C, Makamche F, Mbanya D, Kaptue L, Ndembi N, Gurtler L. Confirmation of putative HIV-1 group P in Cameroon. *J Virol*. 2011; 85: 1403–1407.
15. Plantier JC, Leoz M, Dickerson JE, De Oliveira F, Cordonnier F, Lemee V, Damond F, Robertson DL, Simon F. A new human immunodeficiency virus derived from gorillas. *Nature Med*. 2009; 15: 871–872.
16. Van Heuverswyn F, Li Y, Bailes E, Neel C, Lafay B, Keele BF, Shaw KS, Takehisa J, Kraus MH, Loul S. Genetic diversity and phylogeographic clustering of SIVcpzPtt in wild chimpanzees in Cameroon. *Virology* 2007; 368: 155–171.
17. de Silva TI, Cotten M, Rowland-Jones SL. HIV-2: The forgotten AIDS virus. *Trends Microbiol*. 2008; 16: 588–595.
18. Hamel DJ, Sankale JL, Eisen G, Meloni ST, Mullins C, Gueye-Ndiaye A, Mboup S, Kanki PJ. Twenty years of prospective molecular epidemiology in Senegal: Changes in HIV diversity. *AIDS Res Hum Retroviruses*. 2007; 23: 1189–1196.
19. Berry N, Jaffar S, Schim van der Loeff M, Ariyoshi K, Harding E, N'Gom PT, Dias F, Wilkins A, Ricard D, Aaby P. Low-level viremia and high CD4% predict normal survival in a cohort of HIV type-2-infected villagers. *AIDS Res Hum Retroviruses* 2002; 18: 1167–1173.
20. Rowland-Jones SL, Whittle HC. Out of Africa: What can we learn from HIV-2 about protective immunity to HIV-1? *Nat Immunol* 2007; 8: 329–331.
21. Damond F, Descamps D, Farfara I, Telles JN, Puyeo S, Campa P, Lepretre A, Matheron S, Brun-Vezinet F, Simon F. Quantification of proviral load of human immunodeficiency virus type 2 subtypes A and B using realtime PCR. *J Clin Microbiol* 2001; 39: 4264–4268.
22. Ishikawa K, Janssens W, Banor JS, Shinno T, Piedade J, Sata T, Ampofo WK, Brandful JA, Koyanagi Y, Yamamoto N. Genetic

analysis of HIV type 2 from Ghana and Guinea-Bissau, West Africa. *AIDS Res Hum Retroviruses* 2001; 17: 1661–1663.
23. Gao F, Yue L, White AT, Pappas PG, Barchue J, Hanson AP, Greene BM, Sharp PM, Shaw GM, Hahn BH. Human infection by genetically diverse SIVsm-related HIV-2 in West Africa. *Nature* 1992; 358: 495–499.
24. Chen Z, Luckay A, Sodora DL, Telfer P, Reed P, Gettie A, Kanu JM, Sadek RF, Yee J, Ho DD. Human immunodeficiency virus type 2 (HIV-2) seroprevalence and characterization of a distinct HIV-2 genetic subtype from the natural range of simian immunodeficiency virus-infected sooty mangabeys. *J Virol*. 1997; 71: 3953–3960.
25. Santiago ML, Range F, Keele BF, Li Y, Bailes E, Bibollet-Ruche F, Fruteau C, Noe R, Peeters M, Brookfield JF. Simian immunodeficiency virus infection in free-ranging sooty mangabeys (Cercocebus atys atys) from the Tai Forest, Cote d'Ivoire: Implications for the origin of epidemic human immunodeficiency virus type 2. *J Virol*. 2005; 79: 12515–12527.
26. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute-HIV-1 Infection: Basic, clinical and public health perspectives. *N Engl J Med*. 2011; 364: 1943–1954.
27. Zambia Central Board of Health. *Zambia Demographic and Health Survey 2000–2001*. Calverton, MD: Central Board of Health, Zambia and ORC; 2003.
28. Democratic Republic of Congo: National Multi-Sectoral Programme for the Response to HIV/AIDS. Report of the Implementation of the Declaration of Commitment of the Heads of State and of Government for the Response to HIV/AIDS in the Democratic Republic of Congo, 2005. Kinshasa, Democratic Republic of Congo; 2006.
29. Malawi National Statistical Office, ORC Macro. Malawi Demographic and Health Survey. Calverton, MD: National Statistical Office, Zomba, Malawi and ORC Macro; 2004.
30. Lozano R, Naghavi, Foreman et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–128.
31. Braveman B, Levin M, Kielhofner G, Finlayson M. HIV/AIDS and return to work: a literature review one-decade post-introduction of combination therapy (HAART). *Work J Prev Assess Rehabil*. 2006; 27(3): 295–303.

EPIDEMIOLOGY OF HIV

AKINLOLU G OMISORE
MBCH.B, MPH, FWACP

This chapter considers the epidemiology (the distribution and determinants/transmission) of HIV. HIV has grown to become a pandemic (a disease or health-related event affecting the whole world). Though it is a global problem, currently sub-Saharan Africa is the region most affected by HIV, harbouring 70% of the people living with HIV/AIDS. Eastern Europe and central Asia are also potential flashpoints for an HIV epidemic. There is no major gender predilection for HIV, however, females are often at greater risk of acquiring HIV because of some biological and socio-cultural factors. The current HIV pandemic is being fuelled by some high-risk groups, for instance, men having sex with men (MSM), intravenous drug users and those involved in commercial sex transactions. In sub-Saharan Africa however, additionally heterosexual transmission as well as blood transfusion involving HIV-infected donors play important roles in HIV transmission.

The virus that causes Acquired Immune Deficiency Syndrome (AIDS) is aptly named the Human Immunodeficiency Virus (HIV) and is responsible for the pandemic that has shaped human health and development in the last few decades. HIV/AIDS is easily the world's most serious health and development challenge because of its socio-economic effects, not just on affected individuals and families, but also on whole communities and nations. HIV has impacted the global economy with billions of dollars already spent on it, and many affected countries struggle with other serious medical or financial challenges and cannot on their own mount a strong defence to overcome the scourge of HIV.

The infectious agents responsible for AIDS are two related retroviruses, HIV-1 which is responsible for the global pandemic and HIV-2 which is less easily transmitted than HIV-1 and is confined mainly to West Africa, where it was first recognised (1). HIV-1 has been found in virtually every

country since its detection in 1983. Several sub-types of it (clades) have been recognised.

The first recognised cases of AIDS were revealed in 1981 when the US-based Centers for Disease Control and Prevention reported uncommon clusters of Pneumocystis carinii pneumonia and Kaposi's sarcoma in young men in parts of the United States. These men were found to be homosexuals with their immunity severely compromised (2). The term AIDS had been in use since 1981, but it was not until 1983 that the virus causing the condition was identified and given various names including "Lymphadenopathy Associated Virus" by French Scientists and "Human T-cell Lymphotropic Virus III (HTLV-III)" by American Scientists. It was not until May 1986 that the internationally accepted term of HIV was given by an International Committee on Taxonomy. Since then a lot has been discovered about the epidemiology of HIV/AIDS and this is the focus of this chapter.

HIV Epidemiology: Transmission

There are three main modes of transmission: sexual, parenteral and mother-to-child transmission. HIV is not transmitted by social or casual contact.

Sexual Transmission

Sexual transmission is the commonest mode of transmission of HIV worldwide (3). This usually occurs via unprotected sex with an infected partner, whether of heterosexual (infected man to woman or infected woman to man) or homosexual transmission, the latter especially in males (men having sex with men – MSM). The disease was originally found in male homosexuals and this group is still quite significant when it comes to sexual and overall transmission of HIV. The concentration of the HIV virus in semen is far higher than that of cervical or vaginal secretions, thus sexual acts involving penile penetration and ejaculation transmit HIV more than other sexual acts, thus there is more risk with receptive intercourse than "insertive" intercourse (4).

MSM have been shown to be at higher risk because the sex act involves the weaker rectal mucosa compared to the vaginal mucosa. There is a greater concentration of HIV target cells in the rectal mucosa and it is much more vulnerable to abrasions than the vagina. Regarding sex

recipients, the transmission risk via anal intercourse is 18 times higher than that of vaginal intercourse (5). Generally speaking, it is far easier for females to contract HIV from males than vice versa and some of the factors that make females susceptible are listed in Box 1 below.

Box 1: Vulnerability Factors to HIV in Females
Higher load of HIV virus in semen compared to female genital secretions.
Semen remains in contact with the female genital tract for a longer period.
Females have a bigger genital mucosal surface area exposed during sexual intercourse than males. The case is worsened with the presence of genital ulcers such as chancroid or syphilis.
Females are usually victims of sexual violence compared to males and sexual violence such as rape can also make females vulnerable to contracting HIV as a result of genital abrasions and tears.
Since most women with a sexually transmitted infection (STI) are often without typical STI symptoms, there may be definite challenges in the early detection of STIs in females and poorer access of females to treatment of STIs may increase the chance of girls/women becoming HIV infected.
Peri-menopausal women and adolescent females exposed to HIV and other STIs are more susceptible to HIV as a result of the thinning of mucosa in menopause and the relatively immature/developing vaginal mucosa poorly lined with protective cells in young adolescents.
Age mixing, with young girls having sex with much older males, also increases their risk of developing HIV.
Socioeconomic and cultural/religious factors – women are often unable to negotiate the terms of their sexual interactions with male partners.

Adapted from (1) and (6).

Every sexual act with an HIV-positive person exposes the concerned individual to the risk of infection. It cannot be categorically stated that any or every sexual act will lead to acquisition of the HIV infection, however there is a measure or degree of risk involved with every sexual act committed with an HIV-positive person.

Box 2: Determinants of Sexual Transmission
Pattern of Sexual behaviour – e.g. those with multiple sexual partners and those involved in anal intercourse are at more risk.
Gender – with regard to heterosexual intercourse, it is more likely that a male transmits HIV to a female than a female transmits HIV to a male, as highlighted above.

Sexual debut/First – especially for females with an infected partner.
Overall prevalence of sexually transmitted infections (STIs) including HIV in the community – the higher, the more risk.
The degree and/or stage of infection of the infected partner. The stage of illness of the infected partner as the latter stages are associated with a higher risk of transmission. The single most important predictor of HIV transmission via sex is the plasma viral load.
Male circumcision – said to be relatively protective against HIV transmission compared to uncircumcised males.

Adapted from (1), (4), (7-10).

Parenteral Transmission of HIV

This occurs via two major ways

1. Sharing sharp objects e.g. needles contaminated with HIV;
2. Blood/Organ/Tissue donation.

Globally, most parenteral transmission occurs via unsafe injecting practices. Parenteral transmission is most common among Intravenous Drug Users (IDUs) who re-use needles. This is perhaps the commonest mode of getting HIV in developed countries (11).

Apart from IDUs, parenteral transmission also occurs in people sharing sharp objects such as needles (e.g. repeated use of needles which may be contaminated among clients in resource-poor settings) and needle-related injuries in health workers. Another very common parenteral route of transmission is via blood transfusion, inclusive of blood components such as platelets and factors VIII, and IX derived from human plasma. The risk associated with this is very high and may be in the region of 95%. This route is now virtually non-existent in developed countries of the world because of the effective screening of prospective blood donors, but it still occurs to a considerable extent in developing countries. Parenteral transmission also does occur through infected semen organ donation (1).

Mother-to-child transmission (MTCT) of HIV

Otherwise known as maternal-foetal transmission, this is also an important route for HIV transmission especially in developing countries. It occurs via two major ways

1. HIV passing from an infected mother to her foetus via the placenta or at delivery;
2. Breastfeeding.

When it comes to children, MTCT of HIV is the most important route of transmission and largely responsible for the millions of children worldwide who have been infected with HIV since the advent of HIV. MTCT occurs more in utero (inside pregnancy) and in delivery than during breastfeeding, and prevention of in utero transmission is a major focus in MTCT interventions. MTCT is largely preventable, chiefly by means of the prophylactic use of effective anti-retroviral drugs, elective/planned caesarean section and mothers of new-borns abstaining from breastfeeding their children. Without these interventions, the MTCT rate can be as high as 25% or even much more if the mother breastfeeds. Various factors determine the degree of transmission including whether breastfeeding takes place or not – inclusive of mixed feeding, the length of breastfeeding, cracked or injured nipples in the mother and/or mouth sores in the baby, a concurrent STI, the period of infection in mothers – the child is more susceptible if the mother is newly infected, or if she has full blown AIDS (1, 4).

Box 3: Summary of Transmission – Route, Means and Risk of acquiring HIV infection

Route	Specific Means	RISK
Sexual Intercourse	Vaginal and Anal intercourse majorly. Little or no evidence of transmission through oral intercourse.	Receiving anal intercourse: 0.5% to 3.38% per sex act. Performing anal intercourse through penile insertion: 0.06% to 0.16% per sex act. Male-to-female transmission: 0.08% to 0.19%. Female-to-male transmission: 0.05% to 0.1%.
Parenteral	Contaminated “Sharps” – intravenous drug users, needle-stick injuries, injections and other shared sharp objects.	Transmission risk per injection from a contaminated needle: 0.7% to 0.8%.
	Blood Transfusion Organ/tissue donation –	May be as high as 95% per transfusion.

	semen, kidneys, skin, corneas, heart valves, bone marrow, tendons, etc.	
Mother-to-Child Transmission	In utero, at delivery, post-delivery via breast milk	Without interventions such as drug use (HAART), MTCT may vary from 15% to 45% depending on whether the mother breastfeeds or not.

Adapted from (1) and (4).

NB: These quantified risks are not absolutes and individual factors come into play during HIV transmission irrespective of the route of transmission. For instance, in the case of sexual transmission, attempting to quantify risks may not reveal the true picture as factors like the state of infectiousness and the vulnerability of the infected person and the uninfected person respectively are important determinants of the risk of infection. Similarly, regarding parenteral transmission, an IDU having recurrent and multiple exposures from a fellow drug user who may already have HIV is possibly at greater risk compared to health staff with an accidental needle prick from a patient.

HIV Transmission – High Risk Groups (Key Populations)

The discussion on HIV transmission will definitely be incomplete without mentioning groups of people at greater risk of contracting HIV otherwise known as key populations. Such key populations include sex workers, injection/intravenous drug users, homosexuals and to a lesser extent transgender people, those who engage in trans-generational sex and prisoners (12, 13). These high-risk groups contribute significantly to new HIV infections worldwide and if the HIV epidemic is to come to an end in 2030 in accordance with the Sustainable Development Goals (SDGs), such populations must be targeted with effective interventions such as condoms (male and female), sterile needles and syringes, and pre-exposure prophylaxis. The irony of the whole saga is that there is generally an unwillingness to reach out to members of these key populations because they are usually victims of discrimination and stigmatization. They are thus often denied access to essential services with the consequent result of an increased spread of HIV among the whole population (14, 15).

Until the first decade of the 21st century, the impact that key populations had on HIV transmission was largely undervalued. According to

UNAIDS, at least nine out of every ten new HIV infections in most developed regions of the world in 2014 were among these high-risk groups and their sexual partners, with other less developed regions in the world having about two out of three new infections coming from these groups. The only exception is sub-Saharan Africa where key populations were responsible for just about a fifth to a quarter of new infections (12). However, even in such developing countries, key populations are contributing significantly to new HIV infections.

Taking Nigeria as a country, as far back as 2009-2010, female sex workers (FSW), IDUs, and MSM, who alone constitute just 1% of the adult population, accounted for about 23% of new infections. Along with their partners (just about 3.4% of the adult population), they contribute as much as 40% of new infections (13). The situation in South Africa is no different with the prevalence of HIV in sex workers ranging from 39.7% to 71.8% in her major cities (16).

With this trend, it is imperative that key populations be given special attention if the scourge of HIV/AIDS is to be curtailed to the barest minimum. Each country must take them into cognizance and make sure that HIV prevention services are fully available to them without discrimination and stigma.

HIV Epidemiology: Distribution

There are approximately 36.7 million people currently having HIV (2016 figures), with an expected range of between 30.8 million to 42.9 million. The majority (94%) of these are adults at 34.5 million with the rest being children (individuals less than 15 years). Just a little over half of the adults (17.8 million) affected are women aged ≥ 15 years (17).

Out of the nearly 37 million people living with HIV (PLHIV) globally, 25.6 million people (approximately 70%) are from Africa with the South East Asia, Americas, Europe, Western Pacific and Eastern Mediterranean regions of the WHO contributing 3.5 million, 3.3 million, 2.4 million, 1.5 million and 360,000, respectively (18). About 76 million have contracted HIV since the epidemic started with almost half (35 million people) experiencing AIDS-related mortality. Out of those living with HIV globally, more than two-fifths are unaware that they have HIV and therefore need HIV testing and counselling. In 2016, of the estimated people with HIV/AIDS, just over half (19.5 million people) accessed HIV treatment. More adults (~54%) aged 15 or more years and pregnant

women (~76%) accessed treatment compared to about 43% of children aged 0–14 years (16, 17).

In 2016, an estimated 1.8 million people became newly infected with HIV. AIDS-related deaths have reduced by 48% since 2005 when they reached the highest figures. An estimated 1 million (830,000–1.2 M) people died from AIDS-related morbidities globally in 2016, a much lower figure when compared to the 2005 and 2010 figures – 1.9 million (1.7 M–2.2 M) and 1.5 million (1.3 M–1.7 M) deaths, respectively (17).

Pertinent information captured in this section is displayed in Tables 1-3 below. Figures for the years 2010 and 2015 such as the number of PLHIV [all ages], New HIV Infections [all ages], PLHIV on antiretroviral treatment [all ages] and AIDS-related deaths [all ages] are also compared. The tables show that in virtually all regions of the globe, there is an increase in the number of PLHIV (apparently due to increased survival as more people are on ARVs) and a decrease in "New HIV Infections" between 2010 and 2015. Similarly, generally speaking there is an upsurge in the number of "PLHIV on antiretroviral treatment" and a decrease in AIDS-related deaths. Concerning the percentage coverage of antiretroviral therapy, globally just over half of people with HIV are receiving the needed drugs (18).

References

1. Park K. *Park's Textbook of Preventive and Social Medicine*, 23rd edition. BHANOT, 2015.
2. Joint United Nations Program on HIV/AIDS (UNAIDS). The gap report. Geneva, Switzerland: Joint United Nations Program on HIV/AIDS (UNAIDS); 2014. Available at http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf Accessed January11, 2016.
3. Fox J, Fidler S. Sexual transmission of HIV-1. *Antiviral Res*. 2010; 85(1): 276-85.
4. Public Health Agency of Canada. Infectious Disease Prevention and Control: HIV Transmission Risk; a Summary of the Evidence. 2012.
5. Grulich AE, Zablotska I. Commentary: Probability of HIV transmission through anal intercourse. *Int J Epidemiol*. 2010; 39(4): 1064-5.

6. Glynn JR, Carael M, Buve A et al. Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya and Ndola, Zambia. XIII International AIDS Conference Durban, July 9-14, 2000.
7. Powers KA, Poole C, Pettifor AE, Cohen MS. Rethinking the heterosexual infectivity of HIV-1: A systematic review and meta-analysis. *Lancet Infect Dis*. 2008; 8(9): 553-6.
8. Baggaley RF, White RG, Boily M. HIV transmission risk through anal intercourse: Systematic review, meta-analysis and implications for HIV prevention. *Int J Epidemiol*. 2010; 39(4): 1048-63.
9. Dosekun O, Fox J. An overview of the relative risks of different sexual behaviors on HIV transmission. *Current Opinion in HIV and AIDS* 2010; 5(4): 291-7.
10. Morison L. The global epidemiology of HIV/AIDS. *British Medical Bulletin*, September 2001; 58(1): 7-18. Available at https://doi.org/10.1093/bmb/58.1.7 Accessed January 21, 2015.
11. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA*. 2008; 300(5): 520-9.
12. UNAIDS. Global AIDS Update. 2016 Available at- http://www.who.int/hiv/pub/arv/global-AIDS-update-2016_en.pdf Accessed June 11, 2017.
13. National Agency for the Control of AIDS [NACA], UNAIDS and the World Bank (undated). Modes of HIV transmission in Nigeria: analysis of the distribution of new HIV infections in Nigeria and recommendations for prevention. NACA, Abuja. Available at- http://naca.gov.ng/wordpress/wp-content/uploads/2016/11/MOT-Report-2010_0.pdf Accessed January 20, 2016.
14. Bernard EJ, Cameron S. Advancing HIV Justice 2: Building momentum in global advocacy against HIV criminalisation. HIV Justice Network and GNP+. Brighton/Amsterdam, April 2016. Available at- http://www.hivjustice.net/wp-content/uploads/2016/05/AHJ2.final2_.10May2016.pdf.
15. UNAIDS. Review of data from People Living with HIV Stigma Index surveys conducted in more than 65 countries, 2016.
16. UCSF, Anova Health Institute & WRHI. South African Health Monitoring Study (SAHMS), Final Report: The Integrated Biological and Behavioral Survey among Female Sex Workers, South Africa 2013-2014. San Francisco: UCSF, 2015.
17. UNAIDS. F A C T S H E E T – W O R L D A I D S D A Y 2017. Available at http://www.unaids.org/en/resources/fact-sheet Accessed December 21, 2017.

18. WHO. HIV AIDS Data and Statistics. Available at http://www.who.int/hiv/data/en/ Accessed December 21, 2017.

Table 1: Prevalence of HIV (including new infections) and HIV-related deaths as well as the proportion of people on ART among adults and children by WHO regions (2016)

WHO Region	Adults and children living with HIV	Adults and children newly infected with HIV	Number of People on ART (% coverage)	Deaths due to HIV in 2016
Africa	25.6 million [22.9-28.6 million]	1.2 million [980,000-1.3 million]	13,799,000 (54%)	720,000 [590,000-890,000]
Americas	3.3 million [2.9-3.8 million]	150,000 [130-180,000]	2,169,000 (66%)	54,000 [44,000-65,000]
South East Asia	3.5 million 2.5-8.2 million	150,000 [110-180,000]	1,567,000 (45%)	130,000 [120,000-120,000]
Europe	2.4 million [2.3-2.6 million]	220,000 [210-230,000]	1,121,000 (46%)	49,000 [40,000-56,000]
Eastern Mediterranean	360,000 [290,000-500,000]	37,000 [29,000-57,000]	54,300 (15%)	17,000 [14,000-24,000]
Western Pacific	1.5 million [1.2-2 million]	97,000 [46,000-170,000]	813,000 (55%)	39,000 [25,000-66,000]
Global	36.7 million [30.8-42.9 million]	1.8 million [1.6-2.1 million]	19,523,000 (53%)	1,000,000 [830,000-1,200,000]

Source (18)

Table 2: HIV epidemic and response estimates (people living with HIV and New HIV Infections), global and by region, 2010 and 2015

Area covered	People living with HIV [all ages]			New HIV Infections [all ages]	
	2010	2015		2010	2015
Global	33.3 million 30.9-36.9 million	36.7 million 34.0-39.8 million		2.2 million 2.0-2.5 million	2.1 million 1.8-2.4 million
Asia and Pacific	4.7 million 4.1-5.5 million	5.1 million 4.4-5.9 million		310 thousand 270-360 thousand	300 thousand 240-380 thousand
Eastern and Southern Africa	17.2 million 16.1-18.5 million	19.0 million 17.7-20.5 million		1.1 million 1.0-1.2 million	960 thousand 830,000-1 million
Latin America and the Caribbean	1.8 million 1.5-2.1 million	2.0 million 1.7-2.3 million		100 thousand 86-120 thousand	100 thousand 86-120 thousand
Middle East and North Africa	190 thousand 150-240 thousand	230 thousand 160-330 thousand		20 thousand 15-29 thousand	21 thousand 12-37 thousand
Western and Central Africa	6.3 million 5.2-7.7 million	6.5 million 5.3-7.8 million		450 thousand 350-560 thousand	410 thousand 310-530 thousand
Western and Central Europe and Northern America	2.1 million 1.9-2.3 million	2.4 million 2.2-2.7 million		92 thousand 89-97 thousand	91 thousand 89-97 thousand

Source (12)

Table 3: HIV epidemic and response estimates (people living with HIV on antiretroviral drugs and AIDS-related deaths), global and by region, 2010 and 2015

Area covered	People living with HIV on antiretroviral treatment [all ages]			AIDS-related deaths [all ages]	
	2010	2015		2010	2015
Global	7,501,500	17,025,900		1.5 million 1.3-1.7 million	1.1 million 940,000-1.3 million
Asia and Pacific	907,600	2,071,900		240 thousand 200-270 thousand	180 thousand 150-220 thousand
Eastern and Southern Africa	4,087,500	10,252,100		760 thousand 670-860 thousand	470 thousand 390-560 thousand
Eastern Europe and Central Asia	11,200	321,800		38 thousand 33-45 thousand	47 thousand 39-55 thousand
Latin America and the Caribbean	568,400	1,091,900		60 thousand 51-70 thousand	50 thousand 41-59 thousand
Middle eEast and North Africa	13,600	38,200		9,500 7,400-12,000	12 thousand 8,700-16,000
Western and Central Africa	905,700	1,830,700		370 thousand 290-470 thousand	330 thousand 250-430 thousand
Western and Central Europe and North America	906,200	1,418,900		29 thousand 27-31 thousand	22 thousand 20-24 thousand

Source (12)

VIROLOGY OF HIV

ADEOLA FOWOTADE
MB; BS, MSC, PHD, FMCPATH

The current chapter is focused on the virology of Human Immunodeficiency Virus (HIV). It details a review of the literature on the structure, genetic diversity and lifecycle of HIV. These details are essential, as they serve to allow for the identification of important aspects of the lifecycle of HIV thus providing insight into the development of novel methods for diagnosis of HIV as well as highlighting potential targets for antiviral therapy and vaccination against HIV.

Classification

Both human immunodeficiency viruses, HIV-1 and HIV-2, belong to the Retroviridae family, in the genus of Lentiviruses (1). HIV-1 is the more common of the two, while HIV-2 is confined to some parts of Western and Central Africa.HIV-1 has been reported to share close relations with the viruses found in some higher primates that are resident in West Africa. HIV-2 shows a higher degree of similarity to viruses found among primate sooty mangabeys, also in West Africa. There are three different groups of HIV-1, which have been separated into major (M), new (N) and outlier (O) groups based on the sequences of the gag and env genes (2). Further sub classification within Group M includes the clades A-K. Clade B is the most prevalent in North America and Western Europe and seems to be more efficiently transmitted through homosexual contact and intravenous drug use. Clades B and F are the most common in Brazil, while E is prevalent in South-Eastern Asia (3,4). The clades A, C, D and E are localized to the developing world, and clade C has specifically been associated with the world's worst epidemics. In terms of prognosis, clades C, D and G have been associated with the worse prognosis of progression to AIDS within 5 years of infection, compared with clade A (3,5). HIV-1 diversity plays an important role in diagnostic testing, treatment and monitoring as all these parameters vary between different subtypes or

clades (6). In contrast to HIV-1, less diversity has been reported with HIV-2, however subtypes A-H have been proposed for HIV-2 (7).

Structure

The human immunodeficiency viruses are moderately sized, spherically-shaped viruses and measure approximately 100 nm in diameter (8). The HIV virion consists of a viral envelope and the associated matrix surrounding a capsid, which itself encloses the RNA genome. The integrated form of HIV-1 is known as the provirus and measures approximately 9.8 kilobases in length. The long terminal repeats (LTRs) are found on both terminal ends (9).

The viral envelope is made up of a host-derived lipid bilayer interspersed with protruding glycoprotein, gp41. The gp41 is linked to the surface glycoprotein gp120 in a non-covalent manner (Figure 1). All retroviruses are encoded by three major structural genes: gag, pol and env. Both glycoproteins 41 and 120 are important for the attachment of the virus to the host cell and are encoded by the env gene (10). Additional viral proteins include the matrix protein p17 (beneath the envelope), the core protein p24 which encloses the nucleic acid core, the p6 and the nucleocapsid protein p7 (bound to the RNA), all encoded by the viral gag gene. The viral core contains 2 identical copies of the positive-sense, viral RNA genome, alongside, with the enzymes that play a role in reverse transcription and integration within the host: the protease, reverse transcriptase and integrase enzymes, which are encoded by the viral pol gene (8,10). Other regulatory and accessory proteins coded for by both HIV-1 and HIV-2 include viral infectivity protein (vif), viral protein R (vpr), transactivator of transcription (tat), regulator of viral protein expression (rev) and negative regulatory factor (nef). In contrast to HIV-2, HIV-1 possesses an additional protein: viral protein U (vpu). Similarly, HIV-2 has a specific protein: viral protein X (vpx) (Figure 2) (11).

The Structural, Regulatory and Accessory Proteins of HIV

The genetic makeup of the Retroviridae family is simple but shows great variability. The gene order in all retroviruses is 5'-gag-pro-pol-env-3' (12).The gag gene codes for the core proteins while the pro encodes the protease enzyme. Similarly, the reverse transcriptase enzyme (polymerase)

is encoded for by the pol gene; and the env encodes the glycoproteins that are projected from the envelope.

The gag gene encodes for the Gag precursor protein, also called p55, which is made up of smaller protein units including; matrix [p17], capsid [p24], nucleocapsid [p9], and p6 (13,14).The gp160is an envelope glycoprotein and consists of two subunits; the gp41 and the gp120 (15,16). Alongside the env, pol and gag genes, all retroviruses contain genes that encode for regulatory proteins (rev and tat) and accessory proteins (nef, vif, vpr and vpu). All these proteins play specific roles in the replication cycle of HIV and are thus expressed at different phases of the lifecycle of HIV. The nef gene is independent of the effect of the regulatory proteins, while the other 3 accessory proteins are rev-dependent, and expressed only during the late stage of infection (17).

HIV Tropism

HIV shows tropism for CD4+ T-cells and monocytes. The entrance of the virus into susceptible host cells is mediated by the viral glycoproteins: gp41 and gp120 (18,19). The gp120 moiety consists of nine highly conserved intrachain disulphide bonds and five hypervariable regions, designated V1 through V5 (20). The amino acid sequences vary among HIV-1 isolates and include a particular region, called the third variable loop or V3 loop (20). The V3 loop does not play a role in CD4 binding but functions as a key determinant in the selective tropism of HIV-1 for lymphoid cell lines or primary macrophages (14). Amino acid sequences within the V3 loop allow it to bind to specific chemokine co-receptors based on the HIV strain (21-23). Additionally, the gp120 moiety interacts with dendritic cells via the DC-SIGN receptor thus facilitating HIV entry into lymphoid tissues (24).

Lifecycle and Regulation of HIV Gene Expression

The HIV virion attaches via its surface glycoproteins to macrophages and CD4+ T-cells, then releases the nucleocapsid into the host cell, following the attachment of the viral envelope to the target cell membrane (25,26). The fusion stage involves the formation of a strong attachment between the gp120 of HIV and the CD4 binding domains, followed by a conformational change in the viral envelope, thus facilitating the interaction of the HIV gp120 and the binding domains of the target chemokine receptor (25,26).More recent studies have shown that

productive HIV-1 infection is achieved specifically through pH-independent, clathrin-dependent endocytosis of the virus (27-31).Cell-to-cell spread of the virus is facilitated by the binding of the gp120 to integrin α4β7 thus activating the establishment of virological synapses (25).The reverse transcriptase and integrase enzymes, respectively, ensure reverse transcription of the viral RNA into double-strand DNA, this stage precedes the integration of the viral genome into the host chromosome. The integrated viral DNA remains dormant during the stage of HIV latency and active virus production requires the utilization of specific host transcription factors, including nuclear factor kappa B (NF-κB) (32). The proviral DNA undergoes transcription and subsequent splicing to form mature RNAs. The mature mRNAs translocate from the nucleus to the cytoplasm, where they undergo translation to form the regulatory proteins (33). Part of the newly synthesized full-length RNAs functions as new virions, while other mRNAs are translated into structural proteins Env and Gag (34).HIV-1 and HIV-2 package their RNA in different ways. Unlike HIV-1 which is non-selective, HIV-2 exclusively binds to the mRNA that was utilized in the synthesis of the Gag protein (35,36).

The newly synthesized HIV-1 virions are assembled at the plasma membrane of the host cell (37). The gp41 tethers the gp120 to the surface of the infected host cell (37).Furthermore, the structural proteins Gag (p55) and Gag-Pol (p160) attach to the plasma membrane, alongside the HIV RNA (37). To exit the host cell, the newly formed matured virion undergoes exocytosis (37,38).

Genetic Variability

HIV exhibits a very high genetic variability compared with other viruses due to its rapid mutation rate and fast replication cycle, the multiple introductions of HIV-1 into the human population, the low fidelity and high recombinogenic power of its reverse transcriptase (39-41). The simian immunodeficiency virus (SIV) has been well studied and found to have evolved into many strains. The two common strains are the African green monkey (SIVagm) and the sooty mangabey (SIVsmm), both of which have been associated with a long evolutionary history with their hosts (42). In contrast to HIV, infection with SIV does not progress to AIDS and is not characterized by the typical mutational changes found inhuman HIV infections (43, 44). However, there have been reports of SIV infection in rhesus species and cynomolgus macaques, which has resulted

in AIDS with the virus exhibiting similar genetic diversity typical of HIV infection in humans (45).

Among the four HIV-1 groups, the HIV-1 group M variant is the most common, and is further divided into subtypes; A–D, F–H, J and K. Additionally, circulating recombinant forms (CRFs), known to carry genetic information from two or more subtypes, have been detected in infected humans (46). HIV-2 includes two groups (A and B) and it is worth noting that HIV-2 CRFs have only been reported once with HIV-2 (47,48). Co-infection with distinct HIV subtypes in humans results in CRFs.

Interestingly, CRFs constitute 20% of all HIV-1 infections, with 50% of these infections involving CRF02_AG and CRF01_AE (Figure 3) (49). Current evidence has shown that specific HIV subtypes are preferentially associated with certain behavioural factors, such as intravenous drug users and drug-trafficking regions (50).

In conclusion, HIV-1 is incontrovertibly one of the most studied infectious agents of the last three decades. The availability of new molecular diagnostic technologies has allowed further insight into the HIV structure and replication. Furthermore, reports from various studies have highlighted the different viral subtypes and recombinant forms as well as the significance of such differences in the infection cycle. The current chapter on the virology of HIV provides important information which is useful for the design of novel and therapeutic approaches aimed at interrupting the HIV life cycle.

References

1. Weiss RA, Dalgleish AG, Loveday C, Pillay D. Human Immunodeficiency Viruses. In: Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths PD, Schoub BD (eds). *Principles and Practice of Clinical Virology*. 5th ed. 2004. Chichester: John Wiley & Sons Ltd.,721-57.
2. Tatt ID, Barlow KL, Nicoll A, Clewley JP. The public health significance of HIV-1 subtypes. *AIDS* 2001; 15 (suppl. 5): s59-s7.
3. Noble R. Introduction to HIV types, groups and subtypes. 2006. Accessed from: http://www.avert.org/hivtypes.htm.
4. Requejo HI. Worldwide molecular epidemiology of HIV. *Rev SaudePublica.* 2006; 40:331-45.

5. Kanki PJ, Hamel DJ, Sankale JL, et al. Human immunodeficiency virus type 1 subtypes differ in disease progression. *J Infect Dis.* 1999;179:68-73.
6. Natalya M. Gashnikova, Ekaterina M. Astakhova, Mariya P. Gashnikova, et al.HIV-1 Epidemiology, Genetic Diversity, and Primary Drug Resistance in the Tyumen Oblast, Russia,*BioMed Research International*, 2016; vol. 2016, Article ID 2496280, 13 pages.
7. Santiago Mario L, RangeFriederike,Keele Brandon F, LiYingying, Bailes Elizabeth, Bibollet-Ruche Frederic,Fruteau Cecile,Noë Ronald, Peeters Martine, Brookfield John FY, Shaw George M, Sharp Paul M, Hahn Beatrice H. Simian Immunodeficiency Virus Infection in Free-ranging Sooty Mangabeys (Cercocebusatysatys) from the Taï Forest, Côte d'Ivoire: Implications for the Origin of Epidemic Human Immunodeficiency Virus Type 2. *JVirol*. 2005; 79(19): 12515-27.
8. Compared with overview in: Fisher Bruce, Harvey Richard P,Champe Pamela C. *Lippincott's Illustrated Reviews: Microbiology*. Lippincott's Illustrated Reviews. Hagerstown, MD: Lippincott Williams & Wilkins, 2007, 3. ISBN 0-7817-8215-5.
9. Muesing MA, Smith DH, Cabradilla CD, et al. Nucleic acid structure and expression of the human AIDS/lymphadenopathy retrovirus. *Nature* 1985;313:450-458.
10. Klein Joshua S, Bjorkman Pamela J,Rall Glenn F. Few and Far Between: How HIV May Be Evading Antibody Avidity. *PLOS Pathogens*27 May 2010; 6(5): e1000908. doi:10.1371/journal.ppat.1000908.
11. Nyamweya SI, Hegedus A, Jaye A, Rowland-Jones S, Flanagan KL, Macallan DC. Comparing HIV-1 and HIV-2 infection: Lessons for viral immunopathogenesis.*Rev Med Virol*.July 2013;23(4):221-40.
12. Mushahwar Isa K. Human Immunodeficiency Viruses: Molecular Virology, pathogenesis, diagnosis and treatment. *Perspectives in Medical Virology*2007; 13:75-87.
13. Votteler J and Schubert U.*Human Immunodeficiency Viruses: Molecular Biology*. *Encyclopedia of Virology* (3rd ed.) 2008; 517-525 R.
14. King Steven R. HIV: Virology and Mechanisms of disease. *Annals of Emergency Medicine*1994; 24: 443-449.
15. Capon DJ, Ward RH. The CD4-gp120 interaction and AIDS pathogenesis. *Annu Rev Immunol* 1991;9:649-678.
16. Bernstein HB, Tucker SP, Kar SR, et al. Oligomerization of the hydrophobic heptad repeat of gp41. *J Virol* 1995;69:2745-2750.

17. Clapham PR, McKnight A. HIV-1 receptors and cell tropism. *Br. Med. Bul*. 2001; 58: 43-59.
18. Moore RD, Chaisson RE. Natural History of HIV infection in the era of combination antiretroviral therapy. *AIDS* 13, 1999; 1933-42.
19. Hwang SS, Boyle TJ, Lyerly HK, Cullen BR. Identification of the envelope V3 loop as the primary determinant of cell tropism in HIV-1. *Science* 1991;253:71-74.
20. The interactions of the gp120 V3 loop of different HIV-1 strains with the potent anti-HIV human monoclonal antibody 447-52D.
21. Feng Y, Broder CC, Kennedy PE, et al. HIV-1 entry cofactor: Functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 1996;272:872-877.
22. Deng H, Liu R, Ellmeier W, et al. Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 1996;381:661-666.
23. Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GC, Middel J, Cornelissen IL, Nottet HS, KewalRamani VN, Littman DR, Figdor CG, van Kooyk Y. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. *Cell*. 2000;100:587-97.
24. Pope M, Haase AT (2003). Transmission, acute HIV-1 infection and the quest for strategies to prevent infection. *Nature Medicine* 9(7): 847-52.
25. Chan DC, Kim PS. HIV entry and its inhibition. *Cell*1998; 93(5): 681-4.
26. Wyatt R, Sodroski J. The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. *Science*1998; 280(5371): 1884-8.
27. Daecke J, Fackler OT, Dittmar MT, Kräusslich HG. Involvement of clathrin-mediated endocytosis in human immunodeficiency virus type 1 entry. *J Virol*. 2005; 79(3): 1581-1594.
28. Miyauchi K, Kim Y, Latinovic O, Morozov V, Melikyan GB. HIV Enters Cells via Endocytosis and Dynamin-dependent Fusion with Endosomes. *Cell*2009; 137(3): 433-444.
29. Koch P, Lampe M, Godinez WJ, Müller B, Rohr K, Kräusslich HG, Lehmann MJ. Visualizing fusion of pseudotyped HIV-1 particles in real time by live cell microscopy. *Retrovirology* 2009; 6: 84.
30. Thorley JA, McKeating JA, Rappoport JZ. Mechanisms of viral entry: sneaking in the front door. *Protoplasma*2010; 244(1-4): 15-24.
31. Permanyer M, Ballana E, Esté JA. Endocytosis of HIV: anything goes. *Trends in Microbiology*2010; 18(12): 543-551.
32. Zheng YH, Lovsin N, Peterlin BM. Newly identified host factors modulate HIV replication. *Immunology Letters*2005; 97(2): 225-34.

33. Pollard VW, Malim MH. The HIV-1 Rev protein. *Annual Review of Microbiology*1998; 52: 491-532.
34. Butsch M, Boris-Lawrie K. Destiny of Unspliced Retroviral RNA: Ribosome and/or Virion?.*J Virol*.2002; 76(7): 3089-94.
35. Hellmund Chris; LeverAndrew ML. Coordination of Genomic RNA Packaging with Viral Assembly in HIV-1. *Viruses*. 2016; 8(7): 192.
36. Ricci EP,HerbreteauCH,Decimo D,Schaupp A,Datta SAK, ReinA,Darlix J-L,Ohlmann T.In vitro expression of the HIV-2 genomic RNA is controlled by three distinct internal ribosome entry segments that are regulated by the HIV protease and the Gag polyprotein. RNA2008; 14(7): 1443-55.
37. Hallenberger S, Bosch V, Angliker H, Shaw E, Klenk HD, Garten W. Inhibition of furin-mediated cleavage activation of HIV-1 glycoprotein gp160. *Nature*1992; 360(6402): 358-61.
38. Gelderblom HR. Fine structure of HIV and SIV. In *Los Alamos National Laboratory. HIV sequence compendium*. Los Alamos National Laboratory,1997, 31-44.
39. Robertson DL, Hahn BH, Sharp PM. Recombination in AIDS viruses. *Journal of Molecular Evolution*1995; 40(3): 249-59.
40. Rambaut A, Posada D, Crandall KA, Holmes EC. The causes and consequences of HIV evolution. *Nature ReviewsGenetics.*2004; 5(52-61): 52-61.
41. Perelson AS, Ribeiro RM. Estimating drug efficacy and viral dynamic parameters: HIV and HCV. Statistics in Medicine. 2008; 27(23): 4647-57.
42. Sodora DL, Allan JS, Apetrei C, Brenchley JM, Douek DC, Else JG, Estes JD, Hahn BH, Hirsch VM, Kaur A, Kirchhoff F, Muller-Trutwin M, PandreaI, Schmitz JE, Silvestri G. Toward an AIDS vaccine: lessons from natural simian immunodeficiency virus infections of African nonhuman primate hosts. *Nature Medicine*2009; 15(8): 861-865.
43. Holzammer S, Holznagel E, Kaul A, Kurth R, Norley S. High virus loads in naturally and experimentally SIVagm-infected African green monkeys. *Virology*2001; 283(2): 324-31.
44. KurthR,Norley S. Why don't the natural hosts of SIV develop simian AIDS?*The Journal of NIH Research*1996;8: 33-37.
45. Baier M, Dittmar MT, Cichutek K, Kurth R. Development of vivo of genetic variability of simian immunodeficiency virus. *Proceedings of the National Academy of Sciences of the United States of America*. 1991; 88(18): 8126-30.

46. Daniel MD, King NW, Letvin NL, Hunt RD, Sehgal PK, Desrosiers RC. A new type D retrovirus isolated from macaques with an immunodeficiency syndrome. *Science*1984; 223 (4636): 602-5.
47. Robertson DL, Anderson JP, Bradac JA, et al. HIV-1 nomenclature proposal. *Science* 2000; 288(5463): 55.
48. Ibe S, Yokomaku Y, Shiino T, et al. HIV-2 CRF01_AB: first circulating recombinant form of HIV-2. *J. Acquir. Immune Defic. Syndr*. 2010; 54(3): 241-247. Circulating recombinant forms also occur in HIV-2. Using phylogenetic methods, the authors demonstrated the recombinant nature of HIV-2 isolates.
49. Hemelaar J, Gouws E, Ghys PD, Osmanov S. WHO–UNAIDS. Global trends in molecular epidemiology of HIV-1 during 2000–2007. *AIDS* 2011; 25(5): 679-689.
50. Skar H, Hedskog C, Albert J. HIV-1 evolution in relation to molecular epidemiology and antiretroviral resistance. *Ann. NY Acad. Sci.* 2011; 1230: 108-118.

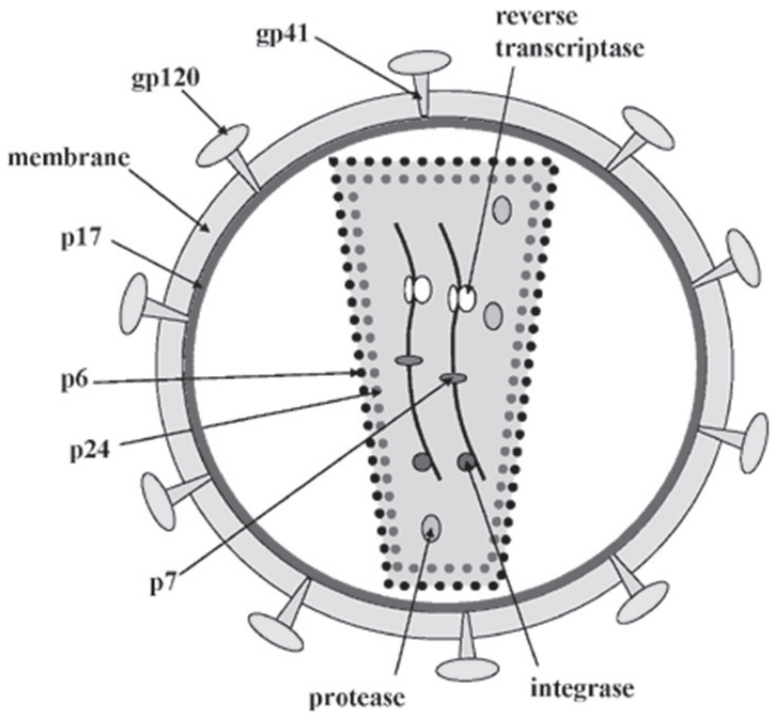


Figure 1: Schematic structure of HIV-1 showing the different viral envelope and core proteins. The trimeric glycoproteins have been simplified to appear as monomers (adapted from Cleghorn FR, Reitz MS, Popovic M, Gallo RC. Human Immunodeficiency Viruses. In: Mandell GL, Bennett JE, Dolin R (eds). *Principles and Practice of Infectious Diseases*.6th ed. 2005. Philadelphia: Churchill Livingstone, 2119-2133.

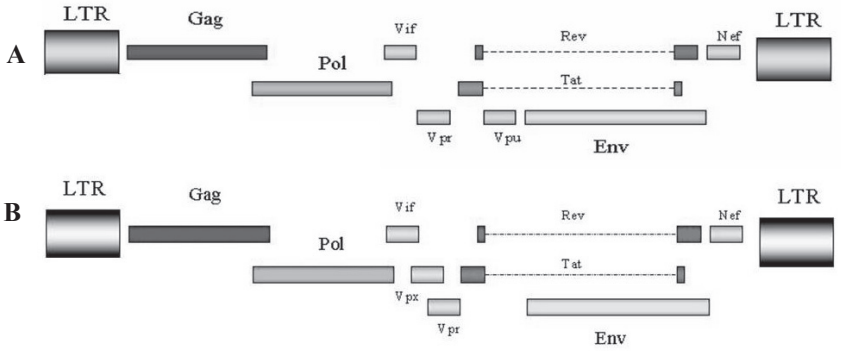


Figure 1: Organisation of the HIV genome. A) HIV-1 genome; B) HIV-2 genome (adapted from

Figure 2: Genomic layout of HIV-1 (A) and HIV-2 (B). Adapted from Rivera, DM and Frye, RE.Pediatric HIV Infection.*Medscape Medical News*. September 13, 2017. Available from https://emedicine.medscape.com/article/965086-overview.

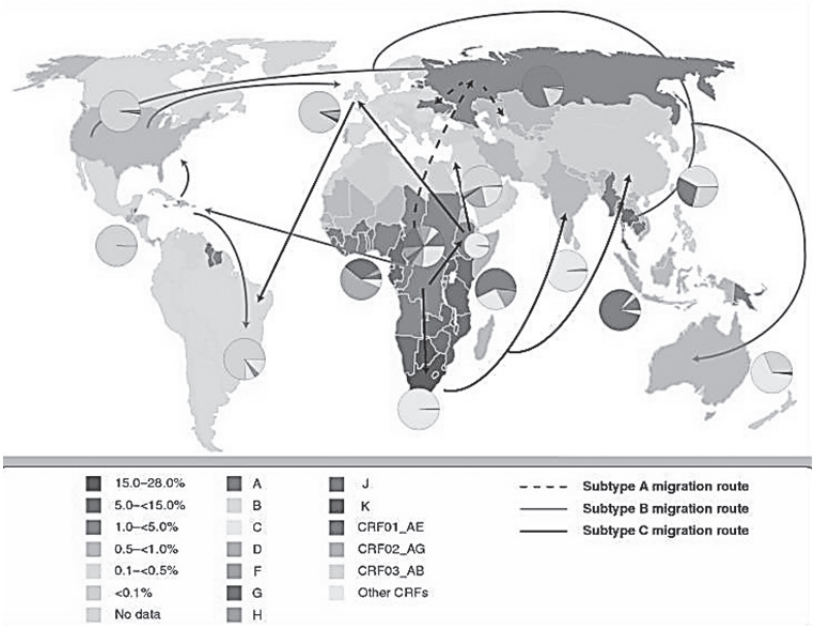


Figure 3: Global distribution of HIV-1 group M. The countries are colour-coded according to their last reported prevalence. The Pie charts represent the distribution of subtypes and circulating recombinant forms over the globe. Arrows represent potential migration routes for A, B and C subtypes. Adapted from *Future Virol* 2012. Future Medicine Limited.

HAEMATOLOGICAL MANIFESTATIONS OF HIV DISEASE

VICTOR O MABAYOJE
MBBS, FWACP

This chapter describes the haematological manifestations of HIV infection and also highlights the causes, expressions and treatment modalities.The main findings were cytopenias, which could be caused by increased destruction, reduced production or a combination of both in varying degrees. The cytopenias may be immune mediated, drug induced or by direct HIV infection. Treatment modalities for thrombocytopenia and coagulation disorders in the HIV setting are in urgent need of attention.The main features of haematological manifestations of HIV disease are peripheral cytopenias. These may be isolated (for example thrombocytopenia), and may be a presenting feature or it could affect all three-cell lines causing a pancytopenia and is usually related to the degree of immunosuppression. The causes and treatment of the various haematological disorders will be discussed in appropriate sections;anaemia, thrombocytopenia, white cell disorders, bone marrow abnormalities and finally coagulation disorders for ease of understanding.

Anaemia

This is a very common finding in HIV-infected individuals. The most common morphological type is the normochromic normocytic anaemia. In Africa it is the most common finding in highly active antiretroviral therapy (HAART) naive patients (1,2).Studies in Europe and North America have demonstrated that at least one-third of patients are affected by anaemia irrespective of prognostic factors such as CD4+ cell counts, diagnosis of AIDs before commencing HAART and transmission risk groups(3). Studies carried out in Nigeria revealed levels of anaemia as high as 60% among HIV-positive individuals. Investigations carried out in Northwest Ethiopia also revealed the study population had significant degrees of anaemia, even those on HAART.

All these findings are highlighting widespread occurrence and the importance of identifying anaemia among diagnosed HIV/AIDs infected individuals. Interestingly, studies carried out in Benin city in Nigeria revealed that anaemia in HIV-positive pregnant women was a significant cause of increased morbidity among them.

Indeed, patients presenting denovo with anaemia should be subjected to the national algorithm for screening for HIV as part of laboratory investigations to determine the cause of anaemia. It is known that the lower the CD4+ cell counts the more likely the patient is to suffer from anaemia.

The causes of anaemia are multifactorial. These include direct infection of stem cells by HIV, lack of production of adequate erythropoietin (EPO) to compensate for the degree of presenting anaemia and soluble factors in the serum which inhibit erythropoiesis(4).

Drug-induced anaemia is a very important cause of anaemia in this subset of patients. The most notorious drug widely implicated is Zidovudine (AZT), which has been found to cause anaemia profound enough to require either treatment with EPO or blood transfusions. AZT is associated with marrow aplasia, megaloblastic maturation and erythroid hypoplasia. It is suggested that treatment with lower doses of AZT would reduce the frequency and severity of anaemia caused by this drug(5).Antineoplastic drugs and antibiotic agents used for the prophylaxis or treatment of HIV-related conditions also cause anaemia. Non-Hodgkin lymphoma (NHL), which is not uncommon in HIV patients, is managed with myelosuppressive agents which could cause anaemia. Other drugs associated with anaemia include stavudine, co-trimoxazole, isoniazid, rifampicin and rifabutin.

A significant number of these findings were discovered shortly after the outbreak of the endemic in the early 1980s hence the reflection in the earlier journal articles(4,5).

Infection of the marrow with Mycobacterium avium complex (MAC) is another cause of anaemia in chronic HIV disease. Patients with this infection are more than five times likely to receive red blood transfusions.

B19 parvovirus infection can also cause marrow suppression by infecting red cell progenitors thereby inhibiting haematopoiesis.

Reactive granuloma formation may follow infection of the marrow with cryptococcus neoformans leading to peripheral cytopenias. B19 infection should be strongly suspected in cases with preserved platelet and white cell counts. There is an associated marked reticulocytopenia. Bone marrow biopsy is not necessary here but the polymerase chain reaction (PCR) is the test of choice. Management includes HAART, red cell transfusions and intravenous immunoglobulin therapy. Though this may be scarce and is expensive.

Tuberculosis, NHL, and histoplasmosis can all infiltrate the marrow with resultant anaemia and pancytopenia in other cases.

Other significant causes include antierythrocyte antibodies which give rise to a positive direct antiglobulin test (DAT) in about 20% of HIV-infected patients with hypergammaglobulinaemia. While these antibodies are thought to behave as polyagglutinins it is not yet clear if they are directed against specific cell surface antigens or just represent non-specific attachment. It should be mentioned however that anaemia in the setting of an HIV-related positive DAT is rare.

The gastrointestinal tract (GIT) is also a source of blood loss in these patients. Along with the usual cases of GIT blood loss e.g., peptic ulcer disease, HIV-related infections such as cytomegalovirus colitis, Kaposi sarcoma and NHL could lead to clinically significant bleeding.

Shigella, amoebiasis,giardiasis and cryptosporidiosis would all cause malabsorption of iron and subsequent anaemia. Lactose intolerance is also a cause of anaemia from the GIT.

The concept of anaemia of hypogonadism, which occurs in HIV-infected men,deserves a mention. There is usually associated fever, weight loss and sexual dysfunction.

A serum testosterone level should therefore be included in the workup of men with anaemia and other features suggestive of hypogonadism. Inflammatory cytokines also play a central role in the pathogenesis of anaemia TNF, IL-1, INF-γ have all been shown to inhibit erythropoiesis. TNF levels are elevated in HIV infection and correlate with the viral load.

Table I. Causes of anaemia in HIV patients

1)Nutritional deficiencies (malnutrition and malabsorption);
2)Anaemia of chronic disease;
3)Myelosuppressive drugs (e.g., zidovudine, antimicrobials, and antineoplastic agents);
4)Hypogonadism;
5)Vitamin B12, iron, or folate deficiency;
6) Haemophagocytosis histocytosis;
7)Myelofibrosis or myelodysplasia;
8)Neoplasia (e.g., non-Hodgkin lymphoma);
9)Opportunistic bone marrow infections (e.g., infection with cytomegalovirus, parvovirus B19, Mycobacterium avium complex(MAC)).

Table II. Risk factors associated with anaemia of HIV infection

1) History of clinical AIDS;
2) CD4+ cell counts <200cells/µl;
3) Plasma virus load;
4) Women;
5) Black race;
6) Zidovudine use;
7) Increasing age;
8) Lower body mass index;
9) History of bacterial pneumonia;
10) Oral candidiasis;
11) History of fever.

Investigation of Patients with Anaemia associated with HIV Infection

A general assessment for anaemia should be carried out as for any other patient. Search for anaemia, jaundice, lymphadenopathy, and hepatosplenomegaly. Any evidence of blood loss should be determined. Evaluation of iron stores e.g., serum iron, iron-binding capacity, and ferritin levels should be carried out.

Serum ferritin is a good indicator for acute and chronic inflammation and would be raised in HIV infection masking depleted iron stores of iron deficiency anaemia (IDA). It may be preferable to determine soluble transferrin receptor levels as this is not affected by inflammation

(sTfr).Furthermore, sTfr levels correlate with the severity of iron deficiency in the body even with evidence of infection/inflammation (6).

Stool and urine for occult blood may suggest malignancy of the GIT or the renal system.Further investigations would be necessary to rule this out.Macrocytosis would suggest tests for vitamin B12 or folate deficiency. In this environment, haemoglobinopathies should be considered (sickle cell disease) and a haemoglobin phenotype/genotype should be done. In children, thalassaemia trait should be ruled out especially if there is a family history and an appropriate ethnic background. Enzyme deficiencies(glucose-6-phosphate dehydrogenase, pyruvate kinase) should be also ruled out.

A re-evaluation of the patient's treatment schedule may be necessary. If patients are on Zidovudine and other causes of anaemia have been excluded a change to another antiretroviral agent should be strongly considered by the switch committee of the HIV management team. The switch committee of an HIV team is set up of various members including pharmacists, doctors and nurses to consider changing the drug combination of a particular patient who is suffering from complications such as recalcitrant anaemia, or failure to respond to therapy as reflected by persistently low CD4 counts and high viral loads despite being on treatment. Stavudine and co-trimoxazole (Bactrim) are also common causes of drug-induced anaemia.

Determination of serum erythropoietin (EPO) levels to consider if exogenous EPO is indicated may be necessary. If a diagnosis of PCP has been established and the patient is placed on Dapsone therapy, a measurement of the serum bilirubin, lactate dehydrogenase (LDH), methemoglobin and haptoglobin levels should be considered to evaluate drug-induced haemolysis. If haemolysis is suspected both direct and indirect antiglobin tests should be done to detect rare cases of autoimmune haemolysis before asserting the blame on the drug therapy.

If there are clinical features such as fever, fatigue, weight loss, and/or diarrhoea suggesting infection or neoplasm, an adeuate evaluation of the patient is necessary.

A mycobacterial blood culture to assess for MAC or *M. Tuberculosis* should be undertaken. Fungal infections such as *Histoplasma capsulatum* could be revealed through the performance of blood cultures.

Bone marrow trephine biopsy can assist in the establishment of disseminated mycobacterial and fungal infections or lymphoma.

If examination of the marrow trephine reveals erythroid hypoplasia with giant pronormoblasts, B19 parvovirus infection should be strongly suspected. PCR (Polymerase chain reaction) based assays for parvovirus DNA in serum can also be used to confirm the diagnosis.

It should be noted however that bone marrow studies should be considered after all other options have been exhausted. The procedure of obtaining a marrow biopsy can be considerably uncomfortable for the patient. Complications include pain and bleeding.

Thrombocytopenia

Studies carried out in Nigeria have revealed varying degrees of anaemia in HIV-positive patients. One such revealed an incidence as high as 10% of the participants suffering from thrombocytopenia (7,8). In the University of Maryland Medical Center it was found that HIV-positive patients had severe thrombocytopenia with counts as low as $10{,}000/mm^3$(9). Thrombocytopenia as a frequent presenting feature has been reported in various parts of the world including the United Kingdom and Europe.

It has been established that there is a rise in mortality and morbidity in patients positive for HIV who are suffering from thrombocytopenia. Early cases of thrombocytopenia (TCP) in this group of individuals are due to the peripheral destruction of platelets. It has also been found that TCP is more likely associated with a decline in CD4 counts and a more rapid progression to AIDS. Many sources have observed that TCP places a limitation on the type and range of medications that may be utilized in HIV-positive individuals and AIDS-related malignancies e.g., lymphoproliferative malignancies. The usual traditional therapies such as transfusions, immunosuppressors, splenectomy, and HAART are associated with risks and limitations. This underlines the urgent need for establishing new therapeutic protocols for this subgroup of HIV patients. Thrombocytopenia like anaemia in HIV-infected persons is multifactorial. Factors which often overlap include peripheral platelet destruction, fragmentation of platelets, reduction in life span and ineffective production or all occurring together to produce thrombocytopaenia in different degrees.

HIV directly affects all haemopoietic cell lineages leading to a wide range of haematological abnormalities. Earlier on in the infection (late 1980s) ultra-structural analysis revealed platelets were especially vulnerable to HIV attack as direct infection could occur through both CD4 and CXCR4 receptors. However, immune destruction of platelets is thought to be responsible for the early onset of TCP suggesting early immune dysregulation.There is also the formation of autoantibodies due to the wide range of immune alterations that occur.

The cross-reaction between gp120 of the human immunodeficiency virus and gp3a thrombocytes has been demonstrated as a contributing factor of thrombocytopenia.

Studies have shown that HIV p24 antibodies cross-react with platelets in 60% of cases, and thrombocyte destruction by these antibodies has been linked with the generation of peroxides and other reactive oxygen species. It has been suggested as previously mentioned that platelets in this setting have a shorter mean life span. Unfortunately, compensation for this reduced life span is not effective enough as indicated by levels of Thrombopoietin (TPO)which are not adequate enough to maintain satisfactory peripheral counts.

A landmark research study by Cole and his colleagues revealed that despite a threefold increase in megakaryocyte substrate, there was no change in the platelet mass turnover. This indicated a disparity between the marrow substrate and the circulating product. This abnormality known as ineffective production is characteristic of HIV thrombocytopenia, but not of other thrombocytopenic groups.

Infectious diseases occurring alongside HIV may also sabotage platelet survival and replenishment. The Swiss group demonstrated that all patients with severe TCP were positive for antibodies against the hepatitis B virus core antigen, compared to 80% of HIV-infected persons without thrombocytopenia. It was therefore presumed that those with hepatic disease were more prone to low levels of serum Thrombopoietin, which led to a low production of platelets.

Controversially, infection with *Helicobacter pylori* is thought to contribute to low platelet counts. Others have argued against this and have proposed that TCP in HIV-infected persons is more associated with a history of injection drug use/abuse (10). No significant treatment protocol exists for the clinical management of HIV-related TCP. However, treatment is

effected and mandatory for those with active acute bleeding and those with severe thrombocytopenia. Platelet counts can be associated with disease progression in HIV. Persistently low counts are a reliable predictor for rapid progression to AIDS. They show a more rapid decline in CD4 counts over time relative to those with normal platelet counts.

After controlling for anaemia, clinical AIDS, CD4 counts, neutropenia, HAART and prophylaxis, Sullivan and his collaborators revealed that thrombocytopenia was significantly associated with decreased survival. All these similar findings by different study groups further emphasize the need for adopted standard treatment protocols for these patients.

It has been revealed that platelets engulf HIV and Staphylococcus aureus. This engulfment is enhanced by platelet activation, leading to the view that platelets have an important role to play in the immune response against HIV. Alternatively, it has also been determined that platelets can transfer CXCR4 to CXCR4-null targets, rendering astrocytes and cardiomyocytes susceptible to HIV infection. This significant impact of TCP on HIV disease underscores even in those receiving HAART the urgent need for therapeutic intervention.

Current therapy of TCP in this subgroup of patients can be divided into five levels. Medications utilized in the management of TCP impair the clearance of platelets coated with antibodies. Receptors coated with the Fc component of IgG (FcRs) on macrophages play an important role in the host's defence against infection including immune-mediated TCP. Therefore, regulation of the expression of these splenic receptors is a vital goal in the immunotherapeutic treatment of thrombocytopenia. Destruction of antibody-coated platelets is inhibited by splenectomy, corticosteroids, danazol, intravenous immunoglobins and vinca alkaloids (vincristine and vinblastine). Whereas glucocorticoids discourage the expression of splenic macrophage Fc receptors and increase cell survival. Immunoglobulins contain both anti-idiotype and anti-cytokine antibodies that inhibit complementary activation in addition to hiding antigen-binding sites. Plasmapheresis may also temporarily remove antibody production and therefore reduce platelet destruction.

Secondly, the therapies mentioned above can act by inhibiting antibody production. This mechanism is mainly associated with microbial pathogens such as HIV, hepatitis B, and *Helicobacter pylori*. It is suggested that treatment of these organisms is associated with improvement in TCP. It should be stated that this view is not universally

accepted as earlier stated indicating the need for further and advanced research. Glucocorticoids, danazol and high dose dexamethasone have been proposed for the treatment of immune thrombocytopenia. They are thought to have better effectiveness and fewer side effects than chronic oral corticosteroids. However, some have reported that glucocorticoids, which treat TCP in non-HIV patients, are not recommended in this setting as they are thought to directly cause an up-regulation of HIV-1 replication and further compromise the immune system increasing the risk of opportunistic infection.

Debilitating proximal myopathy, fulminant Kaposi's sarcoma and pneumocystis pneumonia are complications ascribed to the use of corticosteroids in HIV-infected persons. Danazol, a synthetic androgen has been said to be an effective drug that is beneficial in the long-term management of thrombocytopenia, with fewer severe side effects than glucocorticoids. It is thought to enhance platelet growth and block the effects of antibodies in destroying platelets but its overall efficacy has been relatively unsatisfactory. In some performed studies danazol was found to be the least useful in the management of TCP.

Splenectomy though has been found to be safe and effective in the management of TCP in this setting. It is thought to increase CD3, CD4 and CD8 lymphocyte counts.Splenectomy carries its own risks of infections and septic complications and should only be recommended when other therapies have failed. Prophylactic vaccines have been used to increase the protection of asplenic patients against severe infections. Splenic irradiation has been suggested as an alternative to splenectomy using cobalt 60. However additional studies are required to explore the potential of this form of treatment.

Intravenous immunoglobulins (IVIGs) containing IgG leads to a rapid recovery of platelets though the mechanism is not completely understood. IVIGs have been used both as prophylaxis and definitive treatment. High doses are given (IVIG 7S immunoglobulin 220-400mg/kg, IVIG 1gm/kg body weight) and two injections of 50 mls of 1 gm administered to HIV-positive patients are useful for obtaining a rapid increase in platelet counts in up to 80% of cases. The maximum increase is reached by 7-10 days and maintained for 1-3 months. The disadvantages with IVIGs is that they are very expensive and scarce. So, use is usually strictly reserved for those with acute active bleeding and severe TCP. It is also indicated for those undergoing surgery(11).

Megestrol acetate is synthetic progesterone which was initially prescribed for the cachexia and anorexia of HIV but was later found to have some encouraging effects on patients with thrombocytopenia. It not only increased counts but also prolonged survival.

Platelet transfusions would obviously provide a rapid resolution of cases of thrombocytopenia. However, there are significant dangers associated with this procedure especially in the developing world. The most serious of these is administrative errors leading to ABO-incompatible blood transfusion, transfusion related lung injury and bacterial contamination of platelet products. The issue of transfusion transmissible infections(TTIs) is also of significant importance. These include hepatitis B and C, malaria, syphilis, cytomegalovirus, parvovirus B19 and Chagas. Furthermore, there is always the threat of new emerging infectious pathogens affecting blood safety.

Also of concern for HIV-infected individuals is that blood transfusions may accelerate HIV-I disease progression through activation of HIV-I expression and/or transfusion related immunosuppression. Other risks to be aware of are hypotensive attacks occurring in those on angiotensin converting enzyme (ACE) inhibitors who receive platelet transfusions through bedside leukoreduction filters. If the underlying condition is ITP, platelet transfusions are contraindicated. In this setting, the transfusion may fuel thrombosis and worsen clinical signs and symptoms. Platelet transfusions are costly since platelets have short survival spans and large numbers of platelet units are required for transfusion procedures. While packed red cells may be stored for up to 42 days, platelets cannot be stored for more than five days.

Reports have demonstrated that antiretroviral therapy with Zidovudine, protease inhibitors, and HAART may restore platelet counts. Zidovudine though has the effect of increasing platelet counts but the effect is self-limiting and rather short-lived. The counts are eventually dropping despite increasing the dose of Zidovudine. HAART on its own may initially increase platelet counts but the effect is only temporary and limited to 30-50% of cases.

Newer therapies being considered include cytokines. These are biologically active molecules produced by immune competent cells which regulate the immune response.

Some important cytokines have been identified that exert effects on megakaryocytes encouraging growth and differentiation. They include IL-1, IL-3and IL-6.

Cloning the cytokine genes has facilitated the production of large amounts of these cytokines which have emerged with promising results after having undergone clinical evaluation.

Thrombopoietin (TPO), is a substance which mainly regulates platelet formation and is still surrounded by much controversy and its use is still undergoing clinical trials.

Interferon-Alpha is another promising therapeutic option. It has been found to be useful in those with AZT resistant TCP.Its administration led to a significant increase in IL-6 levels in thrombocytopenic subjects and this explained the ability of interferon-alpha to cause an increase in platelet counts. As a result of these multifactorial, pathogenic mechanisms of thrombocytopenia in HIV, management of this condition remains a clinical challenge for HIV specialists and haematologists. Due to this, investigators are actively developing new pharmacologic interventions including immunotherapy. Despite the occasional rays of breakthroughs, there is still no standard treatment protocol for these patients who are largely treated independently/individually as they present.

This should be seen as alarming as thrombocytopenic HIV-infected patients have the greater probability of being severely affected by this condition. Urgent attention is required for this unique and vulnerable subpopulation of patients in terms of standard treatment options.

White Blood Cells

Leukopenia in HIV patients has been reported severally across Nigeria and other parts of the world(12,13).

The white cell counts consist of the total white cells and differentials which include neutrophils, lymphocytes, eosinophils, monocytes, and basophils, each with its ascribed function.

There is however, a subset of cells called CD4 cells. These cells are of T origin, and the cluster of differentiation (CD) is a glycoprotein found on the surface of T helper cells, macrophages, monocytes and dendritic cells. HIV uses these CD4 T-cells to infect the host through its viral envelope

protein gp120. The subsequent binding to a CD4 receptor causes an alteration in the conformation of gp120 enabling HIV-1 to bind to co-receptors also found on the host cell. These are chemokine receptors CCR5 or CXCR4. The other viral protein gp41, following the structural change allows HIV to insert a fusion peptide into the host cell that encourages the outer membrane of the virus to merge with the cell membrane. It is worthy to note that this stage of infection has been a subject of targeted therapy by the production of fusion peptide inhibitors. However, the success of this therapy is controversial as there were numerous complications including the early development of resistance to the inhibitors(14).

On activated CD4 T-cells, CD4 molecules have the ability to interact directly with the T-cell receptor complex to influence immune response. However, on the flip side together with interacting with the T-cell receptor and also Class II MHC determinants, CD4 serves as a high-affinity focus for HIV as already stated. A similar molecular interaction initiates fusion between HIV-infected CD4 positive cells and uninfected cells resulting in the formation of multinucleated syncitia. This mechanism may in part explain the decline in CD4 counts. Soluble forms of CD4 generated by genetic engineering or solid phase peptide synthesis can completely block HIV infectivity and syncitia in vitro without significant apparent effects on T-cell immunity. Such molecules are currently being investigated for their therapeutic potentials.

HIV infection gradually but surely causes a decline in the number of CD4 cells if unchecked. Initially, the CD4 counts were used to determine when to commence HAART in infected patients. However more recently treatment is commenced once the patient is determined to be positive for HIV. This is thought to protect the immune system and keep away opportunistic infections and subsequently prolong the life of the patient. This also serves as a form of transmission prevention and reduction. The lower the HIV load in an individual the less likelihood of transmission to another.

HIV infection negatively affects the response of the white cells to infection. NK cells have a vital role to play in HIV infection(15). Studies have revealed that there is a reduction in the production of interferon-γ by NK cells. This is thought to be due to an expansion of an unresponsive subset of NK cells. So,reduced numbers and the impaired function of CD4 and CD8 T-cells which also produce IFN-γ could play a role in this impaired response. The average neutrophil count was found to be reduced

in a significant number of HIV-infected patients. The reasons for this are not fully understood but are however thought to be multifactorial. The lower the CD4 count the lower the mean neutrophil count, similar to what occurs in patients with low platelet counts. This could further predispose the HIV-infected patients to opportunistic infections.

In addition, studies have found the significant occurrence of earlier forms of neutrophils in the peripheral blood of patients with HIV infections especially the metamyelocytes and stab forms. Neutrophils are the most common type of white cells. They make up an important part of the innate immune system. The neutrophils are a type of phagocyte and during the acute phase of inflammation are one of the early responders of inflammatory cells to move towards regions of inflammation. This could be as a result of malignancies, bacterial infections, and environmental exposure. They travel through blood vessels, interstitial tissue being facilitated by signals such as IL-8, fMLP, leukotriene B4 and H_2O_2.

The absolute neutrophil count (ANC) is utilized in prognosis and diagnosis. Any value <1,500cells/mm^3 is called neutropenia and this is referred to as severe if the value falls below 500. It should be emphasized that neutrophils play a vital role in the front-line defence against invading pathogens. They attack micro-organisms by phagocytosis, degranulation, and the generation of neutrophil extracellular traps (NETs).

This would explain to a significant degree the suppressed immunity these HIV-patients suffer from making them prone to recurrent and opportunistic infections. The total reduction in white cell counts occurs in HIV infection (leucopenia). Lymphopenia is also a frequent feature in infected patients. These are usually related to the occurrence of lower CD4 counts.The CD4 cells have been the best prognostic factor in HIV patients. Though the low number of infected cells contrasts with the importance of lymphopenia. Mechanisms which might explain this depletion include antibody dependent cytotoxicity. 20% to 50% of antibodies produced in vitro by B lymphocytes are directed against HIV antigens, especially the gp120 and gp41 viral envelope antigens.

If this occurs in vivo it would to an extent explain the lymphopenia in these patients. Also, the programmed cell death of the CD4 lymphocytes appears to be over active in these groups of patients probably because the gp120 viral antigen perturbs the CD4-dependent signal for cell death. TNF may also play a role in early cell death infected contaminated cells.

It has also been shown that the erythrocyte sedimentation rate (ESR) increased with reducing CD4+ cell counts. However, ESR has been discarded as a useful tool in HIV. Studies have found extremely high values in patients with no symptoms and normal CD4 counts making any rational use of the parameter difficult. However, researchers Ndakotsu et al. found ESR values to be of use in monitoring HIV. It may be said that within the context of developing countries ESR may actually find a useful place in the management of the disease condition though a good deal of caution may need to be associated with its interpretation.

Bone Marrow Manifestations

Changes that occur in the bone marrow in HIV disease include hypercellularity, hypocellularity, trilineage dysplasia, myelofibrosis, serous fat atrophy, plasmacytosis, eosinophilia, lymphoid hyperplasia and granuloma formation. Invasion by a number of microorganisms and neoplasms is also known to occur including Burkitt's –like lymphoma, large cell lymphoma and Hodgkin's lymphoma. They all occur with varying degrees of frequency.

In one study the most common finding was hypercellularity, one or more of the three major lineages being affected by hyperplasia, myelodysplasia and reticulothelial iron blockade. Plasmacytosis, fibrosis and lymphocytic aggregates were frequently but less often encountered. This essentially comprises the “AIDS pattern” of bone marrow changes occurring in the setting of HIV infection described by Geller and colleagues.

Despite hypercellularity being so common, this some what contrasts with the peripheral cytopenias encountered especially in the late-stage disease. Hypercellularity is frequently encountered with the opportunistic infection and HAART.

Derangement of the myeloid erythroid ratio has followed several reports. Hypercellularity of the megakaryocytes has been reported by a number of researchers.

As already mentioned, myelodysplasia is also the main feature of this organ when infected with HIV.

One study identified erythrocytic, megakaryocytic and granulocytic dysplasia in decreasing order of frequency. Mechanisms responsible for

this dysplasia include drug toxicity, the effect of opportunistic infections and as a direct effect of HIV infection itself.

In vitro evidence of the defective growth of haematopoietic progenitor cells from infected patients has been reported. Both cell-mediated and humoral inhibition of in vitro haematopoiesis have been described. An imbalance in the CD4-CD8 lymphocyte ratio has been shown to inhibit in vitro haematopoietic progenitor colony formation in these patients, especially a reduction in CD4 cells in cultured material.

Anaemia and leukopenia have been significantly linked to the degree of myelodysplasia. While thrombocytopenia was found to correlate significantly with only megakaryocytic hypoplasia. Though it should be emphasized that the immune-mediated and antiplatelet antibody-mediated destruction of platelets has been shown to be a major cause of thrombocytopenia in HIV infected patients. Inhibition of thrombopoiesis also contributes to this finding.

Anaemia linked with chronic infections, inflammatory and neoplastic disease which is caused by reticuloendothelial iron blockade also appears to be a major cause of anaemia present with HIV infection. An increase in bone marrow iron stores has been reported in 14-55% of HIV-infected patients.

Iron deficiency is also occasionally encountered in these patients.

It has been found that HIV patients suffering from severe malnutrition and weight loss tend to have gelatinous transformation or serous fat atrophy occurring in the bone marrow.

Bone marrow lymphocytic aggregates have been reported widely in these infected patients. Some have noted a resemblance of these aggregates to certain types of non-Hodgkin's lymphoma (NHL).

Opportunistic infections are a well-known phenomenon associated with HIV/AIDs. They could occur in the bone marrow resulting in morphological changes. These micro-organisms include atypical mycobacteria, Cryptococcus, Histoplasma and Pneumocystis.They are all usually accompanied by granuloma formation.

When the lesions are recognized the organisms can readily be demonstrated by special staining techniques.

Infection with HIV appears to run concurrently with an increased frequency of neoplasms many of which may occur in the bone marrow e.g., intermediate to high-grade B-cell lymphomas. Also, Kaposi's sarcoma could occur but with less frequency. HIV-related NHL shows a high incidence of extranodal disease which is frequently found to involve the bone marrow. Also, clinically aggressive Hodgkin's disease often occurs in the advanced disease and has marrow involvement.

Disorders of Coagulation

It has been determined that HIV infection generates coagulation (16) disorders with a state of hypercoagulation sometimes predominating. The chronic inflammation influences thrombotic events by up-regulating procoagulants, reducing the effects of anticoagulants and minimizing fibrinolysis. Nonspecific activation by the viral replication of coagulation through cellular injury and apoptosis leads to tissue factor activation and ultimately leads to the altered production of hepatic coagulation factors.

The production of cytokines can also enable endothelial factors to release tissue factor (TF), reduce endogenous anti-coagulant signals and promote leukocyte infiltration.

On the flip side thrombin can feedback and cause the stimulation of innate immune responses through protease-activated receptor (PAR-1) signalling, leading to inflammatory cytokine production and increased interferon mediated anti-viral responses. In addition, thrombin enhances the adaptive immune response by activating memory CD8+ T-cells in HIV patients, and drives the migration of these cells to areas of tissue injury(17).

No doubt there is a high level of immune activation in HIV infection. This immune dysfunction, increased levels of cytokines, and the activation of lymphocytes and monocytes are classical features of HIV infection. However most of these immunological abnormalities improve with HAART. Factors identified with increased inflammation in HIV infection include the following 1)The increased presence of other organisms such as CMV and other herpes viruses; 2) The mucosal epithelium of the GUT being destroyed by HIV which leads to a persistent movement of bacterial products; 3) Vital regulatory cells such as Th17 and T regulatory cells being continuously lost;4) Insulin resistance; and 5) Persistent HIV replication even during active HAART. These factors combined potentially contribute to cardiovascular disease (CVD) and the risk of other non-AIDs diseases (18).

Tissue factor (TF) is essential for the primary initiation and persistence of thrombosis. It is located on cell surfaces e.g., of monocytes which have been activated, as soluble cell-free TF in plasma and as cell-derived microparticles.

D-dimer levels are increased in HIV infection and this correlates with TF expression and with soluble CD14 (sCD14), a monocyte inflammation marker and co-receptor for bacterial lipopolysaccharide (LPS).

All these factors including the increased expression of TF lead to elevated hypercoagulation states and the subsequent effects of predisposing to thrombotic events and CVD (19). Apart from increased TF expression, and the increases in some procoagulants such as factor VIII and von Willebrand factor due to inflammation, there is a decline in all major anticoagulants (antithrombin, protein C, and protein S) and procoagulants dependent on liver function (e.g., fibrinogen, prothrombin and factor VII). The overall effect of HIV infection has been to increase the chances of coagulation occurring at the expense of maintaining a balance between anticoagulation and procoagulation, keeping the blood in a desirable free-flowing state.

Treatment with HAART has been shown to reverse this effect. It is important to mention that in the early stage of disease a procoagulant state predisposes, produced by the hepatic system which as the disease progresses to late-stage/end stage organ failure is followed by a complete lack of coagulation factors which results in haemorrhage. Platelets when activated at sites of injury or infection, interact with monocytes, lymphocytes and endothelial cells providing an additional link between HIV-mediated inflammation and increased coagulation (20).

In HIV-positive persons platelets show higher activation, chemokine release and reactivity to epinephrine. Even following treatment with HAART, platelet microparticles remain elevated, increase TF expression in comparison with uninfected controls.

Anti-viral medication has been known to contribute to increasing tissue factor levels by platelet activation. Abacavir is most notable for this causing platelet hyperactivity thereby providing a risk for myocardial infarction (MI).

The coagulation system no doubt remains persistently high during long term HIV infection inspite of HAART administration. While the increase

in procoagulant potential maybe somewhat modest, epidemiological association with plasma D-Dimer levels suggests that increased coagulation could lead to increased risk across a broad range of non-AIDS defining clinical diseases that manifest over years. More research is clearly required that should place emphasis on understanding the similarities and differences in altered coagulation during treated HIV disease compared to other disease states taking into consideration the clinical consequences and possible prevention modalities.

Treatment options under review include the use of aspirin, statins and angiotensin receptor blockers. Others are Rosuvastatin which reduces the expression of tissue factor. Rivaroxaban which is a factor Xa inhibitor is also being considered as a treatment option.

References

1) Johannessen A, Naman E, Gundersen SG, Bruun JN. Antiretroviral treatment reverses HIV-associated anemia in rural Tanzania. *BMC Infect Dis*. 2011, 11: 190-10.1186/1471-2334-11-190.
2) Jaganath D, Walker AS, Ssali F, Musiime V, Kiweewa F, Kityo C, Salata R, Mugyenyi P. DART Trial, ARROW Trial: HIV-associated anemia after 96 weeks on therapy: determinants across age ranges in Uganda and Zimbabwe. *AIDS Res Hum Retroviruses*. 2014, 30: 523-530. 10.1089/aid.2013.0255.
3) M Egger et al. Prognostic importance of anaemia in HIV type-I infected patients starting antiretroviral therapy:collaborative analysis of prospective cohort studies. *Antiretroviral therapy*. 2008. 13:959-967.
4) Stella CC, Ganser A, Hoelzer D. Defective in vitro growth of the hemopoietic progenitor cells in the acquired immunodeficiency syndrome. *J. Clin Invest*1978. 80:286-293.
5) Fischl M,Gelpin JE, Levine JD, et al. Recombinant human erythropoietin for patients with AIDS treated with Zidovudine. *N Engl. J Med*. 1990.322:1488-1493.
6) PantelisOustamanolakis, Ioannis E, Ippokratis Messaritakis, Maria Ninirakis, Elias A,Kouroumalis. Soluble transferrin receptor ferritin index in the evaluation of anaemia in inflammatory bowel disease: a case study. *Ann Gastroenterol*. 2011.24(2):108-114.
7) Erhabor O, Ejele OA, Nwauche CA, Buseri FI.Some haematological parameters in human immunodeficiency virus (HIV) infected Africans: the Nigerian perspective. *Niger J. Med*. 2005.14(1):33-8.

8) Ibeh BO, Omodamiro OD, Ibeh U, Habu JB.Biochemical and haematological changes in HIV subjects receiving winniecure antiretroviral drug in Nigeria. *J Biomed Sci.*2013.7(20):73.
9) Bade NA, Giffi VS, Baer MR, Zimrin AB, Law JY. Thrombotic microangiopathy in the setting of human immunodeficiency virus infection: high incidence of severe thrombocytopenia. *J clinApher* 2018.
10) Franchini M, Krampera M, Vaneri D.Helicobacter pylori eradication in adults with idiopathic thrombocytopenic puroura. *Am J. med*. 1; 2003. 114(5):420-1.
11) Hyoung Soo choi, Mi Hong Ji, Sung Jin Kim,Hyo seopAhn..Platelet count recovery after intravenous immunoglobulin predicts a favourable outcome in children with immune thrombocytopenia. *Blood res.*2016. 51(2):95-101.
12) Augustine O Ebonyi, Stephen Oguche, Martha O Ochoga, Oche O Agbaji, Joseph A Arejo-Okopi, Isaac O Abah et al.Changes in the haematological parameters of HIV-I infected children at 6 months and 12 months of antiretroviral therapy in a large clinic cohort, North central Nigeria. *J Virus Erad.*2017. 3(4):208-211.
13) Denue BA, Gashau W, Bello HS, Kida IM,Bakki B, Ajayi B. Relation between some haematological abnormalities, degree of immunosuppression and viral load in treatment-naive HIV-infected patients. *East Mediterr health J*. 2013.19(4):362-8.
14) Wu X, Liu Z, Ding X, Yu D, Wei H,Qin B.Mechanism of HIV-I resistance to an electronically constrained α-helical peptide membrane fusion inhibitor. *J. Virol*2018.14;92(7).
15) Eileen Scully, Galit Alter.NK cells in HIV disease. *HIV/AIDS Rep2016.* 13:85-94.
16) Abdullah A, Hilmi IA, Planinsic R. Diagnostic dilemma of coagulation problems in an HIV-positive patient with end-stage liver disease undergoing liver transplantation. *World J transplant* 2015.24;5(1):34-7.
17) Nasi A, Chiodi F.Mechanisms regulating expansion of CD8+ cells during HIV-I infection. *J Intern Med*.2018.283(3):257-267.
18) Jiang Y, Chai L, Fasae MB,Bai Y..The role of HIV Tat protein in HIV-related cardiovascular diseases. J. *TranslMed*.2018. 8;16(1):121.
19) De Lorenzo F, Collot-Teiveira S, Boffito M, Feher M, Gizzard B, McGregor JL. Metabolic-inflammatory changes and accelerated atherosclerosis in HIV patients: rationale for preventive measures. *Curr Med. Chem* 2008.15(28):2991-9.

20) Mancuso ME, Santagostino E..Platelets:much more than bricks in a breached wall. *Br J Haematol.*2017.178(2):209-219.

NEURO-COGNITIVE ANOMALIES ASSOCIATED WITH HIV/AIDS

DAMILARE ADEDAYO ADEKOMI, PHD
AND AHMAD ADEKILEKUN TIJANI,
MBBS, M.SC, PHD

Given the high epidemiology of HIV across the globe, impaired cognitive functions in the affected individual are on the increase. In this chapter, we highlight relevant information on some of the neurocognitive deficits associated with HIV/AIDS as well as some of the factors responsible for the deficits.

Human immunodeficiency virus (HIV) is a form of virus with an affinity for the nervous system. The virus enters and affects the functional integrity of the brain resulting in the neurotoxic inflammatory responses from the cellular components in the cytoarchitecture of the central nervous system. HIV alters normal behavioural, cognitive, and motor functions in infected individuals. These anomalies range in intensity from mild to severe.

The global epidemiological occurrence of human immunodeficiency virus (HIV) associated with neurocognitive impairment increases with clinical signs and symptoms characterized by neuroanatomical, neurophysiological, neurological and neuropsychological anomalies in long-term treated infected patients. Neurocognitive alteration in HIV confounds the positive outcome of the assessment, diagnosis, and treatment, thereby resulting in increased incidences, morbidity, and complexity of opportunistic and systemic diseases in HIV-infected patients.

The present "up-to-date" statistical appraisal shows that there are over 30 million individuals infected with HIV throughout the whole world and of this prevalence, about two-thirds of these infected individuals reside in sub-Saharan Africa (1). Nigeria ranks second in the total number of people living with HIV (2, 1). Much before the discovery, formulation, and introduction of highly active antiretroviral therapies, about 70% of HIV-

infected individuals displayed neurological complications associated with opportunistic infections/processes (3, 1). Antinori et al. (2007) (4) suggested that HIV dementia is one of the most commonly deleterious complications observed in the affected population. Studies have also shown that the prevalence rate of HIV-associated cognitive impairment in Western and sub-Saharan Africa is about 3% to 65% (5-14, 1). In Nigeria, the comparatively recent introduction of antiretroviral drug therapies and the use of these drugs have been on the increase (16, 17). In countries where these medications are widely available, regression in the relative frequency of occurrence of HIV dementia has been recorded (18). However, the occurrence has been discovered to remain on the increase and to primarily affect infected individuals with the earlier stage of the disease (19, 18).

The global incidences of cognitive impairment progress with increasing systemic disease, and neuropsychological decline is uncommon during the asymptomatic phase of HIV infection (20). More importantly, the subtle but detectable model of cognitive deviation occurs prior to the manifestation of acquired immune deficiency syndrome (AIDS), and subtle alterations in neuropsychological processes in an HIV-infected individual without cognitive impairment present a higher risk of subsequent AIDS and death (21).

HIV continues to be a leading health challenge in the developed and developing world. In the early years of the HIV global pandemic, the cognitive and practical effects of HIV were devastating and overwhelming for infected individuals and their respective families (22). About half of the people living with HIV have some form of the HIV-associated neurocognitive disorder.

Neurocognitive Deficits Associated with HIV

HIV-associated encephalopathy and dementia were among the familiar and frequent medical diagnoses in patients with AIDS at the time of death (23, 22). The epidemiological proportion of HIV-infected people who are between 45 and 50 years of age is approaching about 50% in the developed nations of the world and this is due in large part to the introduction of the effectiveness of the highly active antiretroviral therapies (24); however, HIV-associated neurocognitive disorders remain prevalent (25). HIV-infected adults over 55 years of age comprise the fastest-growing age group in the HIV-positive population (26, 22), and

advanced age at the time of seroconversion increases the risk for neurocognitive dysfunction (27, 22).

Before the availability and accessibility of antiretroviral drugs, neurocognitive dysfunction in the form of dementia is evident in about 30% of the HIV-infected individuals (28). According to the American Academy of Neurology (AAN), there are three classifications of the neurocognitive disorder associated with HIV, these include:

1. Asymptomatic neurocognitive impairment (ANI);
2. Mild neurocognitive disorder (MND); and
3. HIV-associated dementia (HAD).

Asymptomatic Neurocognitive Impairment

This is the most frequently encountered and prevalent (about 40-60%) form of HIV-associated neurocognitive disorders (HAND) (29). ANI is characterized by a mild decrease in cognitive processes and loss of attention and concentration, and from the statistical point of view, it was quantified to be lower than a standard deviation of one, with a mean of demographically modified normative grades in daily physical activities. This significant decline is very difficult to analyze but best evaluated using neurocognitive assessment tools (30). The evaluation of ANI in HIV-infected individuals is often done via specialized neurocognitive examination and may not be apparently clinical. This form of cognitive impairment is characterized by alteration on neurocognitive examination with no evident accompanying modification in daily functioning, it does not include delirium and dementia, and there is no indication of the preexisting aetiology of ANI (25). In ANI, the psychological tests of neurocognitive functions which include fine motor movements, memory, and higher executive functions can detect substandard performances in one or more areas that are too difficult to be noticed by the HIV-infected individual or their families and or relatives. Early assessment and diagnosis help in the timely identification of patients at further risk of a later and more marked functional decline in cognitive processes (29).

ANI impairs health outcomes, occupational, and psychosocial functioning, and quality of life (31, 32, 22). Swift and rapid clinical treatment at the early onset of ANI proved to be most beneficial in achieving abatement or most importantly, a marked delay in the advancement of the deleterious disease.

Mild neurocognitive disorder (MND)

This is associated with mild functional impairment and cognitive difficulties. The neuropsychological examination for MND assesses the following skills in the infected individuals: attention, accuracy of information processing, verbal (language) fluency, learning and memory, psychomotor skills, sensory perceptions, and working memory. This form of cognitive impairment produces mild alteration and interference in daily functions, including at least one of the following: diminished mental intelligence, impaired efficiency in household management, and also diminished social functions. It does not include delirium and dementia, and also, there is no evidence of any form of pre-existing aetiology for MND (33, 34).

HIV-associated dementia (HAD)

HIV-associated dementia (HAD) is a clinical diagnosis associated with cognitive impairment in HIV-infected patients. Its resultant outcome is neuronal cell death (35). Patients with HAD are at risk of developing delirium and this makes it very hard to diagnose as the patients present distinct mental states to different clinicians depending on when the infected individuals are examined. HAD affects approximately two-thirds of AIDS patients (36) and also contributes to severe cognitive impairment and dementia in individuals below 60 years of age (37). HAD is usually observed in seropositive individuals who have CD4 cells at an all-time level below 200/mm^3 (35). During the early clinical stages of HAD, the principal complaints are:

i. slow psychomotor activities;
ii. impairment of short-term memory;
iii. low mood.

The symptoms associated with HAD appear to be mild and/or moderate at the earliest stage of the anomaly, but include some alteration of the normal daily routines of properly managing financial requirements, following and identifying directions, reading, learning, and memory. Many of these clinical and psychological symptoms are frequently indistinguishable from other types of dementia, misinterpreted as inactive or overlooked because the signs are below clinical perceptions, but as the symptoms become more clinically intense, they progress to involve multiple topographies and associated areas of the brain that regulate long-term memory, name and

facial recognition, language expression and comprehension, and organization and management (35).

Like many of the neuropsychiatric complications associated with HIV and AIDS, HAD shares symptoms common to depression, anxiety, and psychotic disorders that may be mistaken for other brain diseases. Major depression symptoms of low mood, loss of pleasure and enjoyment, alteration in sleep pattern, and loss of weight gain are prevalent in HAD (35). A smaller group of affected patients experiences psychotic delusions, higher visual or auditory hallucinations, or mania-type symptoms. With these series of clinical and psychological symptoms, HAD appears to rapidly evolve into the AIDS dementia complex and finally ends in death about two years after medical diagnosis (38).

Within the central nervous system, HIV can promote modifications in the activities of the enzymes of carbohydrate metabolism and of the enzymes of glucose metabolism. After the entrance of the virus into the host genome, it causes the release of deleterious biomolecules such as cytokines, eicosanoids, quinolinic acid, and superoxide anions, and can activate the *N*-Methyl-D-aspartate (NMDA) receptors, which often trigger neuronal toxicity, resulting ultimately in cognitive shortfalls. Activation of glial cells plays an important role in neuron alteration and neurocognitive deficits associated with HIV infection (39, 40). Glial cell activation signifies an inflammatory process which often precedes neuronal loss. Cognitive deficits associated with this are found primarily in the white matter of the frontal cortex and basal ganglia (41-44, 31).

Biomolecules associated with HIV such as HIV proteins, and HIV *Tat*-protein, exhibit neurotoxic potentials. These biomolecules disrupt the functional integrity of neurons and glia cells in the CNS and also contribute to neurodegeneration and neuron cell death, which in turn leads to disruption in the physiology and morphology of synapses in the infected regions of the brain. The ability of HIV to interfere with neural stem cells also modifies the physical and molecular processes involved in neurogenesis and neuronal regeneration within the CNS (45).

Neurocognitive shortfalls in HIV-associated neurocognitive deficits are a worldwide anomaly that affects phenomena such as the rate of information processing, executive functions in higher centres of the brain, psychomotor abilities, attention and episodic memories, sleeping patterns, mental acuity, cardiovascular processes, and language perception.

Neuropathological Deviations Associated with Cognitive Impairment in HIV

After an individual is infected with HIV, the virus enters the brain, and the brain continues to be a continuous pool of supply for the virus even in individuals receiving combination antiretroviral therapy (cART) (46). The absence of circulating HIV–RNA in the blood and cerebrospinal fluid does not signify that infected individuals are free of the virus, its adverse effects on immunity, or at risk for the HIV-associated neurocognitive disorder (47). The continuous and increasing reduction of the neuronal population occurs in patients with chronic HIV regardless of the successful pharmaco-intervention by cART (48), signifying that HIV is capable of causing the neurodegenerative alteration or that both are occurring in the brain of infected individuals.

Phosphorylated tau

Neurofibrillary tangles made up of hyperphosphorylated tau (pTau) are another significant characteristic feature of Alzheimer's disease (AD) observed in people with HIV. Unlike amyloid plaques, pTau occurs in the majority of older adults (22). However, at earlier ages, elevated pTau is seen in the brain of an individual infected with HIV rather than in healthy controls (49). Although pTau levels appear to be unconnected to HIV viral load levels in the brain (50), pTau is connected with the activation of microglial cells.

Tau phosphorylation in HIV arises from the activities of pro-inflammatory cytokines and viral proteins that modify amyloidosis, which precede the formation of tau tangles (33). Higher levels of the tau tangles are also dependent on the cART treatment (49). In the context of HIV, pTau is present in the entorhinal cortex and hippocampus and the surrounding areas (49), which mimics a similar activity observed in a normal aging process as well as AD (51). Some of the studied neurodegenerative alterations associated with cognitive deficits in incidences of HIV include:

Accumulation of Beta-amyloid

Accumulation of beta-amyloid (Aβ) is a pathological characteristic of Alzheimer's disease **(**AD) that has also been found to exist in HIV (52, 53), though Aβ anomalies are more consistent in AD than in HIV, most especially among younger individuals infected with HIV. A common risk

factor for Aβ deposition in HIV is increasing age (22), but evidence from a recent study suggests that HIV and aging independently affect Aβ deposition (54). In HIV, amyloid plaques tend to be diffuse, and plaque depositions occur in neuronal bodies and along axonal paths (52, 53, 55). In AD, neuritic plaques occur in extracellular space (56), but neuropathology studies suggest that, in HIV, Aβ accumulates and is preferentially diffuse in the basal ganglia, frontal lobe, and hippocampus (57). Evidence has shown that long-term use of cART enhances Aβ accumulation (52).

Altered Blood–brain barrier

The permeability of the blood–brain barrier (BBB) is modified in HIV, allowing the discharge and outflow of noxious substances, including infected macrophages from the blood into the brain parenchyma. HIV affects neuronal endocytosis, which on the other hand modifies the functional integrity of the microvascular endothelial cells that make up the BBB (58). HIV disrupts the integrity of tight junctions and the upregulation of adhesion molecules and therefore enhances the virus to pass through the BBB (59). The dysfunction of the BBB in incidences of HIV has been associated with the accumulation of Aβ (60).

References

1. Royal W, Cherner M, Carr J, et al. (2012): Clinical Features and Virological Correlates of Neurocognitive Impairment among HIV-infected Individuals in Nigeria. *J Neurovirol.* 18(3): 191–199.
2. National Agency for the Control of Aids. United Nations General Assembly Special Session (UNGASS) Country Progress Report: Nigeria. 2010.
3. Berger JR, Moskowitz L, Fischl M, et al. (1987): Neurologic disease as the presenting manifestation of acquired immunodeficiency syndrome. *South. Med J.* 80: 683–686.
4. Antinori A, Arendt G, Becker JT, et al. (2007): Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 69(18): 1789–99.
5. Belec PL, Testa J, Vohito MD, et al. (1989): Neurologic and psychiatric manifestations of AIDS in Central African Republic. *Bull. Soc. Pathol. Exot. Filiales*. 82: 297–307.

6. Hall KS, Gao S, Emsley CL, et al. (2000): Community screening interview for dementia (CSI 'D'); performance in five disparate study sites. *Int. J. Geriatr. Psychiatry* 15: 521–531.
7. Howlett WP, Nkya WM, Mmuni KA, et al. (1989): Neurological disorders in AIDS and HIV disease in the northern zone of Tanzania. *AIDS* 3: 289–296.
8. Kanmogne GD, Kuate CT, Cysique LA, et al. (2010): HIV-associated neurocognitive disorders in sub-Saharan Africa: a pilot study in Cameroon. *BMC. Neurol*. 10: 60.
9. Njamnshi AK, Bissek AC, Ongolo-Zogo P, et al. (2009): Risk factors for HIV-associated neurocognitive disorders (HAND) in sub-Saharan Africa: the case of Yaounde-Cameroon. *J. Neurol. Sci*. 285: 149–153.
10. Perriens JH, Mussa M, Luabeya MK, et al. (1992): Neurological complications of HIV-1-seropositive internal medicine inpatients in Kinshasa, Zaire. *J. Acquir. Immune. Defic. Syndr*. 5: 333–340.
11. Robertson K, Kopnisky K, Mielke J, et al. (2005): Assessment of neuroAIDS in Africa. *J. Neurovirol.* 11(1): 7–16.
12. Sacktor N, Nakasujja N, Skolasky R, et al. (2006): Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. *Neurol.* 67: 311–314.
13. Sebit MB (1995): Neuropsychiatric HIV-1 infection study: in Kenya and Zaire cross-sectional phase I and II. *Cent. Afr. J. Med*. 41: 315–322.
14. Wong MH, Robertson K, Nakasujja N, et al. (2007): Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. *Neurology* 68: 350–355.
15. Abimiku AG (2009): Building laboratory infrastructure to support the scale-up of HIV/AIDS treatment, care, and prevention: in-country experience. *Am. J Clin. Pathol.* 131: 875–886.
16. Lum H, Isichei C, Isichei-Wakili M, et al. (2007): Expansion of HIV-1 screening and anti-retroviral treatment programs in a resource-poor setting: results from a faith-based organization in Jos, Plateau State, Nigeria. *Afr Health Sci.* 7: 93–100.
17. Sacktor N, Lyles RH, Skolasky R, et al. (2001): HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998. *Neurol.* 56: 257–260.
18. Heaton RK, Franklin DR, Ellis RJ, et al. (2011): HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J. Neurovirol*. 17: 3–16.

19. Sacktor N, McDermott MP, Marder K, et al. (2002): HIV-associated cognitive impairment before and after the advent of combination therapy. *J. Neurovirol*. 8: 136–142.
20. Selnes OA, Miller E, McArthur JC (1990): HIV-1 infection: No evidence of cognitive decline during the asymptomatic stages. *Neurology* 40: 204–208.
21. Mayeux R, Stern Y, Tang MX (1993): Mortality risks in gay men with human immunodeficiency virus infection and cognitive impairment. *Neurology* 43: 176–182.
22. Cohen RA, Seider TR and Navia B (2015): HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimer's Research and Therapy* 7: 37.
23. Navia BA, Jordan BD, Price RW (1986): The AIDS dementia complex: I. Clinical features. *Ann Neurol*. 19(6): 517–24.
24. Kalinowska S, Trześniowska-Drukała B, Samochowiec J (2013): HIV-associated neurocognitive disorders. *Psychiatria Polska* XLVII (3): 453–462.
25. Ellis RJ, Deutsch R, Heaton RK, et al. (1997): Neurocognitive impairment is an independent risk factor for death in HIV infection. San Diego HIV Neurobehavioral Research Center Group. *Arch Neurol*. 54: 416–424.
26. Hall HI, Song R, Rhodes P, et al. (2008): Estimation of HIV incidence in the United States. *JAMA*. 300: 520–9.
27. Bhaskaran K, Mussini C, Antinori A, et al. (2008): Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol*. 63: 213–21.
28. Dorrell L, Snow MH, Ong EL (1995): Mortality and survival trends in patients with AIDS in north east England from 1984–1992. *J Infect.* 30: 23–7.
29. Heaton RK, Clifford DB, Franklin Jr DR, et al. (2010): HIV associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 75: 2087–96.
30. Vally Z (2011): HIV-associated neurocognitive disorders. *South Afr. J. Psych*. 17(4): 98–102.
31. Sacktor N, Van Heertum RL, Dooneief G, et al. (1995): A comparison of cerebral SPECT abnormalities in HIV-positive homosexual men with and without cognitive impairment. *Arch Neurol*. 52: 1170–1173.
32. Heaton RK, Marcotte TD, Mindt MR, et al. (2004): The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc*. 10: 317–31.

33. Becker JT, Lopez OL, Dew MA, et al. (2009): Prevalence of cognitive disorders differs as a function of age in HIV virus infection. *AIDS* 18: S11–8.
34. Scott JC, Woods SP, Vigil O, et al. (2011) A neuropsychological investigation of multitasking in HIV infection: implications for everyday functioning. *Neuropsychology* 25: 511–519.
35. Watkins CC and Treisman GJ (2015): Cognitive impairment in patients with AIDS – prevalence and severity. *HIV/AIDS – Research and Palliative Care* 7: 35–47.
36. Navia BA and Price RW (1987): The acquired immunodeficiency syndrome dementia complex as the presenting or sole manifestation of human immunodeficiency virus infection. *Arch Neurol*. 44(1): 65–69.
37. McArthur JC, Hoover DR, Bacellar H (1993): Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology* 43(11): 2245–52.
38. Dore GJ, Correll PK, Li Y, et al. (1999): Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS* 13(10): 1249–1253.
39. Budka H (1991): Neuropathology of human immunodeficiency virus infection. *Brain Pathol*. 1: 163–175.
40. Bell JE (2004): An update on the neuropathology of HIV in the HAART era. *Histopathol*. 45: 549–559.
41. Chang L, Ernst T, Leonido-Yee M, et al. (1999): Cerebral metabolite abnormalities correlate with clinical severity of HIV-1 cognitive motor complex. *Neurol.* 52: 100–108.
42. Tate DF (2009): Neuroimaging among HIV-infected patients: current knowledge and future directions. In: *HIV and the brain*. Edited by Paul RH: 75–107.
43. Brew BJ (2007): AIDS dementia complex. In: *Handbook of clinical neurology*. Edited by Portegies P: 79–91.
44. Mohamed MA, Lentz MR, Lee V, et al. (2010): Factor analysis of proton MR spectroscopic imaging data in HIV infection: metabolite-derived factors help identify infection and dementia. *Radiol*. 254: 577–586.
45. Balinang JM, Masvekar RR, Hauser KF, et al. (2017): Productive infection of human neural progenitor cells by R5 tropic HIV-1: opiate co-exposure heightens infectivity and functional vulnerability. *AIDS* 31(6): 753–764.
46. Masliah E, DeTeresa RM, et al. (2000): Changes in pathological findings at autopsy in AIDS cases for the last 15 years. *AIDS* 14: 69–74.

47. Cysique LA, Brew BJ, Halman M, et al. (2005): Undetectable cerebrospinal fluid HIV RNA and beta-2 microglobulin do not indicate inactive AIDS dementia complex in highly active antiretroviral therapy-treated patients. *J Acquir Immune Defic Syndr*. 39: 426–9.
48. Gongvatana A, Harezlak J, Buchthal S, et al. (2013): Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy. *J Neurovirol*. 19: 209–18.
49. Anthony IC, Ramage SN, Carnie FW, et al. (2006): Accelerated Tau deposition in the brains of individuals infected with human immunodeficiency virus-1 before and after the advent of highly active antiretroviral therapy. *Acta Neuropathol*. 111: 529–38.
50. Smith DB, Simmonds P, Bell JE (2014): Brain viral burden, neuroinflammation and neurodegeneration in HAART-treated HIV positive injecting drug users. *J Neurovirol*. 20: 28–38.
51. Price JL, Davis PB, Morris JC, et al. (1991): The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiol Aging*. 12: 295–312.
52. Green DA, Masliah E, Vinters HV, et al. (2005): Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS* 19: 407–11.
53. Brew BJ, Crowe SM, Landay A, et al. (2009): Neurodegeneration and ageing in the HAART era. *J Neuroimmune Pharmacol*. 4: 163–74.
54. Ortega M and Ances BM (2014): Role of HIV in amyloid metabolism. *J Neuroimmune Pharmacol*. 9: 483–91.
55. Everall I, Vaida F, Khanlou N, et al. (2009): Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. *J Neurovirol*. 15: 360–70.
56. Braak H, Alafuzoff I, Arzberger T, et al. (2006): Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 112: 389–404.
57. Nebuloni M, Pellegrinelli A, Ferri A, et al. (2001): Beta amyloid precursor protein and patterns of HIV p24 immunohistochemistry in different brain areas of AIDS patients. *AIDS* 15: 571–5.
58. Banks WA, Ercal N, Price TO (2006): The blood–brain barrier in neuroAIDS. *Curr HIV Res*. 4: 259–66.
59. Anderson E, Zink W, Xiong H, et al. (2002): HIV-1-associated dementia: a metabolic encephalopathy perpetrated by virus-infected and immunecompetent mononuclear phagocytes. *J Acquir Immune Defic Syndr*. 31: S43–54.

60. Andreas IE, and Toborek M (2013): Amyloid beta accumulation in HIV-1-infected brain: the role of the blood–brain barrier. *IUBMB Life* 65: 43–9.

COMPLICATIONS OF HIV INFECTION

EMMANUEL O FARINLOYE
MD, FWACS

The complications from human immunodeficiency virus (HIV) infection are multi-systemic in nature, the occurrences of which may be the reason for seeking medical help and eventual diagnosis of the condition. Over a fifth of HIV- infected people are undiagnosed and could present for the first time with acquired immune deficiency syndrome-defining conditions (1). Many complications of HIV infection are due to its chronic manner, while others arise as a result of the effect of therapy. These complications are global and affect many organs or systems in the human body. The chapters that follow will discuss the details of these complications.

Gastrointestinal Tract (GIT)

The association between HIV infection and GIT complications is well studied. Candidal infection may affect the mouth making the swallowing act very painful. When the oesophagus is involved a sharp substernal pain may be experienced. Patients with low CD4 lymphocyte counts equal to or lower than 200/mm^3 may develop aphthous ulcers caused by Cytomegalovirus or Herpes simplex virus (2). It is important to exclude bacterial infection and confirm diagnosis with a biopsy.

Adults with HIV infection often experience bouts of diarrhoea. In a study, about 4 out of 10 such patients were reported to have had at least an episode of diarrhoea in the preceding 30 days (2). Gut motility is affected when HIV invades the autonomic nervous system causing HIV-induced enteropathy (3).

A bizarre complication in some HIV-infected patients is ileocecal fistula. The aetiological factor is Histoplasma capsulatum infection, which is identified with Internal Transcribed Spacer Primer Sets that reveals the fungal agent. Histoplasma capsulatum infection or Histoplasmosis is an opportunistic infection seen in immunocompromised individuals. Its

disseminated variant occurs in 95% of cases in HIV-infected patients (4). More common manifestations aside from bowel perforation include fever, abdominal pain, diarrhoea, and bleeding (5). The ileocecum and colon are mostly affected though the small bowel could also be involved.

Visceral involvement of Kaposi Sarcoma is common in AIDS patients but many times it is asymptomatic. At post-mortem, areas of involvement include the lungs, stomach, bowel, spleen, and liver (6). Rare cases of appendicitis and bowel obstruction have been reported as a result of Kaposi Sarcoma (7-9). Regression of Kaposi Sarcoma occurs following commencement of highly active antiretroviral therapy.

Hepatobiliary and related Complications

Cholecystitis, especially the acalculous type is not uncommon in HIV-infected individuals. Associated biliary stone formation however is not increased in incidence. Pancreatitis when it occurs is mainly due to antiretroviral drugs used in treating patients (10). Chronic liver disease of viral aetiology could be a co-morbid condition in HIV infection and this has made it mandatory to screen for viral hepatitis whenever HIV infection is diagnosed in any individual (11, 12).

With HIV infection, a person is more likely to develop hepatocellular carcinoma. This occurs because of a compromised immunity leading to failure to fight pre-cancerous conditions. At-risk populations should therefore be screened with an abdominal ultrasonography (13).

Cardiopulmonary Complications

HIV infection increases the risk of cardiovascular disease by causing the elevations of cytokine with associated chronic inflammation of the vascular endothelial bed (14). The vascular damage is then compounded by metabolic derangement and the use of antiretroviral drugs. Higher levels of myocardial infarction and atherosclerotic changes have been reported in HIV patients (15, 16). Myocarditis and pericarditis have been reported, though their occurrence is dwindling probably due to a combination of highly active antiretroviral therapy (17).

Pneumocystis *jiirovesi* is common in HIV infection. It may be the presenting condition in yet-to-be diagnosed HIV patients (18). Patients present with a non-productive cough, fever and dyspnoea on exertion. The

appearance of interstitial infiltrates on the lung fields gives out the diagnosis radiologically. Opportunistic microorganisms such as Legionella species may also cause atypical pneumococcal infections. The incidence of pulmonary cancer and pulmonary hypertension may be increased (19, 20). It is also known that emphysema may develop early in cigarette smokers with HIV leading to chronic obstructive airway disease (21).

Genitourinary Complications

Renal complications attributable to antiretroviral drugs occur. Hypertension and diabetes-related chronic kidney disease do occur in HIV-infected patients (22). The incidence of HIV nephropathy has remained the same in these patients (23). HIV-associated Nephropathy is a cause of renal failure mostly in people of African descent (24). The underlying pathology is that of sclerosing glomerulopathy with associated proteinuria. It often progresses to end-stage renal disease (25). Apart from hypertension and diabetes mellitus which are known causes of chronic kidney disease, co-infection with Hepatitis C is a contributory factor (26). It may have a prevalence of nearly 50% among HIV patients (27). These patients should therefore be screened for kidney disease at the time of diagnosis.

Neuropsychiatric Complications

In its advanced stage, HIV infection can affect the brain and the spinal cord when the vascular endothelial tissues in these places are destroyed and microorganisms such as Toxoplasma *gondii* and Cryptococcus *neoformans* are implicated in this process (28). Neurologic symptoms often reflect the locations of the causative infections and malignancies.

Patients with low CD4 lymphocyte counts may develop HIV-related neurocognitive disorders, which may be mild or severe (29-31). Dementia is an AIDS defining situation in HIV infection. In this condition, there may be 2 or more cognitive deficits that may include memory loss and abnormalities in neurological function, which may impair daily activities. The HIV Dementia scale is an instrument used in assessing the condition (32). The management of these patients is often difficult. Also, early onset Alzheimer's disease is becoming increasingly common even in well-managed cases of HIV infection (33).

Neuropathy is usually a neurological manifestation in HIV infection. This condition is usually made worse by antiretroviral therapy and other co-morbid conditions such as diabetes (34). Nearly half of HIV patients may develop chronic psychiatric disorders (35).

Musculoskeletal Complications

Patients with HIV infection are exposed to an increased risk of osteoporosis development (36). There may also be a higher incidence of pathological fractures (37). Patients are also susceptible to the development of osteomalacia. Osteonecrosis manifesting as joint stiffness may also occur especially at the groin.

Metabolic and Endocrine Complication

Many metabolic abnormalities, e.g., diabetes, are due to the usage of antiretroviral drugs which adversely affect the pancreas and other endocrine glands (38). Patients should therefore be screened initially for glucose and lipid disorders and at least annually subsequently (39). Irregular menses and premature ovarian failure may occur in women as a result of the affectation of the hypothalamo-pituitary-ovarian axis (40).

References

1. Centre for Disease Control and Prevention (CDC). HIV Prevalence estimates – United States, 2006. MMWR Morb Mortal Wkly Rep. 2008; 57(39): 1073–1076.
2. Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhoea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. *Am J Gastroenterol* 2000; 95(12) 3482–3489.
3. Zeitz M, Ullrich R, Schneider T, Kewening S, Hohloch K, Riecken EO. HIV/SIV enteropathy *Ann N Y Acad Sci*. 1998; 859: 139–148.
4. Wheat LJ, Batteigner BE, Sathapataya-vongs B. Histoplasma capsulatum infections of the CNS. A clinical review. *Medicine (Baltimore)* 1990; 69: 244–260.
5. Assi M, Mckinsey DS, Driks MR, O'Connor MC, Bonacini M, Graham B, Manian F. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: a report of 18 cases and literature review. *Diagn Microbiol Infect Dis*. 2006; 55: 195–201.

6. Henge UR, Ruzika T, Tying SK, et al. Update on Kaposi sarcoma and other HIV-associated diseases, part 1: epidemiology, environmental predispositions, clinical manifestations and therapy. *Lancet Infect Dis* 2002; 2(5): 281–292.
7. Zebrowska G, Walsh NM. Human immunodeficiency virus related Kaposi sarcoma of the appendix and acute appendicitis. Report of a case and review of literature. *Arch pathol Lab Med*. 1991; 115(11): 1157–1160.
8. Wang NC, Chang FY, Chou YY, et al. Intussuception as the initial manifestation of AIDS-associated primary Kaposi sarcoma: a case report. *J Formos Med Assoc*. 2002; 101(8): 585–587.
9. Coetzee T, Le Roux CG. Kaposi sarcoma presenting with intestinal obstruction. *S Afr Med J*. 1967; 41(17): 442–445.
10. Zar FA, El-Bayoumi E, Yungbluth MM. Histology proof of acalculous cholecystitis due to cyclospora cayetanensis. *Clin Infect Dis*. 2001; 33(12): E140–E141.
11. Palella FJ Jr, Baker RK, Moorman AC, et al. HIV Outpatient study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006; 43(1): 27–34.
12. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 49(5): 651–681.
13. Braun N, Fox RK, Xiao P, et al. North American Liver Cancer in HIV Study Group. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US–Canadian multicentre study. *J Hepatol*. 2007; 47(4): 527–537.
14. Ross AC, Rizk N, O'Riordan MA, et al. Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis*. 2009; 49(7): 1119–1127.
15. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007; 92(7): 2506–2512.
16. Kingsley LA, Cuervo-Rojas J, Muñoz A, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. *AIDS* 2008; 22(13): 1589–1599.

17. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV- positive patients with cardiac involvement. *J Infect*. 2000; 40(3): 282–284.
18. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000; 30 (suppl 1): S5–S14.
19. Kirk GD, Merlo C, O'Driscoll P, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis*. 2007; 45(1): 103–110.
20. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med*. 2008; 177(1): 108–113.
21. Diaz PT, King ER, Wewers MD, et al. HIV infection increases susceptibility to smoking-induced emphysema. *Chest*. 2000; 117 (5 suppl 1): 285S.
22. Fine DM, Perazella MA, Lucas GM, Atta MG. Renal disease in patients with HIV infection: epidemiology, pathogenesis and management. *Drugs* 2008; 68(7): 963–980.
23. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS.* 2004; 18(3):541–546.
24. Ross Michael J, Klotman Paul E. The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. *Nephrol Dial Transplant*. 2012 doi: 10.1093/ndt/GFR702. Recent Progress in Wearne N, Swanepoel C, Boulle A, et al. [PubMed] [Cross Ref].
25. Winston JA, Bruggeman LA, Ross MD, Jacobson J, Ross L, D'Agati VD, Klotman PE, Klotman ME. Nephropathy and establishment of a renal reservoir of HIV type 1during primary infection. *N Engl J Med*. 2001; 344:1979–1984.
26. Wyatt CM, Malvestutto C, Coca SG, Klotman PE, Parikh CR. The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. *AIDS* 2008; 22(14): 1799–1807.
27. Naicker S, Rahmanian S, Kopp JB. HIV and chronic kidney disease. *Clin Nephrol*. 2015; 83 (7 supp 1): 32–8.
28. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the

National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009; 58 (RR-4): 1–207.
29. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. *Nat Rev Immunol*. 2005; 5(1): 69–81.
30. Bhaskaran K, Mussini C, Antinori A, et al.; CASCADE Collaboration. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol*. 2008; 63(2): 213–221.
31. Ellis R, Heaton R, Letendre S, et al. Higher CD4 nadir is associated with reduced rates of HIV-associated neurocognitive disorders in the CHARTER study: potential implications for early treatment initiation. Paper presented at the 17th Conference on Retroviruses and Opportunistic Infections; February 16–19, 2010; San Francisco, Calif.
32. Power C, Selnes OA, Grim JA, McArthur JC. HIV Dementia Scale: a rapid screening test. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995; 8(3): 273–278.
33. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS* 2005; 19(4): 407–411.
34. Letendre SL, Ellis RJ, Everall I, Ances B, Bharti A, McCutchan JA. Neurologi complications of HIV disease and their treatment. *Top HIV Med*. 2009; 17(2): 46–56.
35. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus- infected adults in the United States. *Arch Gen Psychiatry* 2001; 58(8): 721–728.
36. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; 20(17): 2165–2174.
37. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)- infected versus non-HIV-infected patients in a large US healthcare system. *J Clin Endocrinol Metab*. 2008; 93(9): 3499–3504.
38. Sweet DE. Metabolic complications of antiretroviral therapy. *Top HIV Med*. 2005; 13(2): 70–74.
39. Carolyn Chu, Peter A Selwyn. Complications of HIV Infection: A Systems-based Approach. *Am Fam Physician.* 2011 Feb 15; 83(4): 395–406.
40. Clark RA, Mulligan K, Stamenovic E, et al. Frequency of anovulation and early menopause among women enrolled in selected adult AIDS clinical trials group studies. *J Infect Dis*. 2001; 184(10): 1325–1327.

HIV/AIDS AND THE EYE

MICHAELINE A ISAWUMI
MBBCh, FMCOph, FWACS, MSc- CEH, FICS
AND MUSTAPHA B HASSAN
MBBS, FMCOph, FWACS, FICS

The eye is the organ of sight and one of the most sensitive special organs normally referred to as the window of the body. AIDS, which represents a syndromic disorder of the human following a period of infection with HIV, is one of the common systemic diseases which first manifests in the eye. All parts of the eye are prone to various manifestations of HIV/AIDS including the orbit, eye adnexae, and anterior and posterior segments of the eye.

The effects of HIV/AIDS on the eye could be from the disease itself or as a result of toxicity from the drugs used in the treatment of the disease. Examples of these various manifestations which could serve as HIV markers sometimes include among others orbital cellulitis, Kaposi's sarcoma, Squamous cell conjunctivitis, Herpes Zoster Ophthalmicus and CMV retinopathy. These and more are the subject of this chapter.

Features of most systemic diseases e.g, Diabetes mellitus, Hypertension, leukaemia, etc incuding AIDS usually first manifest in the eye . Of all people living with HIV globally, 9% of them live in Nigeria (1). Although HIV prevalence among adults is remarkably small (3.2%) compared to other sub-Saharan African countries such as South Africa (19.1%) and Zambia (12.5%), the size of Nigeria's population means that there were 3.2 million people living with HIV in 2013 (2). Young adults aged 21 to 30 years were most affected with eye manifestation in a study carried out in Nigeria where 97.5% of the HIV patients had refractive errors, and 25% had reduced vision (3, 4).

How does HIV affect the eye?

HIV breaks down the body's immune system. This makes the eye and other parts of the body susceptible to infection. About 70% of those with advanced AIDS are known to experience eye disorders (5).

It must be noted that the way the disease manifests in the tropical environment may be quite different from that of developed economies. These differences are due to many factors among which are the available treatments for the virus, opportunistic infections and the pattern of their infections (6). Figure 1 shows the anterior and posterior segments of the eye (7).

Ocular features

All parts of the eye are prone to various manifestations of HIV/AIDS including the orbit, eye adnexae, and anterior and posterior segments of the eye. The effects of HIV/AIDS on the eye could be from the disease itself or as a result of toxicity from the drugs used in the treatment of the disease. The common presentations of HIV/AIDS on the eye are hereby enumerated as follows (8).

1. **Orbit**
   Orbital cellulitis which is inflammation of the orbital contents located behind the orbital septum usually occurring from contiguous sinus infections and B-cell lymphoma.
2. **Lids/Adnexae**
   These include the external eye structures like the lids, caruncle, punctum, lacrimal glands and the nasolacrimal duct channels. Blepharitis, Kaposi's sarcoma, multiple molluscum lesions and herpes zoster ophthalmicus (HZO) may occur.
3. **Anterior segment**
   The conjunctiva, cornea, anterior part of the lens and anterior parts of the uvea (iris and ciliary body) make up the anterior segment.
   a. Conjunctival Lesions may be from Kaposi's sarcoma, squamous cell carcinoma, and microangiopathy;
   b. Corneal Lesions such as keratitis due to microsporidia, herpes simplex, and HZO. Keratoconjunctivitis sicca otherwise known as dry eye can also occur;

c. Uveal lesions like anterior uveitis which can result from HZO or secondary to systemic drug toxicity from rifabutin and cidofovir.
Recurrent anterior uveitis may also occur especially in Africa.

4. **Posterior segment**
The posterior segment is made up of the posterior part of the lens, the choroid, retina and optic nerve. Any of these structures can be affected since they are all vascularized. The manifestations following infection from HIV/AIDS can be any of the following:
a. HIV microangiopathy;
b. HIV retinitis;
c. Cytomegalovirus retinitis;
d. Progressive outer retinal necrosis;
e. Choroidal pneumocystosis;
f. Toxoplasmosis – frequently atypical;
g. Choroidal cryptococcosis;
h. B-cell intraocular lymphoma.

5. **Neuro-ophthalmic manifestations**
a. Optic Neuritis;
b. Optic atrophy;
c. Neuroretinitis;
d. Ocular motility disorders secondary to CNS involvement like cerebral toxoplasmosis, neurosyphilis, cryptococcal meningitis, and progressive multifocal leucoencephalopathy.

This chapter will, however, focus on some specific ocular manifestations which are often used as markers for HIV infection in the tropical environment and other commonly occurring general features of HIV/AIDS and the eye.

Markers of HIV/AIDS in Africa

Herpes Zoster Ophthalmicus (HZO), recurrent anterior uveitis, squamous cell carcinomas and Kaposi's sarcoma have been identified as markers of HIV/AIDS in Africa. This means that the occurrence of any of these could signify the presence or onset of HIV/AIDS infection (9, 10).

Kaposi's sarcoma appears as purple-red swellings on the Negroid skin/eyelids, or a red, fleshy mass on the conjunctiva in Caucasians (Figures 2 and 3) (11).

Conjunctival Squamous cell carcinoma

The association of HIV with Conjunctiva squamous cell carcinoma has been well documented (12, 13, 14). It is often used as a marker for HIV infection in Africa. Hence it may be the first presenting sign of HIV, especially in young adults. It usually presents as a florid growth in the limbal region of the bulbar conjunctiva; however, other parts of the conjunctiva may not be spared.

Death is uncommon and it very rarely invades the eyeball or adjacent structures. A 100% cure rate has been achieved using margin free surgery, which is followed by cryotherapy or radiation. Treatment involves complete excision with a wide tumour-free margin. Confirmation of spread may necessitate adjuvant therapy with cytotoxic agents like mitomycin C and 5-fluorouracil (Figure 4).

Herpes Zoster Ophthalmicus

Herpes Zoster Ophthalmicus (HZO) is an infection caused by human herpes virus 3 also known as varicella-zoster virus – the same virus responsible for chicken pox.

HZO usually occurs following a reactivation of a latent infection of the trigeminal nerve secondary to depressed immunity by HIV. The ophthalmic division of the trigeminal nerve is usually commonly affected and it manifests with rashes in the affected dermatome, conjunctivitis, keratitis and anterior uveitis.

Treatment usually takes a prolonged course and is usually resolved with the control of the underlying HIV/AIDS (Figure 5).

HIV microangiopathy

Retinal microangiopathy is the most frequent retinopathy in patients with AIDS, developing in up to 70% of patients, and is associated with a declining CD4+ count. Postulated causes include immune complex deposition, HIV infection of the retinal vascular endothelium, haemorheological abnormalities and abnormal retinal haemodynamics. Cotton wool spots, capillary abnormalities, and retinal haemorrhages are signs that could be seen. The lesions may be mistaken for early CMV

retinitis. However, in contrast to CMV, lesions are usually asymptomatic and almost invariably disappear spontaneously after several weeks.

Cotton wool spots could be due to several causes. Any process that leads to small retinal arterioles could result in diabetes, hypertension, severe anaemia, HIV, or hypercoagulable states, thrombocytopenia, Behçet's, viruses, connective tissue disorders, Lues, and many other conditions.

Cytomegalovirus retinitis

Cytomegalovirus (CMV) retinitis is the most common opportunistic ocular infection among patients with AIDS in the developed world. Since the advent of HAART, its incidence has declined and its rate of progression reduced, even in patients with low CD4+ T cell counts. It also appears that the rates of complications are less than in the pre-HAART era. However, in the tropical environment, CMV retinitis is not that common as most of the patients do not live long enough to develop it or where they do develop it, they are too sick and bedridden with other manifestations of HIV to bother themselves with the eye complaint. With the availability of HAART now in the developing world, these patterns may change with time.

CMV retinitis may be indolent or fulminating: indolent retinitis frequently starts in the periphery and progresses slowly towards the posterior pole. It is usually characterized by a mild granular opacification associated with a few punctate haemorrhages, but vasculitis is absent while fulminating retinitis is characterized by mild vitreitis; vasculitis with perivascular sheathing and often associated with retinal haemorrhages.

A “brushfire-like” extension along the course of the retinal vascular arcades may involve the optic nerve head. Retinal detachment associated with large posterior breaks may occur in the uncontrolled disease which may require vitreoretinal surgery and the use of silicone oil tamponade (Figures 6a & 6b). Systemic treatment involves either the sole use or various combinations of Valganciclovir, Ganciclovir, intravenous Foscarnet, and intravenous Cidofovir. Intravitreal treatment includes the use of the Ganciclovir slow-release device, and the intravitreal injection of *Ganciclovir*, *Fomivirsen* or *Cidofovir*.

Progressive retinal necrosis

Although progressive retinal necrosis (PRN) (formerly progressive outer retinal necrosis – PORN) occurs predominantly in AIDS, it may also occur in patients with drug-induced immunosuppression. PRN is a rare but devastating necrotizing retinitis caused by the varicella-zoster virus. Probably as a consequence of the profound immunosuppression of the host, it usually behaves aggressively.

It presents as a rapidly progressive visual loss which is initially unilateral in 75% of cases often associated with minimal anterior uveitis and vitreitis. Features include yellow-white retinal infiltrates, full-thickness retinal necrosis, early involvement of the macula, and vitreous inflammation which is usually late and reflects extensive retinal necrosis.

Diagnosis is done using a Specific PCR-based diagnostic assay for varicella zoster virus DNA performed on vitreous samples. Treatment involves intravenous and intravitreal Ganciclovir and Foscarnet. Even when instituted early the results are often disappointing. Vitreoretinal surgery for retinal detachment often also yields poor results (Figure 6b).

Exacerbated infections

Herpes simplex corneal ulcers behave abnormally by appearing more peripheral instead of central. Toxoplasma choroidal retinitis appears very fulminating with loss of vision, while anterior uveitis may become fulminating, recurrent and bilateral especially in a young individual. Opportunistic infections with protozoa (e.g., *Toxoplasma gondii* and *Cryptosporidium* spp.), viruses (e.g., CMV, HSV), fungi (e.g., *Pneumocystis jirovecii*, *Cryptococcus neoformans* and *Candida albicans*), and bacteria (e.g., *M. avium-intracellulare* and *Bartonella henselae*) may occur with HIV infections.

Eye features in Children

An alarming proportion of 90% of babies who acquire the disease from infected mothers is found in sub-Saharan Africa. Among the undernourished children, a prevalence rate of infection up to 25% has been seen while CMV retinitis occurs in 3.4% of children who have <50/mL of the CD4 count.

Congenitally acquired herpes zoster in new-borns occurs due to transplacental infection with varicella zoster virus. It can lead to congenital abnormalities. The zoster virus infection may be acquired transplacentally, typically manifesting after birth as cutaneous scars and eye and limb abnormalities. Symptoms are serious if infection occurs in the 3rd trimester or late pregnancy. Acyclovir is given in a dose of 1000 mg/day orally for five days. Topical Acyclovir is applied to the skin or the ophthalmic lesions repeatedly (11, 15).

The treatment depends upon the particular disease and presentation. It is important to note that antiviral drug treatments help in maintaining the health of the immune system. This then assists in reducing the risk of developing HIV-related eye diseases. Routine eye examinations by an ophthalmologist are advocated for HIV infected persons in order to detect any problems as early as possible in order to reduce blinding complications. Untreated cytomegalovirus (CMV) retinitis in a severely immunodeficient patient, presents early in the AIDS epidemic, before the availability of anti-CMV drugs or antiretroviral drugs (6, 15).

The introduction of highly active antiretroviral therapy (HAART) in 1996 was a watershed event in the history of the AIDS epidemic: “a revelation,” said Dr. Heiden, “Immune recovery became a reality, and new cases of CMV retinitis largely disappeared over the next year or two” (6, 16).

Conclusion

Before HAART, there were blinding infections but their incidence has now reduced. Economic status also influences the treatment and that is where the problem really lies in the developing countries. We, however, appreciate the efforts of several NGOs that have been helping with the provision of these drugs for free.

Table 1. Suggested management protocol for Herpes Zoster Ophthalmicus copyright @ (15)

Infection	Treatment
"Shingles"	Acyclovir (Zovirax) 800 mg orally five times daily for 7 to 10 days
Skin	Apply cool compresses
Blepharitis/Conjunctivitis	Topical lubrication. Topical antibiotic.
Epithelial keratitis	Debridement or none
Stromal keratitis	Topical steroids
Neurotrophic keratitis	Topical lubrication Topical antibiotics Tissue adhesives and protective contact lenses to prevent perforation
Uveitis	Topical steroids Oral steroids Oral acyclovir
Scleritis/Episcleritis	Topical non-steroidal anti-inflammatory agents and/or steroids
Acute retinal necrosis/Progressive outer retinal necrosis	IV acyclovir (1,500 mg per m2 per day divided into three doses) for 7 to 10 days, followed by oral necrosis – acyclovir (800 mg orally five times daily) for 14 weeks (12)

References

1. Alastair KOD, Philip IM. *Oxford Handbook of Ophthalmology*. 2nd Edition. Reprint (with corrections). Oxford: Oxford Medical Publications, 2011, 396-9.
2. Jack J Kanski, Brad Bowling. *Clinical Ophthalmology: A Systematic Approach*. Elsevier 2011. 7th Edition. Edinburgh; New York: Elsevier/Saunders, 2011.
3. Emina MO, Odjimogho SE. Ocular problems in HIV and AIDS patients in Nigeria. *Optom Vis Sci.* 2010; 87(12): 979-84. doi: 10.1097/OPX.0b013e3181fef198.
4. Chuka-Okosa C, Oguego N, Ogbonnaya C. Intraocular inflammtions, Uveitis and endophthalmitis. In: *l. Essentials of Ophthalmology in the tropics.* 1st Edition. Faculty of Ophthalmology, West African College of Surgeons. Yaba, Lagos, 2015. Chapter 11; 231-255.
5. Kierstan Boyd. http://www.geteyesmart.org/eyesmart/diseases/aids.cfm. Eye health information from the American Academy of Ophthalmology. The Eye M.D. Association. Accessed 24/3/2016.
6. Lewallen S. HIV/AIDS: What is the Impact on Prevention of Blindness programmes? *Community Eye Health.* 2003; Vol. 16(47): 33-4.
7. Available on www. https://owlcation.com/stem/Anatomy-of-the-Eye-Human-Eye-Anatomy. Accessed 15-2-18.
8. American Academy of Ophthalmology. *Ocular involvement in AIDS. Basic and Clinical Science Course*. 2013-2014 edition. Section 9, Chapter 11: 305-314.
9. MGa W. Eye Complications of Acquired Immune Deficiency Syndrome (AIDS) Part 1. Ocular surface and anterior segment manifestations. *South Sudan Medical Journal* May 2009; 2(2): 3-6.
10. Boateng W. Herpes zoster ophthalmicus in HIV/AIDS. *Comm Eye Health* 2003; 16 47: 35 - 36.
11. Gabrielle Weiner. American Academy of Ophthalmology. HIV and the Eye: Lessons Learned, Challenges Remain *EyeNet Magazine* http://www.aao.org/eyenet/article/hiv-eye-lessons-learned-challenges-remain. Accessed 24/3/2016.
12. Ukponmwan CU, Igbokwe UO, Aligbe JU. Squamous cell carcinoma of the conjunctiva in Benin City, Nigeria. *Nig J Clin Prac*. 2002; 5: 143-147.
13. Guramatunhu S. Squamous cell carcinoma in HIV/AIDS. *Comm Eye Health*. 2003; 16: 37 [PMC free article] [PubMed].

14. Nagaiah G, Stotler C, Orem, Mwanda WO and Remick SC. Ocular surface squamous neoplasia in patients with HIV infection in sub-Saharan Africa. *Curr Opin Oncol.* 2010 Sep; 22(5): 437-442. doi: 10.1097/CCO.0b013e32833cfcf9.
15. Community Eye Health Journal. Herpes zoster ophthalmicus in HIV/AIDS. *Comm Eye Health* 2003; 16 47: 35-36.
16. Kestelyn PG, Cunningham ET. HIV/AIDS, and blindness. Bull World Health Organ., 2001; 79: 208-213.

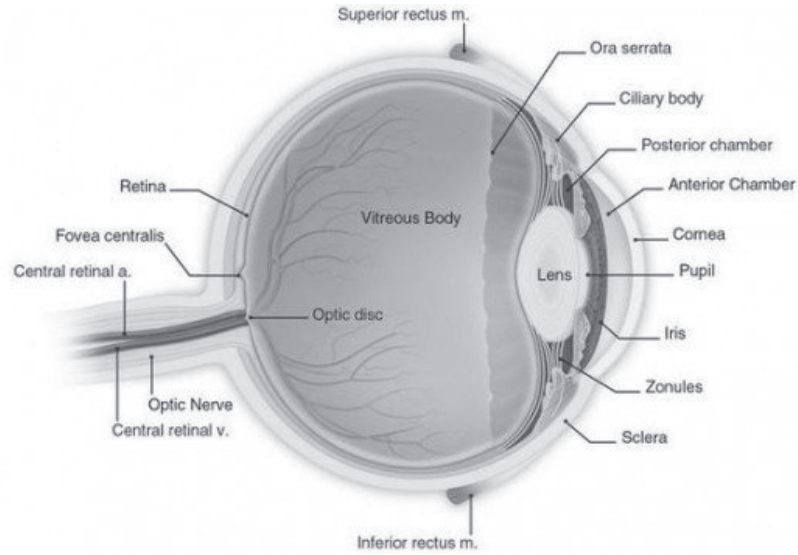


Figure 1: Shows the gross sagittal section of the eyeball (7)
Copyright @ https://owlcation.com/stem/Anatomy-of-the-Eye-Human-Eye-Anatomy-Accessed on 15-2-18

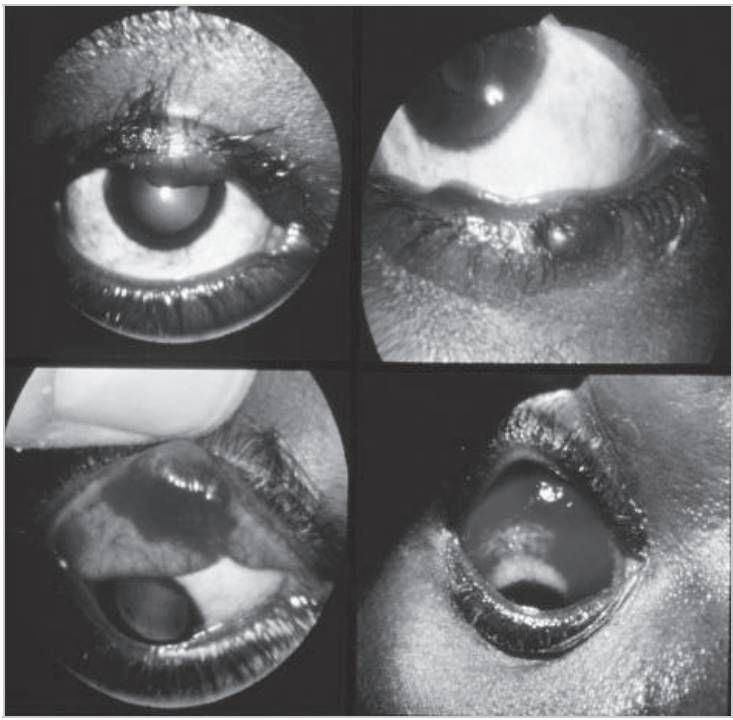


Figure 2: Kaposi's Sarcoma
Examples of sarcoma – Lid and Conjunctival lesions (11) Photos: Philippe Kestelyn

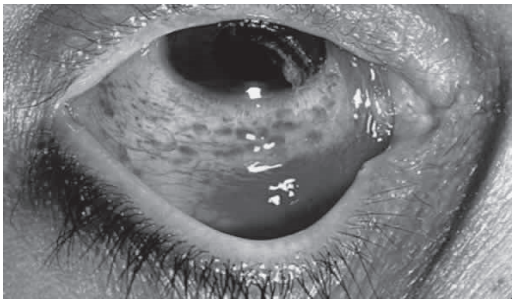


Figure 3: Kaposi's Sarcoma of the conjunctiva
Copyright – 2010-2012 *South Sudan Medical Journal*. Eye Complications of Acquired Immune Deficiency Syndrome (AIDS ...
www.southsudanmedicaljournal.com)

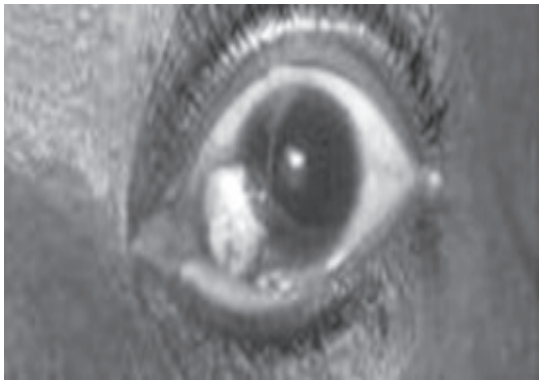


Figure 4: Squamous cell carcinoma of the conjunctiva
Eye Complications of Acquired Immune Deficiency Syndrome (AIDS .. www.southsudanmedicaljournal.com)

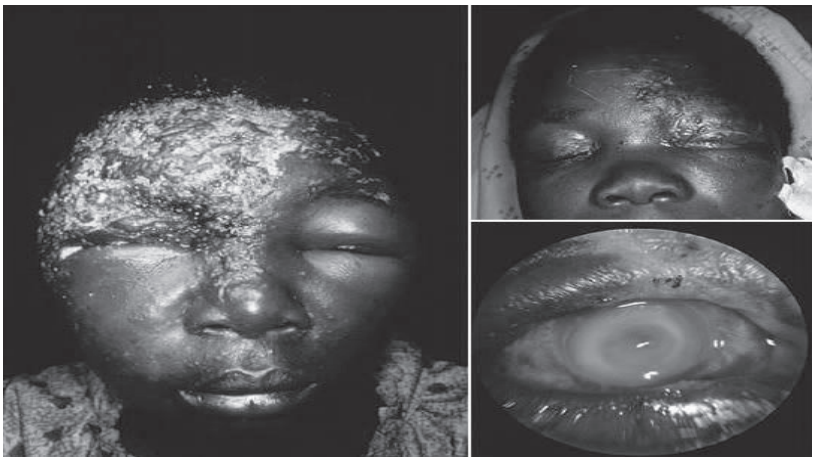


Figure 5: Features sen in Herpes Zoster Ophthalmicus
HZO showing the demarcation affecting one side of the face (picture on left). HZO causing upper eyelid cicatricial ectropion (upper right). HZO with severe corneal involvement (bottom right) © Susan Lewallen & Philippe Kestelyn (bottom right). Copyright @ *Community Eye Health Journal* » Herpes zoster ophthalmicus in HIV/AIDS. *Community Eye Health* Vol. 16 No. 47 2003: 35-36.

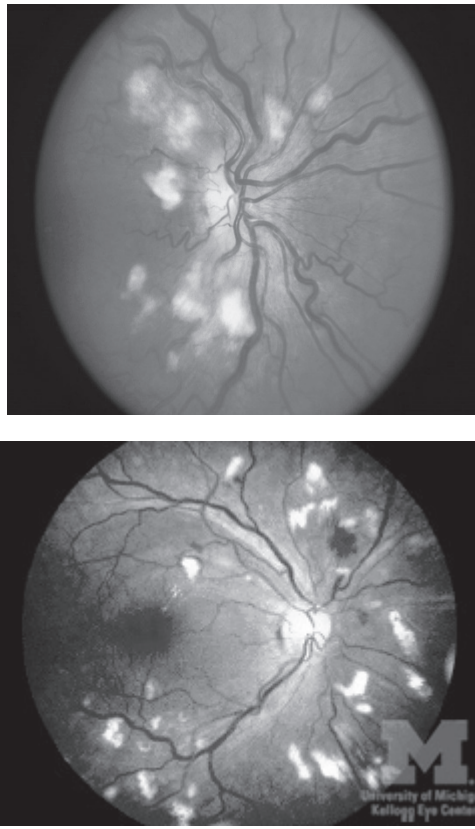


Figure 6a: Cotton wool spots
"These yellow-white spots are called cotton wool spots. They are caused by retinal nerve fiber layer microinfarcts. Exploded retinal ganglion cell axons extrude their axoplasm like toothpaste around the optic disc and along the temporal vascular arcades."

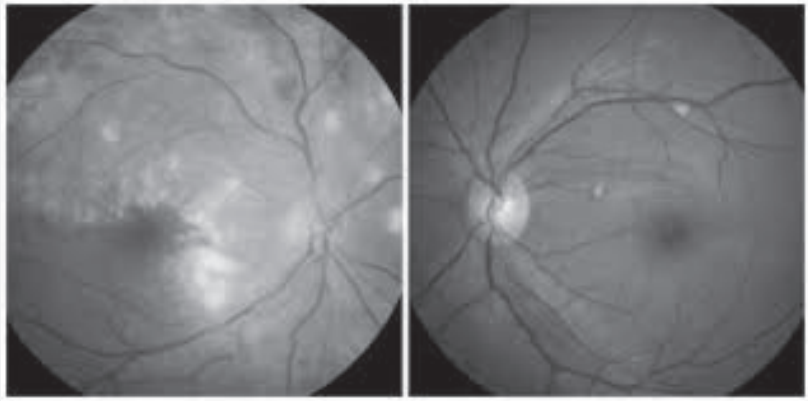


Figure 6b: HIV positive patient who presented with bilateral retinitis, OD>OS. The patient presented with dull eye pain, decreased vision and floaters.
"HIV positive patient who presented with bilateral retinitis, OD>OS. The patient presented with dull eye pain, decreased vision and floaters. The exam revealed cotton-wool spots, retinal haemorrhages, exudates and perivascular sheathing. A moderate vitreitis, OD>OS, was noted on an exam as well".
Copyright @
www.reviewofoptometry.com/content/c/45047/dnnprintmode/true/skinsrc/
Accessed on 4/3/2016.

Otolaryngologic Manifestations of Human Immunodeficiency Virus (HIV) Infection

Adedayo O Olaosun
MBChB, DLO, FWACS, MPH, MSc, Cert (Org. Leadership)
and Adetunji A Haastrup
MBBS, FWACS, FICS

The vast majority of people infected with the Human Immunodeficiency Virus (HIV) will develop manifestations in the head and neck region. While there are no Acquired Immune Deficiency Syndrome (AIDS)-defining conditions specific to this region, many AIDS-defining lesions do manifest in the region. A wide spectrum of problems commonly found in association with HIV infection are also commonly seen in the head and neck. In addition, the finding of certain head and neck pathologies constitutes grounds for offering HIV testing to a patient. Most patients will initially present to the General Practitioner and to other clinicians who are not Infectious Diseases specialists or Otolaryngologists. It is important, therefore, for all clinicians to have a good understanding of the Ear, Nose and Throat manifestations of HIV infection. This facilitates early diagnosis as well as prompt, comprehensive and appropriate care. This chapter discusses the common head and neck manifestations associated with HIV infection.

More than 70% of patients with Human Immunodeficiency Virus (HIV) infection will at some stage present with a Head and Neck or an Ear, Nose and Throat manifestation, many of them with multiple lesions (1, 2, 3, 4). There are no Acquired Immune Deficiency Syndrome (AIDS)-defining conditions specific to the Head and Neck, but many AIDS-defining lesions do manifest in the Head and Neck and a wide variety of pathologies associated with HIV infection are also commonly seen. In addition, there are a number of lesions which if found are indications for offering HIV testing to a patient. A thorough understanding of these HIV related

problems is essential to facilitate early diagnosis as well as comprehensive and appropriate care of the HIV-infected patient. For clarity, the topic is approached by considering the nature of pathologies (cutaneous and mucosal lesions, inflammatory and infective conditions, neoplasms, and neurologic damage) and the sites affected (the skin and the face, the nose and paranasal sinuses, the external, middle, and inner ear and skull base, the oral cavity, the salivary glands, pharynx, larynx, upper oesophagus, and the neck). It is to be noted, however, that there is a considerable overlapping of categories by several of the lesions.

Head and neck manifestations of HIV infection (Classified by Pathology)

Cutaneous and Mucosal Lesions

Cutaneous disorders are very commonly encountered in HIV-infected patients. Up to 90% suffer from skin diseases during their course of illness and skin disorders may be the first manifestation of HIV disease (5). The spectrum of these disorders is wide and includes skin infections, inflammatory conditions, cutaneous malignancy and miscellaneous manifestations including drug reactions. In theory, any of the skin manifestations may be present in the head and neck, but the actual manifestation is determined by the immunologic state, the concurrent use of medication and the pattern of infections in the locality, and the number and degree of manifestations worsen with deteriorating immunity (5, 6, 7). Thus, while head and neck cutaneous manifestations can even be seen early, the occurrence and number of lesions increase with advancing disease. Common head and neck cutaneous lesions include candidiasis, recurrent aphthous ulcers, Kaposi's sarcoma, oral hairy leucoplakia, molluscum contagiosum, herpes simplex, herpes zoster (shingles), psoriasis, seborrhoeic dermatitis and mucosal dryness from salivary gland disease as shown in Table 1. The management of skin disease is important for cosmetic reasons, self-esteem and quality of life issues. Even minor conditions should not be overlooked, and the dermatologist is in the best position to manage these lesions especially if refractory to normal treatment.

Table 1: Common Head and Neck Manifestations of HIV (by pathology)

Cutaneous and Mucosal Lesions	Inflammatory and Infective Conditions	Neoplasms	Neurologic Damage
Candidiasis Recurrent aphthous ulcers Kaposi's Sarcoma Oral hairy Leucoplakia Molluscum Contagiosum Herpes Simplex Herpes Zoster Psoriasis Seborrhoeic dermatitis	Viral: (HSV 1, Varicella Zoster, Cytomegalovirus) Bacterial infections (typical, atypical, mycobacterial) Fungal (Candidiasis, Aspergillosis, etc.) Parasitic (Toxoplasma) Dermatitis (Seborrhoeic) Allergic manifestations Parotitis	Kaposi's Sarcoma Non-Hodgkin's Lymphoma Squamous Cell Carcinoma	Facial Nerve/Central Nervous System Facial-Paralysis Syndromes Bell's Palsy

Table 2: Common Head and Neck Manifestations of HIV (by site affected)

Skin and Face	Nose and paranasal sinuses	External, middle and inner ear	Oral cavity
Fungal infections Seborrhoeic dermatitis Facial Cellulitis Kaposi's sarcoma Molluscum Contagiosum Herpes simplex Herpes zoster (Shingles) Psoriasis Facial warts Facial Nerve/Bell's Palsy	Cutaneous Seborrhoeic dermatitis Nasal vestibulitis, cellulitis Herpes simplex Herpes zoster (Shingles) Kaposi's sarcoma Non-Hodgkin's lymphoma Non-cutaneous Nasal obstruction Adenoid hypertrophy	Otitis externa Otitis media with effusion Eustachian tube dysfunction Kaposi's sarcoma Sensorineural hearing loss	Recurrent aphthous ulcers Oral candidiasis Herpes simplex Herpes zoster (Shingles) Xerostomia Gingivitis, stomatitis & Periodontitis Condylomata Hairy leukoplakia Kaposi's sarcoma Non-Hodgkin's

	Eustachian tube dysfunction Rhinosinusitis (allergic and infective)		lymphoma
Salivary glands	Pharynx, Larynx and Upper Oesophagus	Neck	Skull base and Neurologic
Xerostomia Chronic Parotitis Lymphoepithelial parotid cysts	Acute infections: Pharyngitis Acute Epiglottitis, Laryngitis Candidiasis	Neck mass HIV lymphadenopathy Bacterial Lymphadenopathy Deep neck space Infections Mycobacterial Cryptococcosis Histoplasmosis Coccidioidomycosis Toxoplasmosis Parotid Mass Kaposi's sarcoma Non-Hodgkin's lymphoma	Bell's palsy Facial Nerve/Central Nervous System Facial-Paralysis Syndromes

Inflammatory and infective conditions

As expected in immunocompromised states, infection is common in the Head and Neck and could be life-threatening. The spectrum of infections found is wide and includes viral (HSV 1, Varicella Zoster, Cytomegalovirus), bacterial (usually caused by expected organisms for various infections, but tuberculous and non-tuberculous mycobacteria are common), fungal (Candidiasis, Aspergillosis, Cryptococcosis Histoplasmosis Coccidioidomycosis) and parasitic (Toxoplasma). Usually, infections in the various tissues are caused by pathogens expected in patients with a normal immune system, though they tend to occur more frequently and run a more severe course. Treated promptly, most patients respond to standard medical management. Unusual organisms are however found in the later stages of disease as are unusual opportunistic infections such as those caused by mycobacteria, fungi and parasites.

Neoplasms

Kaposi's Sarcoma and non-Hodgkin's lymphoma are famously associated with HIV disease. Kaposi's Sarcoma is an idiopathic multiple sarcoma and the commonest tumour in HIV infection (1, 8). It is an AIDS-defining cancer and can even manifest early in the course of the disease. It may manifest as multiple synchronous tumours in the body and there may be more than one tumour arising from the skin or mucosal surfaces of the head and neck. Non-Hodgkin's lymphoma usually appears late in the course of HIV disease and presents with fever, night sweats and weight loss associated with a mass. Squamous cell carcinomas have also been found arising from the epithelia in the head and neck of HIV patients. The incidence is not clear, and association with HIV remains controversial. However, such tumours have been found to be very aggressive despite highly active antiretroviral therapy and need to be promptly and aggressively treated (9).

Neurologic damage

Head and neck neurologic damage is most commonly in the form of a seventh cranial nerve palsy (1). Damage to the facial nerve is more common in HIV-infected patients than in immunocompetent individuals (10). It can be a manifestation of central nervous system disease in the so-called Facial Nerve/Central Nervous System Facial-Paralysis Syndrome or it may be an idiopathy (or Bell's palsy) believed to be due to an infection of the nerve in the facial canal by the herpes simplex virus (1, 10). Central nervous system disease causing an upper motor neuron facial nerve palsy has been reported from CNS toxoplasmosis, HIV encephalitis and CNS lymphoma (1). The palsy may be unilateral or bilateral. CNS disease must be promptly treated, but even so, the prognosis for full recovery of nerve function is poor. In cases of Bell's palsy, the paralysis is a lower motor neuron type and prompt treatment with a course of oral prednisolone and acyclovir commenced within the first two weeks of onset (the earlier, the better) is the standard treatment and most patients recover full function within three to four months (11, 12).

Head and Neck Manifestations of HIV Infection (Classified by Site Affected)

Skin and Face: Fungal infections

Fungal infection predominates due to its opportunistic nature. It is the most common skin disorder found among HIV-infected patients and occurs very frequently on the face presenting most commonly as Dermatophytosis and Candidiasis. Other common skin fungal infections include Aspergillosis, Penicilliosis and Cryptococcosis (5). Mostly the fungal infections run a chronic indolent course and can be managed with routine topical and systemic antifungals. However, there is an acute invasive and life-threatening form usually involving aspergillosis which is rapidly progressive and may necrose the face and facial bones within a very short period. Prompt recognition and treatment are essential for survival in acute invasive aspergillosis.

Skin and Face: Viral infections

Common viral infections include herpes simplex, herpes zoster, molluscum contagiosum and facial warts. Herpes simplex is usually due to the reactivation of latent infection with Herpes Simplex Virus and usually manifests as oro-labial vesicles and rarely folliculitis or (13) verrucous lesions and ulcers in advanced HIV disease. Herpes zoster is a recrudescence of varicella zoster infection. It is common in the early stages of HIV infection and may be the first clue of infection. Multi-dermatomal Herpes Zoster, common in advanced HIV disease can also occur in the head and neck along the courses of more than one cranial nerve (13). Molluscum contagiosum is caused by pox virus that selectively infects human epidermal cells and presents with pearly papules with central umbilication, or atypically with lesions such as giant Mollusca in advanced HIV disease (5). Infection with Human Papilloma Virus also frequently occurs and manifests as warts. Antiviral drugs, usually oral (but also systemic in disseminated disease) are used to treat herpes simplex and herpes zoster. Treatment options in molluscum contagiosum and warts include podophyllotoxin, imiquimod, CO2 laser, cryotherapy, curettage, excision and topical tretinoin and cidofovir (5, 13, 14). In general, treatment of these viral lesions is more effective while the HIV patient is on HAART.

Skin and Face: Bacterial infections

Bacterial infections on the face are also common in HIV-infected patients. Acute infections are most commonly caused by Staphylococcus aureus and can manifest as cellulitis, folliculitis, facial abscess, nasal vestibulitis and other skin and soft tissue infections. Acute facial sepsis can have severe manifestations, progress rapidly and lead to systemic sepsis or the intracranial spread of infection in these patients. They should be treated promptly according to local antibiotic policies and sensitivity where applicable with or without surgical intervention. Chronic infections caused by tuberculosis, atypical mycobacteria and syphilis are also found. A high index of suspicion is always needed to direct the appropriate assessment and facilitate early diagnosis and prompt treatment in these chronic infections.

Skin and Face: Other Skin Lesions

Other skin lesions include seborrhoeic dermatitis and psoriasis. Seborrhoeic dermatitis presents with a rash and is said to be common in advanced disease. It can occur anywhere on the head and neck but is particularly common in the post-auricular, nasal, and malar regions and the malar rash can resemble the butterfly pattern of systemic lupus erythematosus (14). Treatment of seborrhoeic dermatitis is usually with topical corticosteroids although eradication of the rash is usually challenging. Psoriasis has been said to often occur as the first clinical manifestation of HIV disease although it is often also seen in advanced disease. The treatment of psoriasis is equally very challenging and may involve topical treatment, phototherapy and systemic treatment (15). Kaposi's sarcoma, manifesting as pink, blue or brown lesions, is also commonly found and should not be confused with benign skin lesions.

Nose and paranasal sinuses

Nasal and paranasal sinus manifestations are known to be among the most common presentations of HIV disease (1) and estimates from prospective studies have described a 30% to 68% prevalence of sinusitis (1, 16, 17, 18, 19). Cutaneous lesions similar to those found on the face are also well documented (16), and several pathologies can result in nasal obstruction. These include adenoid hypertrophy, allergic rhinitis (18), acute and chronic sinusitis, and sino-nasal or nasopharyngeal neoplasms (20). Kaposi's sarcoma and Non-Hodgkin's lymphoma are both also known to

occur in this region in HIV patients (1). As a result of many of these lesions, eustachian tube obstruction and eustachian tube dysfunction commonly supervene, associated with sequelae of middle ear effusion and recurrent middle ear infections. Thus, HIV-infected patients who present with a nasal obstruction need to be thoroughly evaluated as the differential diagnosis ranges from benign problems like allergic rhinitis to sinister malignancies. Assessment should include the evaluation of hidden areas of the upper aerodigestive tract with a flexible nasal endoscopy, appropriate radiological investigations such as CT or MRI and biopsies of any mass or asymmetrically enlarged nasopharyngeal lymphoid tissue found.

The external ear

The external ear which includes the pinna and the external auditory canal can be affected by the same spectrum of pathology as the skin since it is lined by skin. However, the peculiarities of the anatomy may produce additional symptomatology. For example, patients with seborrhoeic dermatitis may present with itchy ears and scaly ear discharge. A conductive hearing loss may also supervene as debris continues to accumulate. In the same way, neoplasms like Kaposi's sarcoma may cause hearing loss by obstructing the canal or eroding into the middle ear, but it can also invade the labyrinth and lead to vestibular symptoms. Also, herpes zoster (affecting the geniculate ganglion of the facial nerve called herpes zoster oticus or Ramsay Hunt syndrome) may present with a lower motor neuron facial nerve palsy, deafness, vertigo and pain. Infection of the external ear may present as pinna cellulitis, bacterial otitis externa or a fungal infection (Otomycosis). The organisms implicated are as expected for the immunocompetent individual. There is, however, an increasing incidence of unusual infections with organisms like Mycobacterium tuberculosis and Pneumocystis carinii. When otitis externa does not respond to standard antibiotic regimens, necrotizing otitis externa, also known as "malignant otitis externa" because of its invasive nature should be suspected. This is a severe manifestation of otitis externa usually found in immunocompromised individuals where the infection spreads to the skull base leading to skull base osteomyelitis and lower cranial nerve palsies usually initially affecting the facial nerve. This diagnosis can be confirmed using computed tomography (CT) scans of the temporal bone. The most common pathogen involved is Pseudomonas, but fungi such as Aspergillus may also be responsible (22).

The middle ear

In the middle ear, the most common otologic problems reported in HIV-infected patients are middle ear effusion (serous otitis media) and recurrent acute otitis media. The tendency to develop these conditions is high when there is nasal obstruction, recurrent sinusitis, allergies, tumours and subsequent eustachian tube obstruction or dysfunction. The usual organisms found in immunocompetent patients, *Streptococcus pneumoniae* and *Haemophilus influenza*, predominate but mycobacteria and fungi have also been isolated in HIV patients. Ear infections are especially common in paediatric patients with HIV disease due to a combination of the risk posed by the normal paediatric susceptibility to middle ear infection (22) as a result of the eustachian tube anatomy in children and depressed cell-mediated immunity. HIV patients are also at risk of severe morbidity and mortality from complications of otitis media including mastoiditis, labyrinthitis, neck abscesses, venous sinus thrombosis and intracranial spread of infection. Prompt broad-spectrum anti-infective treatment and close surveillance as well as prompt management of complications are mandatory in these patients.

The inner ear

Sensorineural hearing loss and vertigo can occur in the HIV-infected patient (23, 24). Sensorineural hearing loss can be unilateral or bilateral. It may be due to direct CNS infection by the HIV virus or damage of the cochlear nerve by the neurotropic HIV virus. It may also be due to other CNS infections, for example, syphilis and cryptococcal meningitis, neoplasms or ototoxic medications. A thorough evaluation is necessary to detect the cause, type and degree of hearing loss and to facilitate appropriate treatment and hearing rehabilitation. Vertigo can also occur in the HIV-positive patient usually co-existing with other neurologic symptoms. Vertigo is frequently secondary to CNS involvement but can also be due to a direct affectation of the vestibular system by the virus or as a complication of middle ear infection. Thorough clinical and laboratory audio-vestibular assessment is, therefore, necessary to determine the nature and map out a management strategy.

The Oral cavity

The oral cavity is a prime spot in the head and neck where multiple pathologies can frequently occur. The spectrum of oral diseases includes

infectious, benign inflammatory, neoplastic, and degenerative processes. Oral candidiasis, recurrent aphthous ulcers, Herpes simplex, Herpes zoster (Shingles), Xerostomia, Gingivitis, Stomatitis and Periodontitis, Condylomata, Hairy leukoplakia, Kaposi's sarcoma and Non-Hodgkin's lymphoma are some of the more common lesions. Oral candidiasis (thrush) is the most common oral condition in HIV-infected individuals (1, 5). It is also one of the commonest ENT manifestations of HIV (1, 5). It can present as tender, white, pseudomembranous or plaque-like lesions with underlying erosive erythematous mucosal surfaces (the commonest presentation), the atrophic form, the chronic hypertrophic form or the clinically obvious angular cheilitis (a non-healing fissure at the oral commissure) (1, 5). Treatment is with topical antifungals in early disease but systemic in advanced disease with systemic therapy.

Herpes simplex and varicella zoster also present in the oral cavity. Oral herpes simplex presents as "cold sores" or "fever blisters" but sometimes with bigger lesions on the palate, gingiva or another intraoral mucosal surface (1, 5). Mild oral herpes infections can usually be treated conservatively, but high-dose oral acyclovir should be used for more severe lesions (1, 25). Oral varicella zoster presents along the distribution of the trigeminal nerve as crops of vesicles on the hard or soft palate, lips and gingiva or as the corneal infection (zoster ophthalmicus). Verrucae (warts) and condylomata from Human Papilloma Virus infection are other viral lesions that can be found in the oral cavity.

Other benign oral cavity lesions include bacterial infections (stomatitis, gingivitis and periodontitis), oral hairy leukoplakia (a whitish, vertically corrugated lesion on the anterolateral edge of the tongue related to Epstein Barr Virus) and xerostomia ("dryness of mouth" due to salivary gland disease which may be associated with oral "thrush"). The major malignancies found are Kaposi's Sarcoma, Non-Hodgkin's Lymphoma and Squamous Cell Carcinoma (1). Fifty per cent of Kaposi's Sarcomas are found in the mouth (95% of these are on the palate or gingival surface) (1). Oral Non-Hodgkin's Lymphoma is usually sited on the gingiva and palate with extension to Waldeyer's ring, especially the tonsils. Squamous Cell Carcinoma may also occur in the oral cavity (1). Careful evaluation is needed to ensure that these lesions are not confused with the many benign lesions that can occur in the oral cavity.

Salivary glands

HIV salivary gland disease (HIV-SGD) is a distinct disorder characterized by recurrent or persistent major salivary gland enlargement and xerostomia (26). The parotids are most frequently affected, often with profound bilateral enlargement (26). Patients usually present with several months of progressive parotid swelling with minimal tenderness. Xerostomia leads to the loss of the antibacterial properties of saliva and creates a host of other oral cavity problems such as infection, dental caries, periodontal disease, soreness, fissuring of the buccal mucosa and tongue, and dysphagia (1, 26). HIV-SGD in the parotid gland is uniquely characterized by the formation of lymphoepithelial cysts within the gland (1, 26); these and the finding of lymphoepithelial cysts in a parotid gland and chronic parotitis especially if bilateral are reasons to offer a patient HIV testing.

Pharynx, Larynx and Oesophagus

Many of the problems of the oral cavity can also affect the pharynx, larynx and oesophagus due to the anatomical and functional relationships. Prominent lesions in the area include candidiasis, herpes simplex, recurrent aphthous ulcerations, acute adult epiglottitis, benign lymphoid hyperplasia, Kaposi's sarcoma and Non-Hodgkin's lymphoma. Candidiasis in the pharynx or the oesophagus can lead to odynophagia and/or dysphagia, and in the larynx to hoarseness and even aspiration and airway compromise in florid lesions. Appropriate diagnostic studies including endoscopy and radiologic investigations will often help in the diagnosis.

Adult acute epiglottitis also deserves special mention since, as in the immunocompetent population, it is rapidly progressive and life-threatening. The patient presents with a sore throat and severe odynophagia with drooling, the severity of which does not correlate with a normal oral cavity and oropharyngeal findings on examination. There may be fever, but this is inconstant, and its absence may belie the grave danger that the patient is in. If not promptly treated the sore throat worsens, and the patient may develop stridor and airway obstruction. In these cases, it is the lack of clinically apparent disease in the setting of such severe symptoms that should raise the suspicion of acute epiglottitis. Diagnosis is confirmed by examination of the hypopharynx and larynx, using a flexible nasal endoscope. Management is with intravenous broad-spectrum antibiotics and close airway observation. Preparation should also be made for intubation if necessary. Lack of improvement in 48 to 72 hours is an

indication for laryngoscopy and biopsy to rule out infection with an unusual organism or underlying malignancy as airway obstruction is also the most feared complication of malignancy in this area, and these patients are also prone to Kaposi's sarcoma and Non-Hodgkin's lymphoma.

The neck

The major manifestation of HIV in the neck is an enlarging neck mass. This is present in up to 91% of HIV-infected patients who have head and neck manifestations (27) and HIV testing should be offered to patients with lymphadenopathy of unknown cause. The commonest causes of these masses are HIV lymphadenopathy, infections, parotid gland enlargement and neoplasms. HIV lymphadenopathy can occur in the neck as part of the persistent generalized lymphadenopathy seen in HIV patients. Up to 70% of HIV patients will develop persistent generalized lymphadenopathy within the first few months of infection (28). Infectious processes in the neck can be due to a variety of organisms. Bacterial infections are common, and they may progress to cause deep neck space infections. The majority of organisms causing these infections are similar to those found in immunocompetent patients, but there are also infections of atypical organisms including tuberculous mycobacteria, atypical mycobacteria, fungi (Cryptococcus, Coccidioides, Histoplasma, Pneumocystis) and parasites (Toxoplasma). Assessment of the neck mass in the HIV patient should be thorough especially to able to identify atypical infections and neoplasms and to chart appropriate treatment. Open neck biopsies are discouraged to prevent the seeding of tumours. Similarly, incisions of neck abscesses are to be avoided until chronic granulomatous diseases from atypical infections like tuberculosis are ruled out to avoid creating a wound that would not heal.

Conclusion

In a nutshell, while there is no AIDS-defining condition specific to the head and neck region, many head and neck pathologies can be found in HIV-infected patients. Most patients will initially present to the general practitioner and many will present to other clinicians. It is important that all clinicians familiarize themselves with the ENT manifestations of HIV so that they are recognized early and appropriate management is promptly instituted.

References

1. Lee CL, Tami TA. Otolaryngologic Manifestations of HIV. HIV InSite. University of California, San Francisco Center for HIV Information, 2017. Available at http://hivinsite.ucsf.edu/InSite?page =kb-04-01-13#S2.4X. Accessed July 16, 2016.
2. Tshifularo M, Govender L, Monama G. Otolaryngological, head and neck manifestations in HIV-infected patients seen at Steve Biko Academic Hospital in Pretoria, South Africa. *S Afr Med J* 2013 May 16; 103(7): 464-6.
3. Prasad HK, Bhojwani KM, Shenoy V, Prasad SC. HIV manifestation in Otolaryngology. *Am J Otolaryngol*. 2006 May-June; 27(3): 179-85.
4. Alabi BS, Salami AK, Afolabi A, Dunmade D, Aremu SK, Olawunmi O, Akande HJ, Odeigha LO. Otolaryngologic manifestations among HIV/AIDS patients in a Nigerian tertiary health institution: an update. *Archives Int. Otorhinolaringol*. (Impr.) Sao Paulo Oct./Dec. 2010 14(4) Available at http://dx.doi.org/10.1590/S1809-48722010000400003.
5. Pennys NS. *Skin manifestations of AIDS*. London: Martin Dunitz, 1995, 189.
6. Raju PV, Rao GR, Ramani TV, Vandana S. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. *Int J Dermatol* 2005; 44: 646-9.
7. Ho KM, Wong KH. Dermatologic manifestations in HIV disease. In Chan KCW, Wong KH, Lee SS, editors. *HIV Manual* 2001, 231-45.
8. Singh B, Har-el G, Lucente FE. Kaposi's sarcoma of the head and neck in patients with acquired immunodeficiency syndrome. *Otolaryngol Head Neck Surg*. 1994 Nov; 111(5): 618-24.
9. Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. *Arch Dermatol*. 2002 Jun; 138(6): 758-63.
10. Lalwani AK, Sooy CD. Otologic and neurotologic manifestations of acquired immunodeficiency syndrome. *Otolaryngol Clin North Am* 1992; 25: 1183-97.
11. Murr AH, Benecke JE. Association of facial paralysis with HIV positivity. *Am J Otol*. 1991 Nov; 12(6): 450-51.
12. Schielke E, Pfister HW, Einhäupl KM. Peripheral facial nerve palsy associated with HIV infection. *Lancet* 1989 Mar; 1(8637): 553-4.
13. Weinberg JM, Mysliwiec A, Turiansky GW, Redfield R, James WD. Viral folliculitis. Atypical presentations of herpes simplex, herpes zoster, and molluscum contagiosum. *Arch Dermatol* 1997; 133: 983-6.

14. Eisenstat BA, Wormser GP. Seborrheic dermatitis and butterfly rash in AIDS. *N Engl J Med*. 1984 Jul; 311(3): 189.
15. Patel RV, Weinberg JM. Psoriasis in the Patient with Human Immunodeficiency Virus, Part 2: Review of Treatment. *Cutis*. 2008 September; 82(3): 202-10.
16. Hadderingh RJ. Recurrent maxillary sinusitis in AIDS patients. In: *Program and Abstracts of the V International Conference on AIDS*. Ottawa, 1989; 255.
17. Lamprecht J, Wiedbrauck C. [Sinusitis and other typical ENT diseases within the scope of acquired immunologic deficiency syndrome (AIDS)] HNO. 1988 Dec; 36(12): 489-92.
18. Sample S, Lenahan GA, Serwonska MH, et al. Allergic diseases and sinusitis in acquired immune deficiency syndrome. *J Allergy Clin Immunol* 1989; 83: 190.
19. Spech TJ, Rehm SJ, Longworth DL, et al. Frequency of sinusitis in AIDS patients (PTS). In: *Program and Abstracts of the IV International Conference on AIDS*. Stockholm, 1988; 7088.
20. Rubin JS, Honigberg R. Sinusitis in patients with the acquired immunodeficiency syndrome. *Ear Nose Throat J.* 1990 Jul; 69(7): 460.
21. Menachof MR, Jackler RK. Otogenic skull base osteomyelitis caused by invasive fungal infection. *Otolaryngol Head Neck Surg.* 1990 Mar; 102(3): 285-9.
22. Kohan D, Rothstein SG, Cohen NL. Otologic disease in patients with acquired immunodeficiency syndrome. *Ann Otol Rhinol Laryngol*. 1988 Nov-Dec; 97(6 Pt 1): 636-40.
23. Bell AF, Atkins JS, Zajac R, et al. HIV and sensorineural hearing loss (SNHL). In: *Program and Abstracts of the IV International Conference on AIDS*. Stockholm, 1991; 7009.
24. Sooy CD. Impact of AIDS on Otolaryngology-Head and Neck Surgery. In: Meyers EN, ed. *Advances in Otolaryngology. Head and Neck Surgery*. Vol 1. Chicago: Year Book 1987, 1-27.
25. Greenspan D, Schiodt M, Greenspan JS, et al. *Aids and the Mouth: Diagnosis and Management of Oral Lesions*. Copenhagen: Munksgaard, 1990.
26. Shetty K. Implications and management of xerostomia in the HIV-infected patient. *HIV Clinician* March 2005: 1-4.
27. Hadderingh RJ, Tange RA, Danner SA, Eeftinck Schattenkerk JK. Otorhinolaryngological findings in AIDS patients: a study of 63 cases. *Arch Otorhinolaryngol*. 1987 244(1): 11-4.
28. Lang W, Anderson RE, Perkins H, Grant RM, Lyman D, Winkelstein W, Royce R, Levy JA. Clinical, immunologic, and serologic findings

in men at risk for acquired immunodeficiency syndrome. *The San Francisco Men's Health Study* JAMA. 1987 Jan; 257(3): 326-30.

HIV/AIDS AND THE RESPIRATORY SYSTEM

ABIONA OLUWADAMILOLA ODEYEMI
MBBS, FMCP

The respiratory system is the most frequently affected organ system by HIV infection and respiratory pathology is most commonly associated with morbidity and mortality among patients living with HIV/AIDS (1). Respiratory symptoms occur frequently among HIV-infected individuals. This was observed by the Pulmonary Complications of the HIV Infection Study, which was a large, prospective, observational cohort study conducted at 6 sites across the United States (2). Respiratory symptoms may result from a wide spectrum of respiratory diseases. The spectrum of respiratory diseases associated with HIV infection ranges from infectious (Table 1) to non-infectious diseases (Table 2) (3, 4). While some of these complications are HIV-associated such as *Pneumocystis jirovecii* pneumonia (PJP) and recurrent bacterial pneumonia, others are not HIV-associated but have been found to occur with increased frequency in patients with HIV infection; examples include pulmonary arterial hypertension, chronic obstructive pulmonary disease and lung cancer. Evaluating respiratory symptoms in HIV-infected patients can be challenging for several reasons. Although each of these conditions has characteristic clinical and radiographic presentations, there can be a considerable overlap in these presentations. There is, therefore, no constellation of symptoms, physical examination findings, laboratory abnormalities, and chest radiographic findings that are pathognomonic or specific for a particular disease. Hence, definitive microbiologic or pathologic diagnosis is recommended whenever possible.

The advent of highly active antiretroviral therapy has dramatically improved the prognosis of HIV-infected patients. Furthermore, the spectrum of pulmonary diseases has changed significantly. Studies have revealed a reduction in overall pulmonary mortality and morbidity among HIV-infected patients (5). It has also been observed that there is a decline of pulmonary disease as a cause of hospitalization for HIV-infected patients compared with other causes. However, there has been no

significant decline of some non-infectious pulmonary complications since the use of highly active antiretroviral therapy (HAART) became widespread (5).

This chapter highlights the anatomy and defence mechanism of the respiratory system, the pathogenesis of HIV infection, the role of HAART, the diagnostic approach and common respiratory manifestations of HIV infection.

Anatomy and Defence Mechanism of the Respiratory System

The respiratory tract extends from the nose down to the alveoli. It is divided into the upper and lower respiratory tract. The upper respiratory tract consists of the nose, paranasal sinuses, nasopharynx and larynx while the lower respiratory tract begins at the junction of the larynx with the trachea and includes the trachea, bronchi, bronchioles and alveoli. Lining the upper respiratory tract are vascular mucous membranes with ciliated epithelium on their surfaces (6). The trachea and bronchi form an interconnecting tree of conducting airways which eventually joins, through around 64,000 terminal bronchioles, with the alveoli to form the acini (6). The lower respiratory tract is lined with ciliated epithelium down to the terminal bronchioles. Sensory nerve receptors involved in the cough reflex can be found in the larynx and the large bronchi (6). The lungs are specifically designed for the uptake of oxygen and the elimination of carbon dioxide through the process of ventilation and molecular diffusion. To prevent ill health, purified air must be presented to the alveolar epithelial surface to aerate pulmonary capillary blood. Ambient air, containing microorganisms, environmental debris, and possibly solubilized toxins, which is occasionally mixed with aspirated oropharyngeal secretions, must be cleansed. Most of the air moving through the nasal cavity has turbulent flow characteristics due to the nasopharyngeal anatomy (7). As a result of these characteristics and air flow dynamics, most airborne particulate matter and highly reactive gases impact or are absorbed along the mucosal surfaces and so are removed in the upper respiratory tract. The pharyngeal tonsils (aggregates of lymphoid tissue in the posterior pharynx) also help in clearing the large amounts of airborne material deposited in the nose and other aspects of the upper respiratory tract. The upper respiratory tract also helps to warm and humidify the air. Almost all the airborne materials which get to the upper respiratory tract are gradually moved posteriorly along the nasal mucous

layer to the posterior pharynx, where they eventually get swallowed. Clearance by the upper respiratory tract is ineffective for gases of low reactivity and particles of 1 μm in size and below. Hence, a significant fraction of these airborne pollutants is deposited in the small airways and alveolar regions (7).

The respiratory system has very efficient defence mechanisms including humidification of the inspired air, clearance of inhaled particles, and humoral and cellular mechanisms (8). Clearance of inhaled particles usually occurs through the cough reflex, mucociliary clearance and alveolar clearance (8). As much as 90% of the particles with a diameter greater than 10 μm are removed in the nostril or nasopharynx (8). The cough reflex is the watch-dog of the lung and helps in the elimination of mucus and foreign materials through the shearing forces developed during the process of coughing (8). The mucociliary clearance functions from the terminal bronchiole to the larynx through its constituent of mucus, cilia and their coupling mechanism. Alveolar clearance plays a very crucial and important role in eliminating particles with a diameter below 5 μm which may be deposited in the alveoli. About 80% of particles between 0.1 μm and 0.5 μm in diameter are exhaled in the air stream with only 20% being retained. Most of the particles which get deposited in the alveoli end up being phagocytized by alveolar macrophages (8). Critical for alveolar stability as well as for alveolar humoral and cellular defences is a thin layer of liquid surfactant which lines the alveolar wall. The lining liquid defending the alveolus contains several non-specific agents. The alveolar mucosal surface also contains the IgA antibody which also plays a defensive role (8). Several inhaled particles act as an antigen which stimulates an immune response by lung lymphocytes and alveolar macrophages. The B and T lymphocytes recognize specific antigens. The B cells produce antibodies, while the T cells regulate and have a helper, suppressor or cytotoxic function. The alveolar macrophages and mast cells serve as effectors by removing bacterial, viral, toxic or other particles that get to the alveoli (8).

Pathogenesis of HIV infection

Following infection with HIV there is a gradual but inexorable loss of host immunity described as a syndrome of immune dysregulation, dysfunction, and deficiency, which involves several aspects of the immune system. HIV is tropic for CD4+ lymphocytes and monocytes (9). Infection of pulmonary macrophages and lymphocytes with HIV-1 plays a crucial role

in the development of respiratory disease in AIDS (10). HIV variants in the lung may be genetically distinct from those in blood or other tissues, and this viral compartmentalization may be due to the selective recruitment of particular variants to the lung or to localized viral evolution (10). As in all tissues, HIV infection leads to the massive depletion of CD4+ T cells of the effector-memory type from mucosal-associated lymphoid tissue of the respiratory system (11, 12). Furthermore, the appearance of HIV in the lung may lead to intense infiltration of CD8+ T lymphocytes in the interstitial and alveolar spaces. This lymphocytic alveolitis can be seen in all stages of HIV infection, but it is most prominent in patients with early to middle stage disease, and it occurs as a consequence of the compartmentalization of HIV-specific cytotoxic T cells (12). During the chronic phase of untreated HIV infection, generalized immune activation occurs with an associated decline in the naive and memory T-cell pool leading to systemic CD4+ lymphocyte depletion (11, 13). Aside from being decreased in number, T cells also mount abnormal host responses to T-cell-dependent antigens. HIV infection has also been associated with B-cell dysfunction which manifests as abnormal polyclonal activation, hypergammaglobulinaemia, and lack of specific antibody responses (13). This combination of immune dysfunction, dysregulation, and depletion of CD4+ lymphocytes leads to increased risk of infections and other complications throughout the period of HIV infection. HIV infection also results in an alteration in several aspects of host defence in the respiratory tract which leads to an increased risk for respiratory tract infections. Examples include abnormalities in mucociliary function and soluble defence molecules contained in respiratory secretions (14). Within the lung parenchyma, innate and adaptive immune responses to pathogens have also been observed to be impaired (15). For instance, it has been observed that alveolar macrophages, which serve as the main reservoir of HIV within the lung, have been demonstrated to have deficiencies in pathogen recognition. In addition, animal models suggest that HIV-related proteins may disrupt the barrier function of the alveolar epithelium (16). The relationship between this persistently increased inflammation and the pathogenesis of chronic respiratory diseases in HIV-infected individuals remains poorly understood (11).

Role of Highly Active Antiretroviral Therapy

Adherence to a regimen of an effective combination of HAART leads to a containment of HIV multiplication, and preservation or improvement in

immunological function, with a reduced incidence of opportunistic infections, morbidity and mortality (17). A reduction in the frequency of PJP and other infections and the possibility of successfully discontinuing prophylaxis against PJP and other infections in patients who have a sustained increase in CD4+ lymphocyte counts of >200/µl are reflective of improved immunity (18, 19). Adherence to therapy is vital to its success and suboptimal adherence leads to inadequate viral suppression and the appearance of resistant strains of HIV. However, HAART does not appear to reduce the risk of all HIV-associated disorders, including lymphoma and invasive cervical cancer (20). Despite the benefits of HAART, it is not without its challenges. These challenges include drug-drug interaction, adverse reactions and immune reconstitution inflammatory syndrome (IRIS) which involves the lungs on many occasions. Examples of drug-drug interaction include that which occurs with antituberculous drugs, imidazoles, and lipid-lowering drugs (21, 22). Adverse effects of HAART include anaemia, lactic acidosis, insulin resistance, accelerated atherosclerosis, hyperlipidemia, and changes in body habitus (23). A granulomatous disorder that resembles sarcoidosis has also been observed in some patients taking HAART (24, 25).

Diagnostic Approach

The approach to respiratory disease in HIV-infected patients begins with a detailed history and physical examination. This is followed by chest radiograph, laboratory testing and other investigations as deemed necessary. Although every one of the opportunistic infections and neoplasms has a characteristic clinical presentation, these presentations can vary and overlap significantly. As a result, no combination of symptoms or signs is diagnostic of a particular disease. Efforts should be made at making a definitive diagnosis whenever possible as this is preferred to empirical therapy.

History

Certain aspects of the patient's history may be suggestive of one disease process over another. Aside from the more common symptoms including fever, cough and dyspnoea, other aspects of the history may help to differentiate between PJP and bacterial pneumonia. For example, patients with bacterial pneumonia usually present to the hospital after about 3-5 days of symptom onset, while patients with PJP present to the hospital with symptoms averaging 28 days (26). While patients with PJP typically

present with shortness of breath and a dry cough, patients with bacterial pneumonia usually have copious abnormally coloured sputum. Dyspnoea may occur in various infective disease processes, but may also be the only symptom of sarcoidosis or pulmonary hypertension. A drug history, including prophylaxis for PJP and tuberculosis (TB), and HAART usage is also important. For instance, studies have shown that patients who are taking PJP prophylaxis are nine times less likely to develop PJP than those not taking it (27). Prophylactic treatment with co-trimoxazole (sulphamethoxazole/trimethoprim) is also associated with reduced incidence of bacterial infections in addition to PJP and T. gondii reactivation (27, 28). However, in patients who take pentamidine inhalation for PJP prophylaxis, atypical and often apically pronounced manifestations of a PJP are to be expected. In addition, respiratory symptoms occurring following the institution of HAART may be due to IRIS (5).

Also important in the history is the patient's immune status which is determined by the patient's present CD4+ T-cell count. Knowledge of the stage of immunodeficiency provides a guide to the likely differential diagnoses. There are clear relationships between respiratory conditions and various CD4+ T-cell strata (Table 3) (29). Regardless of the CD4+ T-cell count however, strong consideration should be given to a diagnosis of tuberculosis. This is because despite the fact that the risk of tuberculosis infection increases with a declining CD4 + T-cell count, over half of all cases of tuberculosis in HIV patients occur at a CD4+ T-cell count above 200/μl (30, 31).

A history of how HIV infection was acquired is also important. Pulmonary Kaposi's sarcomas are found almost solely in homosexual males while bacterial pneumonia is common in intravenous drug abusers (32, 33).

Also important is the history of residence and travel. Patients who have lived in or visited countries with a high prevalence of TB, such as South East Asia and African countries, are at increased risk for pulmonary tuberculosis (PTB). Residence in or travel to areas endemic for some fungi also predisposes to infection with these organisms. *Histoplasma capsulatum* is endemic to North America and the Caribbean basin (34, 35).

Lastly, a history of cigarette smoking is also a very important part of the history. Cigarette smoking has been observed to be commoner in HIV-positive than in HIV-negative persons despite being more harmful in HIV-positives (36, 37). In addition, studies have shown that smoking is

associated with increased morbidity and mortality, and to suboptimal effects of HAART in HIV-infected individuals (38, 39, 40).

Physical examination

Aside from tachypnoea, the physical examination may be normal in HIV-infected patients with PJP, although fine crackles may be present. Signs of consolidation suggest bacterial, mycobacterial or fungal disease. Examination for extrapulmonary features should be carried out, as disseminated disease processes may present with respiratory symptoms. Cardiovascular signs should be assessed as cardiovascular diseases such as endocarditis, cardiomyopathy and pericardial effusions can also present with dyspnoea. Signs associated with immunodeficiency (e.g., oral thrush) should be elicited as these may influence the differential diagnosis if a current CD4+ T-cell count is not available. The skin should be examined for the presence of Kaposi's sarcoma (KS) and the cutaneous lesions of cryptococcosis. The presence of neurological signs may suggest disseminated toxoplasmosis or cryptococcosis. Hepatosplenomegaly may be seen in patients with *Mycobacterium avium* complex infection, non-Hodgkin's lymphoma or cytomegalovirus infection.

Investigations

Blood tests

HIV-infected patients usually have several laboratory abnormalities which may result from the HIV infection itself, from an HIV-related opportunistic infection or neoplasm, from the use of HAART or an HIV-related condition. Although some selected blood tests may provide important clues to the diagnosis of respiratory diseases in HIV-infected patients, no laboratory abnormality is specific for a particular respiratory disease. A number of useful laboratory tests include the CD4+ T-cell count, a complete blood count with a white blood cell (WBC) count and differential, the serum lactate dehydrogenase (LDH) and the arterial blood gases. As discussed earlier, the importance of the CD4+ T-cell count cannot be overemphasized as it gives a guide to the degree of immunosuppression and the possible differential diagnosis.

Leukocytosis with relative neutrophilia and a left shift is frequently observed in those who have bacterial pneumonia. Neutropenia is associated with an increased likelihood of bacterial and certain fungal

infections especially the *Aspergillus* species. However, persons with PJP may have an increased, normal, or even decreased WBC count, in which case it may be a reflection of the degree of underlying immunosuppression. Taking bone marrow suppressive medications, or the presence of an infiltrative marrow infection or neoplasm are other factors that may associate with a low WBC count (41).

Elevated serum LDH is sometimes suggestive of a diagnosis of PJP. However, LDH measurement has greater utility as a prognostic test than as a diagnostic test (42, 43, 44). The diagnostic sensitivity of an elevated serum LDH for PJP has been observed to be in the range of 83%-100% (43). However, it must be emphasized that the serum LDH level is nonspecific for PJP and may be elevated in many respiratory and non-respiratory conditions (including bacterial pneumonia). Furthermore, the serum LDH level may be normal or only minimally elevated in patients who have PJP. Despite these limitations as a diagnostic marker, the degree of elevation of the serum LDH has been demonstrated to correlate with the prognosis and response to therapy (43). Patients with PJP and a markedly elevated serum LDH or a rising serum LDH despite PJP treatment have a worse prognosis and a decreased survival rate.

Measurement of the arterial blood gases concentration usually reveals hypoxaemia, an increased alveolar-arterial oxygen difference, and a respiratory alkalosis. These measurements are non-specific for any disease condition but can be regarded as a marker of severity or to prognosticate (41).

In cases of suspected cryptococcal disease, serum cryptococcal antigen titer can be used as evidence of disseminated disease. It may also be necessary to obtain bacterial and mycobacterial blood cultures in some HIV-infected patients with respiratory disease.

Sputum investigations

All HIV-infected patients presenting with a productive cough should have their sputum routinely sent for Gram stain, bacterial and fungal culture and sensitivity testing. In addition, it is also usually necessary to send sputum for acid-fast bacilli, Xpert MTB/RIF assay (a nucleic acid amplification based test) and mycobacterial culture in order to diagnose mycobacterial infection. In cases of suspected PJP, induced sputum should be collected and sent for immunofluorescence, Giemsa or silver staining or polymerase chain reaction (PCR).

Chest radiography

The chest radiograph is an important aspect in the diagnostic evaluation of HIV-infected patients with respiratory symptoms. In patients who have bacterial, tuberculous, cryptococcal or lymphomatous disease, the chest radiograph may reveal the presence of focal consolidation and/or pleural effusion. Pleural effusion may also be caused by KS. The presence of pleural effusion makes PJP unlikely. However, multiple disease processes may co-exist in patients who have low CD4+ T-cell counts. The typical radiological pattern of TB, with upper lobe consolidation and cavitation, may not be seen in a patient with low CD4+ T-cell counts. Pneumothorax can be seen in many processes. Cavities are usually caused by *Mycobacterium tuberculosis*, bacteria, *Nocardia* spp., fungi and some atypical mycobacteria. Diffuse bilateral infiltrates are seen in patients who have PJP, but many other diseases may have a similar radiographic pattern. It is however important to note that in advanced HIV disease, the chest radiograph may be normal in patients who have diseases such as pulmonary Tuberculosis or PJP (45) (see Table 4).

Chest computed tomography (CT)

A chest CT scan is unnecessary in a lot of cases. This is because the clinical and chest radiographic presentation suggests a single diagnosis or a few differentials to consider. High-resolution computed tomography (HRCT) can however be useful in cases of suspected PJP where the chest radiograph is normal. In such cases the HRCT usually reveals ground-glass opacity with a patchy distribution. Although the occurrence of ground-glass opacity is not specific for PJP as it may be seen in many other pulmonary diseases, its absence makes the diagnosis of PJP unlikely (46). Chest CT may also be of help in diagnosing neoplasms such as pulmonary Kaposi's sarcoma or non-Hodgkin lymphoma which usually reveals nodules >1 cm in diameter (46).

Fiberoptic bronchoscopy

Fiberoptic bronchoscopy has been found to be of great value in the evaluation of HIV-associated respiratory diseases. In general, bronchoscopy should be considered for patients whose diagnosis remains unknown despite less invasive diagnostic studies (e.g., induced sputum), and for patients whose empirical therapy is failing. During bronchoscopy, bronchoalveolar lavage (BAL) with or without a transbronchial biopsy

(TBB) is performed. The decision on the choice of procedure to perform depends on the suspected diagnosis and on the sensitivities of these procedures for that diagnosis. Studies have revealed that the yield from these two procedures was complementary in identifying pathogens. While the sensitivity of BAL was 86% and that of TBB was 87%; the use of both procedures in combination yielded a sensitivity of 98% for all pathogens and 100% for Pneumocystis (47). The sensitivity of the BAL fluid examination for Pneumocystis has been observed to be 97% or higher. Hence, except in the rarest of cases, Pneumocystis can be excluded with a negative BAL fluid examination. The sensitivity of bronchoscopy for diagnosing a number of other important pathogens, including tuberculosis and endemic fungal pneumonias can also be improved by TBB (47). In addition, tissue confirmation from TBB or another biopsy specimen is mandatory to establish a diagnosis of cytomegalovirus pneumonia, invasive aspergillosis, and pulmonary non-Hodgkin lymphoma.

Infectious Respiratory Complications

Respiratory infections occur commonly among HIV-infected patients accounting for 98% of respiratory complications (3). Organisms most commonly identified are listed in Table 1. The most frequent respiratory diagnoses are upper respiratory tract infection, acute bronchitis, and acute sinusitis. They occur at all strata of CD4 + T-cell counts and have higher rates compared with HIV-negative control (3). Some of the infectious respiratory diseases are discussed briefly below.

Bacterial infections

Bacterial infections may develop in the early stages of HIV infection (CD4+ T-cell count >500 cells/µl), or at any time during the course of disease with the frequency increasing as the CD4 count decreases. With the advent of HAART, the overall incidence of bacterial pneumonia has reduced although it remains a cause of increased morbidity and mortality (48). One of the reasons for the persistence of bacterial pneumonia may be as a result of the increased prevalence of cigarette smoking among HIV-infected individuals. This is because cigarette smoking has been shown in several studies to be linked with high rates of pneumonia among HIV-infected patients at all CD4+ T-cell counts (33, 48, 49). The most frequent clinically apparent parenchymal lung infection in HIV-infected individuals is recurrent pyogenic bacterial pneumonia (defined as at least two episodes within 12 months) (4). Hence, its inclusion in the Centre for Disease

Control's list of AIDS-defining conditions (50). Bacterial pneumonia occurs about five times more often in HIV-infected patients than in otherwise similar but HIV-negative individuals (4). The bacterial pathogen involved is similar to that of community-acquired pneumonia in the general populace and *Streptococcus pneumoniae* is also the most frequently encountered pathogen (33, 51, 52). *Staphylococcus aureus* and gram-negative organisms especially *Pseudomonas aerugionsa* occur more frequently in advanced HIV disease (5). The clinical presentation (fever, cough, purulent sputum) and the course are similar to those of an HIV-negative population. There is however an increased tendency for rapid progression with the development of cavitation, parapneumonic effusion and empyema formation (6). Treatment is similar to that for HIV-negative patients. Co-trimoxazole for PJP prophylaxis has been observed to lead to a decreased incidence of bacterial pneumonia (48).

Acute bronchitis, bronchiolitis and bronchiectasis due to a pyogenic airways infection as compared to immunocompetent persons have also been observed to have an increased incidence in HIV-infected individuals with CD4 counts of <100 cells/µl even in those who have no history of cigarette smoking (28).

Mycobacterium tuberculosis

TB is an AIDS-defining illness (50). HIV-infected individuals have a 16-27 times higher risk of developing tuberculosis than HIV-negative individuals and it is the most frequent cause of death among HIV-infected patients being responsible for 37% of deaths in this patient population (53). Similar to bacterial pneumonia, although TB may occur at relatively high CD4+ T-cell counts, it tends to become increasingly common with lower CD4+ T-cell counts. It has been reported that the likelihood of drug-resistant tuberculosis is greater among HIV-infected patients than among others and drug-resistant tuberculosis has been linked with decreased survival (53). The clinical symptoms of PTB include productive cough sometimes with haemoptysis: fever, night sweats, dyspnoea and chest pain. Similar symptoms occur in disease caused by other mycobacteria. Radiographic findings of TB are dependent on the severity of immunosuppression. At higher CD4+ T-cell counts the appearances are typical of post-primary TB, similar to that which occurs in the general population with features such as focal consolidation and cavities located at the upper zones with or without pleural involvement (see Figure 1). With reduced CD4+ T-cell counts the features resemble primary infection,

manifesting with lymph node enlargement, pleural disease and a tendency to haematological and bronchopulmonary dissemination (see Figure 2). Diagnosis is by acid-fast bacilli microscopy, mycobacterial culture or the nucleic acid amplification test, particularly Xpert MTB/RIF assay of expectorated or induced sputum. Xpert MTB/RIF assay has been recommended by the World Health Organization as the initial diagnostic test in individuals with HIV-associated TB (54). It permits rapid diagnosis of tuberculosis with high specificity and sensitivity (approaching that of culture) and it can simultaneously detect TB and rifampicin resistance. Treatment and response to therapy are similar in both the HIV-infected and HIV-uninfected population. Problems encountered during treatment include toxicity from antituberculous drugs which is commoner in the HIV-infected population and drug-drug interactions with HAART.

Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii (formerly *Pneumocystis carinii*) is a fungus which was previously thought to be a protozoan. Although the frequency of occurrence of *Pneumocystis jirovecii* has reduced significantly since the advent of HAART and Pneumocystis prophylaxis, it is still the most frequently encountered opportunistic infection in HIV-infected individuals and occurs with a CD4+ T-cell count below 200 cells/μl (55). It presents with fever, breathlessness, hypoxia and a dry cough. Some patients may present with features suggestive of pneumothorax which include acute dyspnoea with pleuritic chest pain (56). The chest radiograph may not reveal any abnormality in 10% of cases (41, 57, 58), but a chest HRCT usually reveals ground-glass infiltrate (see Figure 3). Other chest X-ray findings may include diffuse, bilateral, often perihilar reticular opacities, poorly-defined ground-glass opacities usually in the upper lobes (58, 59). In about 10% of cases, cystic lesions may be observed and these may lead to the development of spontaneous pneumothorax (see Figure 4) (60, 61). These features are most commonly observed in patients receiving prophylaxis with aerosolized pentamidine and co-trimoxazole (62, 63). Diagnosis is by the identification of cysts or trophic forms (or both) on a stained respiratory specimen. The specimen used includes expectorated or induced sputum; pulmonary secretions obtained by nasotracheal suction, BAL, or percutaneous aspiration of the pulmonary parenchyma; and pulmonary tissue obtained by transbronchial, thoracoscopic, or open-lung biopsy. Sputum induction and BAL are however most widely used. Stains commonly used include methenamine silver, toluidine blue-O, Giemsa or Diff-Quik. PCR-based techniques may also be used for diagnosis.

Treatment of choice is high dose co-trimoxazole for 21 days. Other treatment options include intravenous pentamidine, clindamycin plus primaquine, trimethoprim plus dapsone, trimetrexate (sometimes used together with dapsone), and atovaquone (64). Adjunctive therapy with corticosteroids is recommended in patients who have moderate-to-severe pneumocystis pneumonia (65).

Non-infectious Respiratory Complications

Kaposi's Sarcoma

Despite the falling incidence in response to the widespread use of anti-herpes virus drugs and HAART, Kaposi's sarcoma remains the most frequent AIDS-associated malignancy (66, 67). Human herpes virus-8 (also known as Kaposi's sarcoma associated herpes virus) has been identified as the causal agent for KS (68, 69). Kaposi's sarcoma affects almost exclusively either homosexual or bisexual men and their partners (70). Pulmonary involvement can occur in up to one-third of people with known KS. The course of this disease is variable, ranging from slowly progressive to aggressive. Diagnosis usually follows the appearance of the cutaneous disease. KS may affect the oropharynx, larynx, lung parenchyma, pleura, and chest wall in addition to the gastrointestinal system, with widespread lymph node involvement. Upper respiratory tract involvement is usually absent in patients who have pulmonary lesions. The intrathoracic disease may manifest as pleural disease, parenchymal disease, adenopathy, and endobronchial lesions (71). In the majority of patients, chest X-ray reveals bilateral perihilar pulmonary infiltrates which extend into the pulmonary parenchyma along the bronchovascular bundles (see Figure 5). Although the mortality of patients who have KS has reduced significantly since HAART and a newer combination therapy were introduced, the prognosis of patients who have pulmonary KS remains poor (72).

Lymphoma

AIDS-related lymphomas are typically high grade, B-cell, non-Hodgkin's lymphoma (NHL). It occurs in about 10% of AIDS patients and is the second most common AIDS-associated malignancy (73). Lung involvement is usually seen together with other sites of disease but may occasionally be the initial or predominant site of disease. Chest X-ray

sometimes reveals multi-nodular infiltrates, consolidation, mass lesions, diffuse or focal interstitial infiltrates, hilar adenopathy and effusions.

Bronchial carcinoma

Bronchial carcinoma has been observed to occur more frequently in HIV-infected patients than in the general smoking population. The most common histology observed is adenocarcinoma (8). There is no clear association between the frequency and CD4 cell count. HIV-infected individuals who have bronchial carcinoma have their life span significantly reduced compared with HIV-negative subjects with bronchial carcinoma and the prognosis remains poor for these patients despite HAART (8).

Pulmonary hypertension

In HIV-infected individuals, pulmonary hypertension has an incidence estimated to be 0.5%, compared with 0.02% in the general population (74). It occurs at all CD4+ T-cell counts and has similar pathological findings to those of primary pulmonary hypertension. Treatment with HAART has been observed to reduce right ventricular systolic pressure and improve survival (74).

Immune Reconstitution Inflammatory Syndrome

IRIS is characterized by a contradictory deterioration of the clinical state which is related to a resurgence of the immune system following a period of immunosuppression. It typically occurs following the commencement of HAART in HIV-infected individuals. It occurs on account of the reconstitution of the immune system which results in host inflammatory responses to previously recognized or unrecognized infections. IRIS has also been observed to be due to the host inflammatory response to self-antigens or malignancy, manifesting as worsening autoimmune disease or cancer. It has been observed in various pulmonary diseases including PTB, *Mycobacterium avium* complex, PJP, KS, lymphoma, sarcoidosis and cancer (75, 76). The most frequent infectious triggers are mycobacterial infections, especially *M. tuberculosis* and *Mycobacterium avium* complex. A high viral load and a low CD4+ T-cell count are predisposing factors (5). Most cases of IRIS occur during the first 1 to 3 months after the initiation of HAART, although cases may occasionally present several months after the initiation of HAART (76). Generally, in patients who

have IRIS, HAART should be continued, although each case may be individualized following a careful review (64). Treatment is by nonsteroidal anti-inflammatory agents and corticosteroids which decrease inflammation. Indications for steroids include an excessive inflammatory response which can be particularly harmful, such as in lesions involving the central nervous system or causing airway compromise.

Table 1: Infectious Respiratory Complications*

BACTERIA	*Streptococcus pneumoniae* *Haemophilus influenza* *Pseudomonas aeruginosa* *Staphylococcus aureus*
MYCOBACTERIA	*Mycobacterium tuberculosis* *Mycobacterium avium complex* *Mycobacterium kansasii*
FUNGI	*Pneumocystis jirovecii* *Histoplasma capsulatum* *Aspergillus species (most commonly A. fumigatus)* *Cryptococcus neoformans* *Coccidioides immitis* *Blastomyces dermatitidis* *Penicillium marneffei*
PARASITES	*Toxoplasma gondii* *Strongiloidis stercorali*
VIRUSES	Cytomegalovirus

* Organisms listed above are examples of the most commonly identified organisms. Any infectious agent can be involved.

Table 2: Non-Infectious Respiratory Complications

MALIGNANCIES	Kaposi's sarcoma Bronchogenic carcinoma Non-Hodgkin's lymphoma
INTERSTITIAL LUNG DISEASES	Lymphocytic interstitial pneumonitis Nonspecific interstitial pneumonitis Sarcoidosis
OBSTRUCTIVE AIRWAY DISEASES	Chronic obstructive pulmonary disease Asthma

PULMONARY VASCULAR DISEASES	Pulmonary arterial hypertension
HAART RELATED CONDITIONS	Immune reconstitution inflammatory syndrome

Table 3: Relationship Between Respiratory Complications And Various Cd4 Strata

CD4 cell counts when conditions begin to occur	Respiratory complications
>500µl	Sinusitis, acute pharyngitis, bronchitis, pulmonary TB, bacterial pneumonia
200-500/µl	Recurrent bacterial pneumonia, varicella zoster pneumonitis
100-200/µl	PJP, disseminated TB
50-100/µl	pulmonary Kaposi's sarcoma, *Toxoplasma gondii* infections
<50/µl	Fungal pneumonia (*Histoplasma capsulatum*, *Coccidioides immitis*, *Aspergillus* species, *Candida* species), disseminated MAC, CMV pneumonitis, herpes simplex pneumonitis

MAC = *Mycobacterium avium complex*, CMV = Cytomegalovirus, TB = Tuberculosis

Table 4: Differential Diagnosis Of Chest Radiograph Abnormalities

	PJP	Bacteria	M.TB	Fungi	NHL	KS	MAC	CMV
Normal	Yes		Yes	Yes		Yes		
Focal consolidation/ infiltrate	Yes	Yes	Yes	Yes	Yes			
Miliary	Uncommon		Yes	Yes				
Diffuse or multifocal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Reticular or granular		Yes	Yes	Yes	Yes			Yes
Nodular	Uncommon	Yes	Yes	Yes	Yes	Yes		
Cystic lesions	Yes			Yes				
Cavities	Uncommon	Yes	Yes	Yes				
Pneumothorax		Yes	Uncommon	Uncommon				
Lymphadenopathy			Yes	Yes	Yes	Yes	Yes	
Pleural effusions		Yes	Yes	Yes	Yes	Yes		

CMV = cytomegalovirus; KS = Kaposi's sarcoma; MAC = Mycobacterium avium complex; M.TB = Mycobacterium tuberculosis; NHL = non-Hodgkin's lymphoma; PJP = Pneumocystis jirovecii pneumonia.

Adapted from Table 13.5 in Morris A, Huang L. Evaluation and management of respiratory complications of HIV infection. In: Crowe S, Hoy J, Mills J, editors. *Management of the HIV-infected patient*. London: Martin Dunitz, 2002, 217.

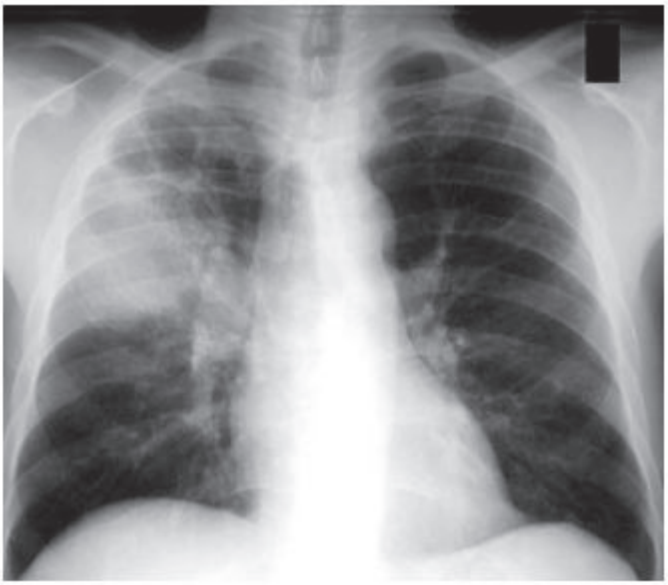


Figure 1: Chest X-ray of an HIV-infected patient with CD4+ T-cell count >200 cells/mm^3 showing right upper lung zone consolidation with cavitation. The patient's sputum was positive for acid-fast bacilli and mycobacterial culture yielded *Mycobacterium tuberculosis*. Courtesy of Laurence Huang, MD

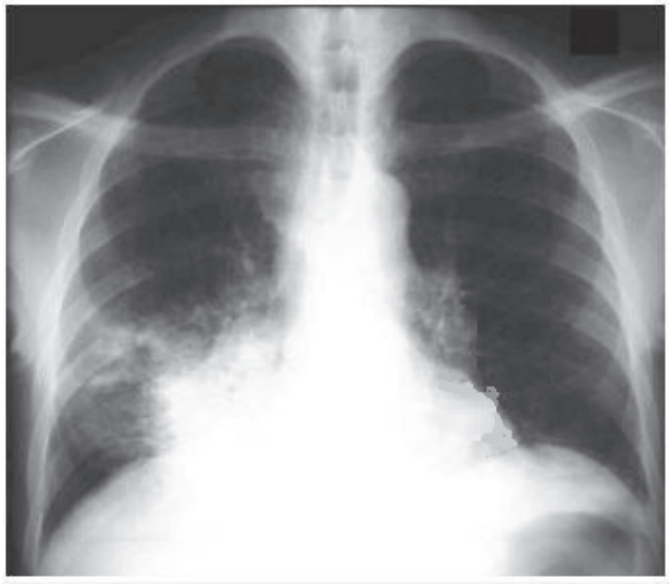


Figure 2: Chest X-ray of an HIV-infected patient with CD4+ T-cell count <200 cells/mm^3 showing right lower lung zone consolidation but with no cavitation. Courtesy of Laurence Huang, MD

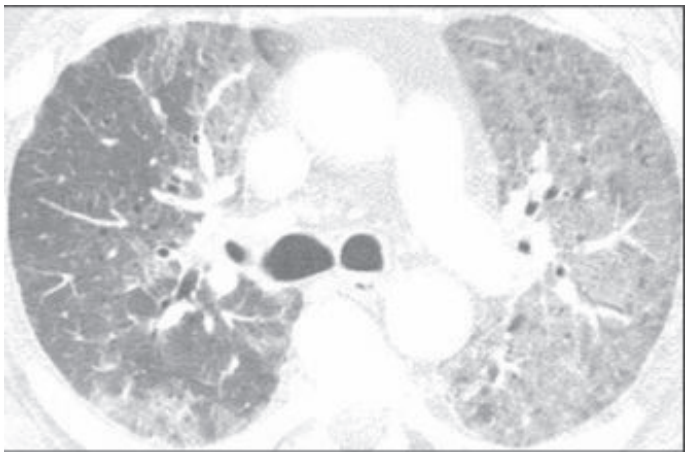


Figure 3: HRCT in a patient with PJP showing patchy areas of ground glass opacity.
Courtesy of Kanne JP, Yandow DR and Meyer CA

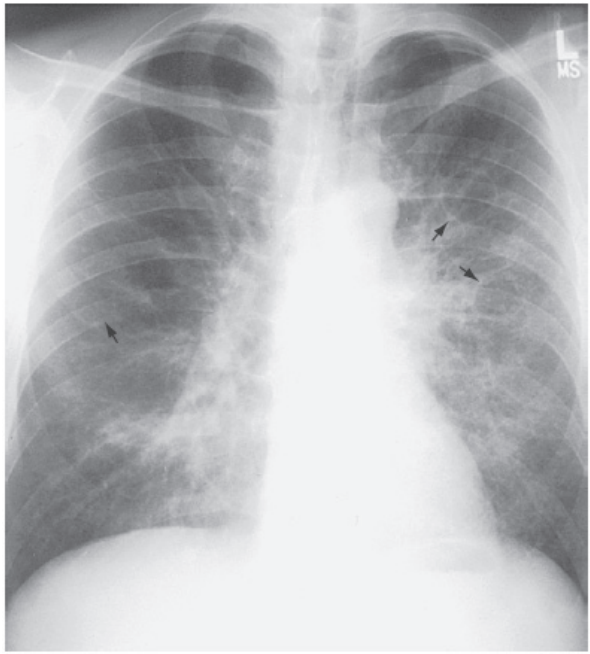


Figure 4: Chest X-ray of an HIV-infected patient with PJP which shows bilateral, mostly perihilar, granular opacities and three cysts (arrows) (Courtesy of L Huang)

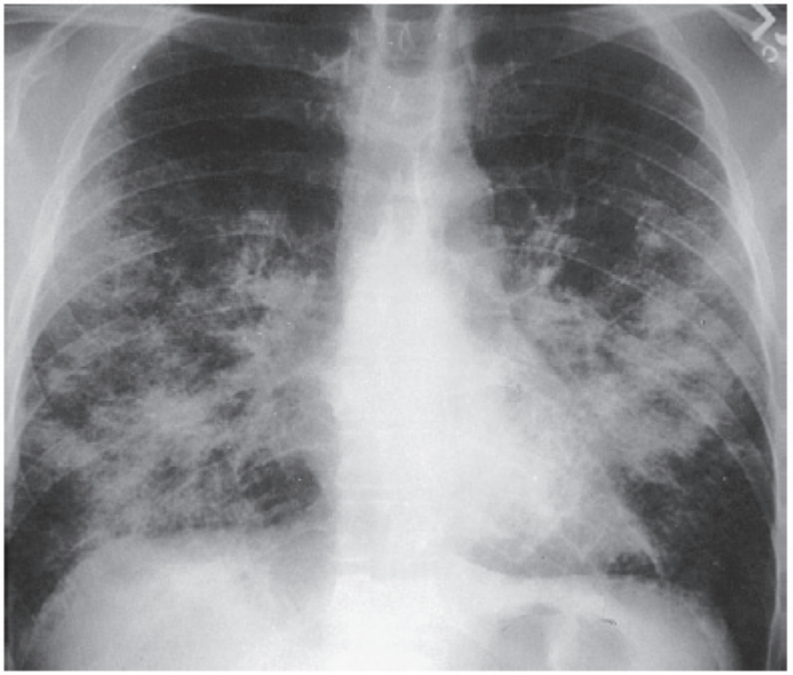


Figure 5: Chest X-ray of an HIV-infected patient with pulmonary Kaposi's sarcoma (Courtesy of L Huang)

References

1. Lanjewar DN, Duggal R. Pulmonary pathology in patients with AIDS: an autopsy study from Mumbai. *HIV Med*. 2001; 2: 266–271.
2. The Pulmonary Complications of the HIV Infection Study Group. Design of a prospective study of the pulmonary complications of human immunodeficiency virus infection. The Pulmonary Complications of the HIV Infection Study Group. *J Clin Epidemiol* 1993; 46(6): 497–507.
3. Murray JF, Mills J. Pulmonary infectious complications of human immunodeficiency virus infection. *Am Rev Respir Dis*. 1990; 141: 1356–1372, 1582–1598.
4. White DA, Matthay RA. Noninfectious pulmonary complications of infection with the human immunodeficiency virus. *Am Rev Respir Dis*. 1989; 140: 1763–1787.

5. Grubb JR, Moorman AC, Baker RK, Masur H. The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. *AIDS* 2006; 20: 1095–1097.
6. Crompton GK, Haslett C, Chilvers ER. Diseases of the respiratory system. In: Haslett C, Chilvers ER, Hunter JA and Boon NA (eds). *Davidson's Principles and Practice of Medicine*. 18th edition, Michigan, Churchill Livingstone. 1999, 303–391.
7. Mercer RR and Crapo JD. Normal Anatomy and Defense Mechanisms of the Lung. In Baum GL, Glassroth JL, King TE, Crapo JD, Karlinsky J. (eds.) *Baum's Textbook of Pulmonary Diseases*. 7th edition. Lippincott Williams & Wilkins Publishers, 2003, 1–35.
8. Chhabra SK. Respiratory system; structure and function. In: Yash Pal Munjal (ed.) *API Text book of Medicine*. 9th edition. Mumbai: Association of Physicians of India, 2012, 1686–1689.
9. Rosen MJ, Beck JM (eds.). *Human immunodeficiency virus and the lung*. New York: Marcel Dekker, 1998.
10. Benfield TL, Lundgren JD, Masur H. HIV-1, cytokines, and the lung. In: Nelson S, Martin TR (eds.). *Cytokines in pulmonary disease: infection and inflammation*. New York: Marcel Dekker, 2000, 331–364.
11. Grossman Z, Meier-Schellersheim M, Paul WE, et al. Pathogenesis of HIV infection: What the virus spares is as important as what it destroys. *Nat Med.* 2006; 12: 289–295.
12. Semenzato G. Immunology of interstitial lung diseases: cellular events taking place in the lung of sarcoidosis, hypersensitivity pneumonitis and HIV infection. *Eur Respir J* 1991; 4: 94–102.
13. Derdeyn CA, Silvestri G. Viral and host factors in the pathogenesis of HIV infection. *Curr Opin Immunol*. 2005; 17: 366–373.
14. Shellito JE. Failure of host defenses in human immunodeficiency virus. Semin Respir *Crit Care Med*. 2004; 25: 73–84.
15. Beck JM. The immunocompromised host: HIV infection. *Proc Am Thorac Soc*. 2005; 2: 423–427.
16. Lassiter C, Fan X, Joshi PC, et al. HIV-1 transgene expression in rats causes oxidant stress and alveolar epithelial barrier dysfunction. *AIDS Res Ther*. 2009; 6: 1–10.
17. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med.* 1998; 338: 853–860.
18. Currier JS, Williams PL, Koletar SL. Discontinuation of Mycobacterium avium complex prophylaxis in patients with

antiretroviral therapy induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2000; 133: 493–503.
19. Masur H, Kaplan JE, Holmes KK, et al. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Ann Intern Med.* 1999; 131: 873–908.
20. Jones JL, Hanson DL, Dworkin MS, et al. Effect of antiretroviral therapy on recent trends in selected cancers among HIV infected persons. *J Acquir Immune Defic Syndr*. 1999; 21: S11–S17.
21. Kosel BW, Aweeka F. Drug interactions of antiretroviral agents. In: Volberding PA, Jacobson MA (eds.) *AIDS clinical review*. New York: Marcel Dekker, 2000, 193–227.
22. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med*. 2001; 164: 7–12.
23. Liss M, Boyle BA. HAART-associated body habitus and metabolic changes, Part 2. *AIDS Reader* 2000; 10: 688–691.
24. Naccache J-M, Antoine M, Wislez M, et al. Sarcoid-like pulmonary disorder in human immunodeficiency virus-infected patients receiving antiretroviral therapy. *Am J Respir Crit Care Med*. 1999; 159: 2009–2013.
25. Narita M, Ashkin D, Hollender ES, et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998; 158: 157–161.
26. Kovacs JA, Hiemenz JW, Macher AM, et al. Pneumocystis carinii pneumonia: A comparison between patients with the AIDS and patients with other immunodeficiencies. *Ann Intern Med*. 1984; 100: 663–671.
27. Stansell JD, Osmond DH, Charlebois E, et al. Predictors of Pneumocystis carinii pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997; 155: 60–6.
28. Beck JM, Rosen MJ, Peavy H. Pulmonary Complications of HIV. Report of the fourth NHLBI Workshop. *Am J Respir Crit Care Med*. 2001; 164: 2120–2126.
29. Hanson DL, Chu SY, Farizo KM, et al. Distribution of CD4+ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses. The Adult and Adolescent Spectrum of HIV Disease Project Group. *Arch Intern Med*. 1995; 155: 1537–42.

30. Lange C, Schaaf B, Dalhoff K. HIV and lung. *Pneumologie*. 2004; 58: 416–427.
31. Wood R, Maartens G, Lombard C. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. 2000; 23: 75–80.
32. Biggar RJ, Burnett W, Mikl J, et al. Cancer among New York men at risk of acquired immunodeficiency syndrome. *Int J Cancer* 1989; 43: 979–985.
33. Hirschtick R, Glassroth J, Jordan M, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med*. 1995; 333: 845–851.
34. Stansell JD: Pulmonary fungal infections in HIV-infected persons. *Semin Respir Infect*. 1993; 8: 116–123.
35. Wheat LJ, Kauffman CA. Histoplasmosis. *Infect Dis Clinics North Am*. 2003; 17: 1–19.
36. Reynolds NR. Cigarette smoking and HIV: more evidence for action. *AIDS Educ Prev*. 2009; 21: 106–121. doi: 10.1521/aeap.2009.21.3_supp.106 PMID: 19537958.
37. Tesoriero JM, Gieryic SM, Carrascal A, et al. Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation. *AIDS Behav*. 2010; 14: 824–835. doi: 10.1007/ s10461-008-9449-2 PMID: 18777131.
38. Shirley DK, Kaner RJ, Glesby MJ. Effects of smoking on non-AIDS-related morbidity in HIV-infected patients. *Clin Infect Dis*. 2013; 57: 275–282. doi: 10.1093/cid/cit207 PMID: 23572487.
39. Marshall MM, McCormack MC, Kirk GD. Effect of cigarette smoking on HIV acquisition, progression, and mortality. *AIDS Educ Prev*. 2009; 21: 28–39. doi: 10.1521/aeap.2009.21.3_supp.28 PMID: 19537952.
40. Rahmanian S, Wewers ME, Koletar S, et al. Cigarette smoking in the HIV-infected population. *Proc Am Thorac Soc*. 2011; 8: 313–319. doi: 10.1513/pats.201009-058WR PMID: 21653534.
41. Laurence Huang. *Pulmonary manifestation of HIV*. Available from: http://hivinsite.ucsf.edu/InSite?page=kb-04-01-05.
42. Kales CP, Murren JR, Torres RA, et al. Early predictors of in-hospital mortality for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Arch Intern Med*. 1987; 147(8): 1413–1417.
43. Zaman MK, White DA. Serum lactate dehydrogenase levels and Pneumocystis carinii pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis*. 1988; 137(4): 796–800.

44. Garay SM, Greene J. Prognostic indicators in the initial presentation of Pneumocystis carinii pneumonia. *Chest*. 1989; 95(4): 769–772.
45. Morris A, Huang L. Evaluation and management of respiratory complications of HIV infection. In: Crowe S, Hoy J, Mills J (eds.) *Management of the HIV-infected patient*. London: Martin Dunitz, 2002, 211-25.
46. Gruden JF, Huang L, Turner J, et al. High-resolution CT in the evaluation of clinically suspected Pneumocystis carinii pneumonia in AIDS patients with normal, equivocal, or nonspecific radiographic findings. *AJR Am J Roentgenol.* 1997; 169(4): 967–975.
47. Broaddus C, Dake MD, Stulbarg MS, et al. Bronchoalveolar lavage and transbronchial biopsy for the diagnosis of pulmonary infections in the acquired immunodeficiency syndrome. *Ann Intern Med*. 1985; 102: 747–752.
48. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV Epidemiologic Research (HER) study. *Clin Infect Dis*. 2006; 43: 90–98.
49. Gordon FM, Roediger MP, Girard PM, et al. Pneumonia in HIV-infected persons: Increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med*. 1996; 80: 775–801.
50. Centers for Disease Control and Prevention: 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *JAMA*. 1993; 269: 729–730.
51. Le Moing V, Rabaud C, Journot V, et al. Incidence and risk factors of bacterial pneumonia requiring hospitalization in HIV-infected patients started on a protease inhibitor-containing regimen. *HIV Med*. 2006; 7: 261–267.
52. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: Impact of immune status. *Am J Respir Crit Care Med*. 1995; 152: 1309–1315.
53. WHO. *HIV-Associated TB Facts 2016*. Available from: http://www.who.int/entity/tb/areas-of-work/tb-hiv/tbhiv_factsheet_2016.pdf?ua=1. Accessed on 10th March 2018.
54. WHO. *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update*. Geneva: WHO, 2013. Available from: http://www.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf?ua=1. Accessed on 10th March 2018.

55. Morris A, Lundgren JD, Masur H, et al. Current Epidemiology of Pneumocystis Pneumonia. *Emerg Infect Dis*. 2004; 10(10): 1713–1720.
56. Fujii T, Nakamura T, Iwamoto A. Pneumocystis pneumonia in patients with HIV infection: clinical manifestations, laboratory findings and radiological features. *J Infect Chemother*. 2007; 13(1): 1–7.
57. Oh Yu W, Effmann E, Godwin D. Pulmonary infections in immunocompromised host: the importance of correlating the conventional radiologic appearance with the clinical setting. *Radiology* 2000; 217: 647–656.
58. Kuhlman J. Pneumocystis infections: the radiologist's perspective. *Radiology* 1996; 198: 623–635.
59. Thomas CF, Limper AH. Pneumocystis pneumonia. *N Engl J Med*. 2004; 350: 2487–2498.
60. Gallant J, Ko A. Cavitary pulmonary lesions in patients infected with human immunodeficiency virus. *Clinical infection diseases* 1996; 22: 671–682.
61. Boiselle PM, Crans Jr CA, Kaplan MA. The changing face of Pneumocystis carinii pneumonia in AIDS patients. *AJR*. 1999; 172: 1301–1309.
62. Franquet T, Giménez A, Hidalgo A. Imaging of opportunistic fungal infections in immunocompromised patient. *European Journal of Radiology* 2004; 51: 130–138.
63. McLoud T, Naidich D. Thoracic disease in the immunocompromised patient. In: Federle M. (ed.) *Radiology of the inmunocompromised patient*. Philadelphia: WB Saunders, 1992, 525–555.
64. Centers for Disease Control and Prevention: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR*. 2009; 58: 1–207.
65. The National Institutes of Health – University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med*. 1990; 323: 1500–1504.
66. Ledergerber B, Telenti A, Egger M. Risk of HIV-related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study. *BMJ*. 1999; 319: 23–4.
67. Grulich AE. Cancer risk in persons with HIV/AIDS in the era of combination antiretroviral therapy. *AIDS Read*. 2000; 10: 341–6.

68. Cathomas G, Tamm M, McGandy CE, et al. Detection of herpesvirus-like DNA in the bronchoalveolar lavage fluid of patients with pulmonary Kaposi's sarcoma. *Eur Respir J*. 1996; 9(8): 1743–6.
69. Fife K and Bower M. Recent insights into the pathogenesis of Kaposi's sarcoma. *Br J Cancer*. 1996; 73(11): 1317–22.
70. Biggar RJ, Burnett W, Mikl J, et al. Cancer among New York men at risk of acquired immunodeficiency syndrome. *Int J Cancer* 1989; 43: 979–985.
71. Traill ZC, Miller RF, Shaw PJ. CT appearances of intrathoracic Kaposi's sarcoma in patients with AIDS. *Br J Radiol*. 1996; 69(828): 1104–7.
72. Palmieri C, Dhillon T, Thirlwell C, et al: Pulmonary Kaposi sarcoma in the era of highly active antiretroviral therapy. *HIV Med* 2006; 7: 291–293.
73. Armenian HK, Hoover DR, Rubb S, et al. Risk factors for non-Hodgkin's lymphomas in acquired immunodeficiency syndrome. *Am J Epidemiol*. 1996; 143(4): 374–9.
74. Opravil M, Pechere M, Speich R, et al: HIV-associated primary pulmonary hypertension: A case control study. Swiss HIV Cohort Study. *Am J Respir Crit Care Med*. 1997; 155: 990–995.
75. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med*. 2000; 133: 447–454.
76. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004; 18: 1615–1627.

HIV/AIDS AND THE CARDIOVASCULAR SYSTEM

PATIENCE O AKINWUSI
BSC, MBCHB, FWACP, FAHA, FESC
RASAAQ A ADEBAYO
MBCHB, MPA, FWACP, CERT INTERVENTIONAL CARDIOLOGY (ALEXANDRIA UNIV, EGYPT)
VICTOR O ADEYEYE
MBCHB MPA, FMCP, FWACP
AND MICHAEL O BALOGUN
BSC,MBCHB, FMCP,FWACP, FRCP (GLASG), FSM, FESC

Both HIV infection, on a long-term basis, and the side effects of its treatment with Highly Active Anti-Retroviral Therapy (HAART) cause cardiovascular diseases (CVD). Attempts to reduce the duration of HAART increased the CVD rate; this suggests that the pathogenesis of CVD in HIV infection is likely to be multifactorial.These factors are the HIV infection itself, the attendant immune activation and coagulopathy. HIV infection on its own causes dilated cardiomyopathy with congestive cardiac failure and is termed HIV-associated Cardiomyopathy. Also the CVD risk factors and HIV infection can act synergistically to cause cardiovascular disease. Some opportunistic infections affect the myocardium leading to cardiomyopathy.Advanced HIV infection may lead to pericardial effusions.Left ventricular systolic and diastolic dysfunctions occur in HIV infection, the diastolic dysfunction may precede the systolic dysfunction. In essence, HIV infection has increased the prevalence of CVD and heart failure.

The Center for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA was primarily responsible for discovering Acquired Immunodeficiency Syndrome (AIDS) in 1981, when *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia was diagnosed in five previously

healthy homosexual men and in another subset of 26 others who all had Kaposi's sarcoma (KS) in Los Angeles,and in both New York and Los Angeles respectively (1,2).Further investigations recovered human immunodeficiency virus (HIV) from a patient with lymphadenopathy in 1983, and this was unequivocally linked as the aetiology of AIDS in 1984 (1).The development of a sensitive enzyme-linked immunosorbent assay (ELISA) in the USA, in 1985, helped in mapping out the epidemiology of the disease globally (1).

Cardiovascular Diseases in HIV-infected Individuals

The advent of human immunodeficiency virus (HIV) infection heralded an increase in CVD and heart failure with it becoming one of the most common aetiologies of acquired heart disease and specifically symptomatic heart failure (3). HIV infection on its own causes cardiac complications on a long-term basis (3), so do HAART-related side effects as part of the lipodystrophy syndrome (1,4). As these drugs continue to prolong life, they also impact negatively on atherosclerotic disease and cardiovascular risk cumulating in the increase in prevalence of ARV therapy-induced cardiac diseases (5).Autopsy findings showed that 25 to 75% of HIV patients had heart disease. Dilated cardiomyopathy with congestive cardiac failure (CCF) is the most common direct clinical effect of HIV infection, occurs as a late complication, is known as HIV-associated cardiomyopathy and the histological findings are those of myocarditis hence the proposal that intravenous immunoglobulin (IVIg) could be employed for treatment(1). HIV can be isolated directly from cardiac tissues in this disease (1).

Statistics in 2005 had shown that both adults and children living with HIV constituted 38.6 million, also about 10% of those infected in the USA were older than 50 years (2,3). Acceptance of antiretroviral therapy had been witnessing a tremendous increase in low- and middle-income countries such that the figure increased from 240,000 to approximately 1.3 million between 2001 and 2005(2,3). Access to HAART is however limited to 20% of those needing it (3).

The estimated global prevalence of HIV-related heart failure is put at 4-5million based on a 2-year to 5-year incidence of symptomatic heart failure which ranges from 4% to 28% (3).

In the paediatric age group bracket of 10 years, chronic cardiac disease accounted for 25% mortality; while 28% had serious cardiac events

following an AIDS-defining illness. The typical symptoms are oedema and dyspnoea. ARV therapy also prolongs life in this age group(3).

Reversible drug-induced cardiomyopathy may occur when HIV-infected patients are placed on IFN-α or nucleoside analogue (1).Stoppage of these drugs leads to the reversibility of the cardiomyopathy (1).

There are opportunistic diseases that can cause cardiomyopathy because they affect the myocardium and they include Chagas disease, Kaposi's sarcoma, toxoplasmosis and cryptococcosis (1,2).In one series, most patients with HIV infection and a treatable myocarditis were found to have myocarditis associated with toxoplasmosis (1).In a study, toxoplasmosis-induced myocarditis accounted for treatable myocarditis in the majority of patients infected with HIV (1).Sani and Okeahialam reported that Nigerian HIV-positive asymptomatic subjects had a higher prevalence of QTc prolongation compared to HIV-negative subjects and, as they moved to AIDS, the prevalence of QTc prolongation increased. This makes for increased cardiovascular mortality (6). In another review, they noted that a variety of potential aetiologies have been postulated in HIV-related heart disease, including myocardial invasion with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, and prolonged immunosuppression (5).

Pericardial disease with effusion and tamponade, marantic and infective endocarditis, arrhythmias, dilated cardiomyopathy with global left ventricular dysfunction, metastatic cancer, pulmonary hypertension and nonspecific or infectious myocarditis have been found in association with HIV/AIDS (2,3).The prevalence of drug-related cardiotoxicity, cardiac autonomic dysfunction, coronary artery disease and dyslipidaemia has been on the increase since HAART commenced (7). Most of these patients also had evidence of central nervous system toxoplasmosis. Thus, MRI or double-dose contrast CT scan of the brain must form part of the diagnostic workup of patients with advanced HIV infection and cardiomyopathy (1).

Diverse cardiovascular problems are seen in patients with HIV infection. Pericardial effusions may be found in advanced HIV infection with the following as predisposing factors: tuberculosis, congestive heart failure, mycobacterial infection, cryptococcal infection, pulmonary infection, lymphoma, and Kaposi's sarcoma (1). Although pericarditis is quite uncommon, moderate to severe pericardial effusions were seen in 5% of patients with HIV disease in one series (1).Tamponade and death had been

reported in patients with pericardial KS, probably due to acute haemorrhage (1).

There should be an index of suspicion of nonbacterial thrombotic endocarditis in patients with unexplained embolic phenomena (1). Intravenous pentamidine should not be given rapidly to avoid cardiovascular collapse with its attendant hypotension (1). Coronary artery disease is being increasingly diagnosed at autopsy and this has been linked to a high percentage of patients having hypercholesterolaemia and hypertriglyceridemia (1). This occurs as a side effect of HAART and occurs more in patients with HCV co-infection (1).The precise clinical significance of these findings is not yet elucidated but the available data suggest a direct link between the development of ischaemic heart disease and the duration of HAART therapy(1). Emerging evidence based on one large series suggested the likelihood of multiple factors being responsible for cardiovascular diseases associated with HIV infection (1). These factors are the HIV infection itself, the attendant immune activation and coagulopathy(1). This large study identified the total rate of myocardial infarction (MI) as 3.5/1000 years with 28% being fatal. Also, MI constituted 7% of mortality in the subset of fatal MI, with a 26% incremental risk in MI for every year of therapy on HAART (1). This is in view of the remarkable increase in patients' survival on HAART, coupled with a paradoxical increase in the cardiovascular disease rate on reducing the duration of HAART hence the likelihood that the pathogenesis of cardiovascular disease in HIV infection is multifactorial (1).

Cardiovascular Diseases in HIV Infection

The CVD risk factors and HIV infection can act synergistically to cause cardiovascular disease (4). HAART – naive HIV infection – increases serum levels of lipids (4). Longstanding HIV infection increases hypercoagulation and systemic inflammation while it decreases endovascular reactivity; however, with the appropriate HAART these conditions may be partially reversible (4). Abacavir has the side effects of increased platelet activation and/or decreased vascular reactivity which may lead to an increased risk of myocardial infarction (4).

Even in patients on HAART, the traditional risk factors (increasing age, hypertension, hyperlipidaemia, smoking and diabetes mellitus) still play an important role in CVD (4).

Despite the negative impact of some ARVs on CVD risk, the potent HAART still remains the mainstay of therapy of HIV infection because of the much more long-term outstanding benefits of immune reconstitution and chronic HIV suppression (4).

It is advocated that routine CVD assessment and appropriate interventions should be done for HIV patients (4).

AIDS and Related Disorders: Treatment

General Principles of Patient Management

In line with the CDC guidelines, health professionals must obtain an individual patient's consent for HIV testing to be included as part of routine laboratory investigations for him or her (1).

The diagnosis of HIV infection in any person is devastating no matter how emotionally stable the individual, hence the health care provider must be ready to put support systems in place immediately for the newly diagnosed patient (1, 8,9,10). The treatment of patients with HIV infection requires the ability to deal with the problems of a chronic, potentially life-threatening illness in addition to comprehensive knowledge of the course, complications, therapy and in-depth experience with ARV (1, 8,9,10).

The majority of the AIDS-defining conditions witnessed a marked reduction with the commencement and widespread use of HAART in the USA in 1995 to1996 (1). Strict adherence to the ARV drugs regimen is the key to the adequate suppression of HIV replication, which is a major mechanism that confers longevity and better quality of life to patients with HIV infection (1).The once-a-day regimen and co-formulations of ARVs aided strict compliance (1).

There have been major breakthroughs in the treatment of patients with HIV infection. The development and appropriate use of potent combination ARV therapy and other treatment and prophylactic interventions are providing patients living with HIV/AIDS with the best opportunity to live a long and healthy life (1). The attending physician must educate patients concerning the natural history of their illness and listen and be sensitive to their fears and concerns in addition to having an up-to-date knowledge of the latest drugs available for the patients (1). The physician and the patient must take therapeutic decisions together or a close relative must stand in as proxy where the patient cannot take such

decisions (1). There are several examinations and laboratory studies that must be done to grade the disease and also serve as a baseline for future reference. The following are essential in addition to routine chemistry:CD4+ T-cell count, two separate plasma HIV RNA levels, fasting lipid profile, fasting glucose and haematology screening panels, serologies for hepatitis A, B, and C, Pap smear, and chest x-ray, HIV resistance test, an RPR or VDRL test and an anti-*Toxoplasma* antibody titer (1).

A purified protein derivative (PPD) test should be done, and an MMSE (Mini-mental status examination) performed and recorded. Patients should be immunized with pneumococcal polysaccharide and, if seronegative for these viruses, with hepatitis A and hepatitis B vaccines (1).The status of hepatitis C infection should be determined. In addition, patients should be counselled with regard to sexual practices and needle sharing, and counselling should be offered to those whom the patient knows or suspects may also be infected (1).

These baseline activities are necessary to plan short- and long-term medical management strategies based on the most recent information available and subject to modification as new information becomes available (1).There are medical advances in the field of HIV and a variety of sites on the internet regularly update their information inclusive of consensus panel reports on therapy, to keep interested people abreast of the latest developments (1).

Combination antiretroviral therapy (ART), or highly active antiretroviral therapy (HAART), is the cornerstone of the management of patients with HIV infection. HIV drug therapies that are currently being used are in four categories: those that inhibit the viral integrase enzyme, those that inhibit the viral reverse transcriptase enzyme, those that interfere with viral entry, and those that inhibit the viral protease enzyme (1).The following are the Federal Drug Agency (FDA)-approved reverse transcriptase inhibitors: non-nucleoside reverse transcriptase inhibitors nevirapine, delavirdine, and efavirenz; the nucleoside analogues zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine;and the nucleotide analogue tenofovir (1).

These were in the first class of drugs that were licensed for the treatment of HIV infection to be used as combination therapy (1). Monotherapy promotes drug resistance so easily and as such no ARV should be used alone (1).The lipodystrophy syndrome has been associated with HAART

and this consists of fat redistribution, hyperlipidaemia and glucose intolerance/insulin resistance (1,3).The HIV-1 protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, lopinavir/ritonavir, atazanavir, tipranavir, and darunavir) are a major part of the arsenal against HIV infection (1).The mechanism of action of the entry inhibitors is by preventing the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion. The fusion inhibitor enfuvirtide, or T-20, was the first drug in this class to be licensed followed by the CCR5 antagonist maraviroc (1).Clinical trials are still being conducted on a number of additional small molecules that bind to HIV-1 co-receptorsv(1). The integrase inhibitors are the newest class of ARV compounds. Raltegravir inhibits the viral enzyme integrase and is the first of this class to be approved (1). It was approved in 2007 for the treatment of drug-experienced patients with HIV infection in combination with other ARVs (1).

Left Ventricular Systolic Dysfunction

The characteristic signs of heart failure may be masked or changed in the setting of concurrent pulmonary infections, pulmonary hypertension, anaemia, portal hypertension, malnutrition, or malignancy in HIV-infected patients hence presentations of patients with left ventricular systolic dysfunction may vary from being asymptomatic to New York Heart Association Class III or IV heart failure (3).

Echocardiography is useful for assessing left ventricular systolic function in this population (3) and should be performed in any patient with elevated cardiovascular risk, with any clinical manifestations of cardiovascular disease, or with unexplained or persistent pulmonary symptoms or viral co-infections at the baseline and every 1 to 2 years thereafter, or as clinically indicated (3). Olusegun-Joseph et al. identified by echocardiography early abnormalities in 100 treatment-naive patients. Significant echocardiographic abnormalities found included systolic dysfunction and diastolic dysfunction. Other abnormalities were pericardial effusion in 47% and dilated cardiomyopathy. One patient had aortic root dilatation, another had mitral valve prolapse and another had isolated right heart dilatation and dysfunction. They concluded that cardiac abnormalities are more common in HIV-infected people than in normal controls. A careful initial and periodic cardiac evaluation to detect early involvement of the heart in HIV disease is recommended (11).

Left Ventricular Diastolic Dysfunction

Diastolic dysfunction occurs frequently in long-term survivors of HIV infection and this may actually precede systolic dysfunction (3).

Other Investigations

An electrocardiogram can reveal nonspecific conduction defects or repolarization changes (3). The chest radiograph has low sensitivity and specificity for congestive heart failure in patients with HIV infection (3). Levels of brain natriuretic peptide have been inversely correlated with left ventricular ejection in both a large population of patients without HIV infection and in small populations of HIV-infected patients. This can actually be used in the differential diagnosis of HIV-induced congestive cardiomyopathy (3).

Course of Disease

The echocardiographic criteria for asymptomatic left ventricular dysfunction are fractional shortening less than 28 percent, with global left ventricular hypokinesis and patients with these may have transient disease (3).

Therapy

HIV-associated cardiomyopathy is treated like non-ischaemic cardiomyopathy with diuretics, digoxin, beta blockers, aldosterone antagonists, and angiotensin-converting enzyme inhibitors, as tolerated (3).

The patient should be investigated extensively for opportunistic or other infections and appropriate treatment should be instituted to ameliorate or resolve the cardiomyopathy (3). Biopsy of the right ventricular myocardium may be needed to identify infectious causes of failure and for suggesting targeted therapy. Medical therapy should be followed up with serial echocardiographic studies at 4-month intervals (3).

Infusions of immunoglobulin given every month to HIV-infected children have minimized left ventricular dysfunction, increased left ventricular wall thickness, and reduced peak left ventricular wall stress, suggesting

that impaired myocardial growth and left ventricular dysfunction can be immunologically mediated (3).

Heart transplantation has been reported in one HIV-infected man believed to have anthracycline-related cardiomyopathy (3). At 24 months of follow-up, his course was complicated by more frequent and higher-grade episodes of rejection than average, but otherwise it was relatively uneventful and productive (3). Clinical and echocardiographic findings have suggested that diastolic dysfunction is relatively common in long-term survivors of HIV infection. Left ventricular diastolic dysfunction may precede systolic dysfunction (3).

The risk of CVD may be reduced with ART treatment in patients with HIV infection, even when the CD4 T-cell counts are high; however, clinical trials and long-term observational studies will confirm this (12). Older drugs have adverse cardiometabolic risks which the newer generation protease inhibitors, chemokine receptor 5 antagonists, and integrase inhibitors appear to be free from (12). Recent studies suggest that apart from the well-known risk of coronary heart disease, chronic HIV infection is associated with increased risk of heart failure, arrhythmias and ischaemic stroke; so also has increased CVD risk been associated with active viral replication and immunodeficiency(12).

Novel methods of imaging subclinical vascular disease keep showing that immune activation and inflammation are likely to be the mediators of CVD among patients with HIV (12).

Prognosis

The increased mortality in HIV-infected patients with cardiomyopathy is not dependent on a high risk group, age, sex, and CD4 count (3). Left ventricular dysfunction was a major determinant of AIDS-related death in patients before HAART therapy (3). This was clearly demonstrated in a study where those with left ventricular dysfunction had a shorter median survival of 101 days while those with normal hearts had a longer median survival of 472 days despite both groups being at a similar stage of infection (3).

Acute-onset congestive heart failure in HIV-infected adults and children has an unpleasant prognosis with mortality from primary heart failure exceeding 50% within 12 months of presentation (3). However, if these

patients develop chronic-onset heart failure, they may respond better to medical treatment (3).

Future Perspectives

As HIV-infected patients live longer, HIV-related cardiovascular disease will become the commonest cause of mortality and a vital area of research (3).Findings of research on HIV-related CVD and using HIV as a model of chronic immunosuppression in a large population may translate to other populations (3). Statins, anti-inflammatory drugs or immunomodulatory agents may be used as innovative and evidence-based supportive therapies to improve outcomes.

Commencement of early treatment with ART is targeted as a likely strategy to reduce CVD risk for patients infected with HIV (12).

A good understanding of genetic predispositions to QT prolongation may serve as a useful guide to treatment. In the same vein, understanding the aetiologies of cardiomyopathy may be beneficial to various kinds of research efforts, such as the effects of cytokine, mitochondrial, and neurohormonal pathways (3).

In the setting of at-risk populations having cardiomyopathies that are not well understood, observations of increased mortality in association with left ventricular mass and very mild left ventricular dysfunction may enhance diagnostic testing (3).

References

1. Fauci AS, Braunwald E, Kasper DL, et al. (eds.).*Harrison's Principles of Internal Medicine*. New York:MacGraw-Hill, 2008.
2. Valentin Fuster, Robert A. Oâ€™Rourke, Richard A. Walsh, et al. *Hurst's The Heart*. 12th Edition. New York: The McGraw-Hill Companies, 2008.
3. Libby P, Bonow RO, Mann DL, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*.8th Edition. Philadelphia: Saunders Elsevier,2008.
4. Palella FJ Jr, Phair JP. Cardiovascular disease in HIV infection. *CurrOpin HIV AIDS*.2011;6(4):266-271.

5. Sani MU, Okeahialam BN. Epidemiology and pathogenesis of human immunodeficiency virus (HIV) related heart disease: a review. *Niger J Med*. 2005;14(3):255-260.
6. Sani MU,Okeahialam BN. QTc interval prolongation in patients with HIV and AIDS.*J Natl Med Assoc*.2005;97(12):1657-1661.
7. Sani MU, Okeahialam BN, Aliyu SH, et al. Human immunodeficiency virus (HIV) related heart disease: a review.*Wien KlinWochenschr*. 2005;117(3):73-81.
8. Analysis of the nature of Administration and the Content of Services provided in a model of Community – Home-based Care Programme for People Living with HIV/AIDS in OsunState: A Case Study of Living Hope Care and Support Outfit,Ilesa. Field Report Presented by Dr RA Adebayo to the Department of Public Administration, O.A.U. Ile-Ife in May 2002 in part fulfillment for the Master's award in Public Administration.
9. Adebayo RA, Oladoyin AM, Irinoye OO. Comprehensive Care for People Living with HIV/AIDS: Issues and Problems of Social Integration in Nigeria. *Niger J Med*.2003; 12:12-21.
10. Adebayo RA, Irinoye OO, Oladoyin MA, et al. Community-home Based Care (CHBC) for People Living with HIV/AIDS.Example from Living Hope Care and Support Organization in Osun State, Nigeria. *African Journal of Nursing and Midwifery*. 2004; 6:49-55.
11. Olusegun-Joseph DA, Ajuluchukwu JN, Okany CC, et al. Echocardiographic patterns in treatment-naive HIV-positive patients in Lagos, South-West Nigeria.*Cardiovasc J Afr*.2012;23(8):e1-e6.
12. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? *Curr Opin HIV AIDS*.2014;9 (1):54-62.

HIV AND THE GASTROINTESTINAL TRACT

DA OFUSORI, PHD AND BA FALANA, PHD

Human immunodeficiency virus (HIV) has been known to cause Gastrointestinal Tract (GIT) dysfunction characterized by tubulin depolymerization, induction of local cytokines, and breakage in the defence mechanism thus leading to a wide range of clinical and pathogenic consequences. GIT symptoms that are associated with HIV infection include HIV enteropathy, GIT bleeding, abdominal pain, and diarrhea amongst others. The introduction of highly active antiretroviral therapy (HAART) has drastically reduced opportunistic aetiologies, along with HIV enteropathy. HAART not only improves the systemic immune system but also the local cellular immunity of the GIT.

The GIT consists of the stomach and intestine. The GIT plays a vital role in the digestion of food making the ingesta absorbable into the system. Various diseases take their toll on the GIT (1, 2, 3). HIV is a lentivirus that is found in the body fluids of an infected person such as breast milk, semen and vaginal fluids and blood. It gradually attacks the immune system, which is the body's natural defence against illness. In the GIT, the histoarchitecture of the mucosa presents a tight epithelial junction which allows the local immune system of the GIT to protect against any pathogenic organisms (4). A breakage in the defence mechanism in a situation such as HIV infection leads to a wide range of clinical and pathogenic consequences. This is because the GIT serves as an important barrier between pathogens in the external environment and the body's sterile internal environment (5). This allows for opportunistic infections of the GIT in individuals with a "preserved" immune system (lowest cluster of differentiation (CD) 4 count greater than 200 cells/mm^3) (6). There are several GIT symptoms that are associated with HIV infection; these range from HIV enteropathy, GIT bleeding, abdominal pain, diarrhea, etc. It should also be noted that multiple GI symptoms are also common in the case of HIV infection (6).

Types of GIT Symptoms Associated with HIV Infection

HIV enteropathy

Several microanatomical changes are associated with the GIT mucosa in cases of HIV infection. These changes were first observed and termed "HIV enteropathy" (7).

The consequence of HIV enteropathy is tubulin depolymerization and induction of local cytokines (4). Apart from structural and immunological abnormalities, HIV enteropathy is also characterized by altered epithelial ionic balances and enterocyte apoptosis (5, 8, 9). Microstructural evaluation of the small and large intestine by Sestak (10); Zeitz et al. (11); and Clayton et al. (12) revealed villous atrophy, crypt hyperplasia, and epithelial hypoproliferation. All these structural deficiencies result in inflammation, increased permeability, and malabsorptions (of bile acids and vitamin B12) (4).

GIT bleeding

Diagnostic and therapeutic challenges may be difficult in cases of GIT bleeding which occur in less than 1% of patients with HIV disease (6). It should be noted that GIT bleeding also occurs in HIV-associated opportunistic infections such as stress-related ulcer disease, inflammatory bowel disease, diverticular disease and colonic polyps, and neoplasia. None of these diseases occur more commonly in HIV-infected patients than in healthy persons (13, 14).

The likelihood that upper gastrointestinal (GI) bleeding is related to HIV infection is reliant on the patient's CD4+ cell count; the lower the CD4+ cell count, the greater is the likelihood of having an HIV-related cause of the bleeding (15). Other causes of upper GI bleeding in HIV-infected patients include Kaposi's sarcoma (KS), bacillary angiomatosis, and mucosal ulcerations secondary to viral diseases. In the upper endoscopic examination by Bernardo et al. (16), violaceous plaque-like lesions and several patchy erythematous and haemorrhagic lesions were observed in the stomach (Fig. 1).

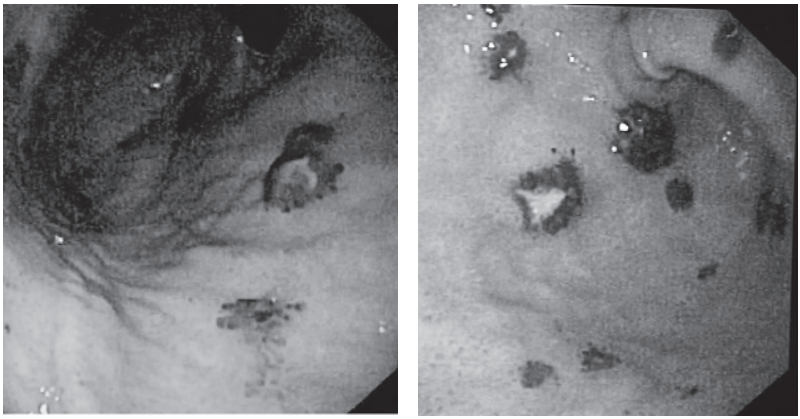


Figure 1: Showing upper endoscopy of fundus, body, and antrum of the stomach with multiple patchy, raised, erythematous and haemorrhagic lesions of 8 mm diameter (16)

Anorectal Disease

Masses or fissures may easily be palpated in the region of the anal canal in the HIV-infected patient. It is therefore often suggested that patients with anorectal symptoms should have anoscopy and sigmoidoscopy with mucosal biopsy, even if the mucosa appears presumably normal during gross examination. The healing of anorectal disease is highly dependent on the stage of HIV disease; interventions such as surgical or nonsurgical therapy may be employed. Surgery is the best therapy for the earlier stages of HIV infection (17, 18, 19) even though the healing rates may be very slow if the immunity is still low. Success has been achieved using debridement and either systemic or intralesional corticosteroids in patients with idiopathic ulcerations. Efforts should be aimed at identifying infections and providing symptomatic relief, reserving more aggressive measures for those in whom less invasive efforts fail (6).

Abdominal Pain

Abdominal pain is very frequent in patients with HIV infection, and in some cases may present a disastrous complication but as at the time of writing, data are not available on the exact regularity of this symptom. There are several factors to be considered when diagnosing the HIV-infected patient with abdominal pain which range from manifestations of

opportunistic infections to neoplasms and common causes of abdominal pain that occur in otherwise healthy persons (6). Some of the causes of abdominal pain in HIV disease have been documented (20, 21).

Diarrhea

A careful study of the patient's medical history should not be underestimated. Such history will confirm if there are other medications, lactose or food/fatty food intolerance, inadvertent use of cathartics (e.g., megadoses of vitamin C, lactose-containing medications, sorbitol-containing foods), and symptoms suggestive of a systemic infection or neoplasm (6). Even though the clinical history alone may not establish a specific diagnosis due to infection, a careful history can aid in localizing the segment of luminal GI tract most severely involved (6).

Once dietary causes and medications are excluded, the most important goal in evaluating diarrhea in patients with HIV disease is to identify treatable infections or neoplasms. Some of the immediate evaluations should include stool cultures for enteric bacteria, a specimen for Clostridium difficile toxin (in the setting of antibiotic use), and at least three stool specimens for ova and parasite examination (including acid-fast bacilli and trichrome stain) (6). If a diagnosis is not reached following careful stool analysis, sigmoidoscopy or colonoscopy has been advocated (6, 22). A small-bowel biopsy should be obtained in any HIV-infected patient undergoing an upper endoscopy for evaluation of diarrhea (6).

Esophageal Motility disorder

A prospective study documented by Zalar et al. (23) aimed at determining the presence of motility disorders in HIV patients with esophageal symptoms (with or without associated lesions detected by endoscopy) and in HIV patients without esophageal symptoms and normal esophagoscopy. It was concluded that a motility disorder occurs in HIV patients without regard to esophageal symptoms and/or the presence of mucosal esophageal lesions.

Complications associated with patients living with HIV

Liver dysfunction

Hepatic abnormalities have been implicated in patients living with HIV. In fact, they have been documented to be a key issue in the management of HIV-infected patients. In most cases, liver dysfunction corresponds with opportunistic infections such as mycobacteria, microsporidiosis, and cytomegalovirus (24, 25, 26).

Before the development of HAART, treatment was often restricted to symptomatic therapies and/or anti-infective or anticancer therapies characterized by hepatic side effects (27). The advent of HAART (regimens composed of nucleoside reverse-transcriptase inhibitors, protease inhibitors, and/or nonnucleoside reverse-transcriptase inhibitors) resulted in a significant decrease in morbidity and mortality among HIV-infected patients (27, 28).

Prompt diagnosis of hepatic abnormalities in HIV patients enhances the effectiveness of HAART and by extension, enhances the survival rate of HIV-infected patients. Other pathogenic mechanisms implicated in HIV patients with liver abnormalities may hinder or prompt an accurate diagnosis as shown in Figure 2.

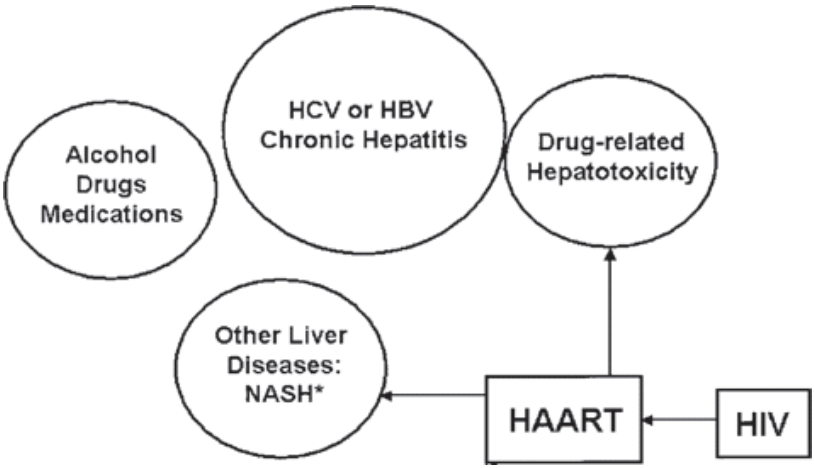


Figure 2: Showing potential causes of liver enzyme elevations in HIV-infected patients (27)

Hepatobiliary Abnormalities

The liver and biliary tract can easily be infected in HIV/acquired immunodeficiency syndrome (AIDS) patients. Keaveny and Karasik (29) noted that a variety of viral, bacterial, fungal, and other opportunistic infections can present with hepatobiliary involvement at either the primary site of infection or secondary to a disseminated process. It was particularly noted that co-infections with hepatitis B and C are frequent as a result of a shared means of transmission of these viruses with HIV. The typical presenting features of hepatobiliary infections are right upper quadrant (RUQ) pain and abnormal liver function tests. Initial evaluation should include a RUQ ultrasonogram, which will usually identify abnormalities in the biliary tract and may demonstrate some parenchymal abnormalities as well (29). Chung et al. (30) observed hepatobiliary abnormalities in sonography in children with HIV infection. Out of 41 children with HIV infection 26 (63%) were presented with hepatobiliary abnormalities; with Hepatomegaly prominent in 13 patients while abnormal hepatic echotexture was evident in 13 patients.

Lymphoma of the GIT and HIV

Malignancies are the major cause of about 10% of HIV-related deaths in the past (31). This is because HIV leads to impairment of cellular immunity which eventually climaxes into a condition known as neoplasms (32, 33, 34, 35). It is disheartening to know that even with a good initial response to chemotherapy HIV-associated GI lymphoma has a poorer prognosis and a higher perforation rate than HIV negative patients (36). With the advent of antiretroviral therapy (ART), there has been some improvement (31). The gastrointestinal tract (GIT) is the common site of extranodal lymphomas (37). There is close proximity between GIT lymphomas and chronic inflammation. An understanding of marginal zone and mucosa-associated lymphoid tissue (MALT) in health and disease has made diagnosis easier (38).

In patients living with HIV, the following malignancies are recognizable:

1. KS:

KS is a vascular tumour caused by human herpes virus 8 (HHV8) infection. There are basically 4 types of KS (16):

i Classic – occurs in elderly men and it is associated with visceral disease just in 10% of cases;
ii Endemic/African – more common in children;
iii Iatrogenic – occurs due to suppressed immunity in organ transplantation; and
iv AIDS-related KS.

It should be noted that AIDS-related KS is not curable and its treatment with HAART and pegylated liposomal doxorubicin (LD) is palliative (16). GI KS is diagnosed less in patients with HIV infection despite being the most common neoplasm among HIV-infected individuals. Patients with GI KS have other health issues such as skin lesions. KS in the GI tract can be diagnosed immunohistochemically by adopting the methods for CD31, CD34, and LNA-1. Silva et al. (39) evaluated the extension of KS in HIV-infected patients by performing an upper GI endoscopy. The result identified reddish elevated lesions in the body of the stomach as shown in Fig. 3 which is suggestive of KS lesions. On histological examination, spindle-cell proliferation within the submucosa was evident (Fig. 4). Further investigation using immunochemistry for CD31 and multiple cells positive for human herpes virus 8 (HHV8) confirmed the diagnosis of KS (Fig. 5).

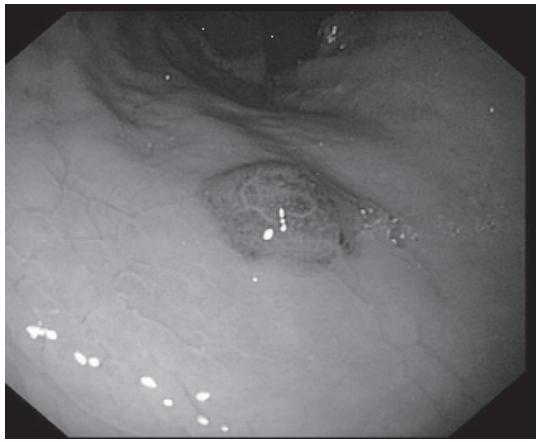


Figure 3: Endoscopic findings, revealing reddish, elevated lesions in the greater curvature of the proximal body (39)

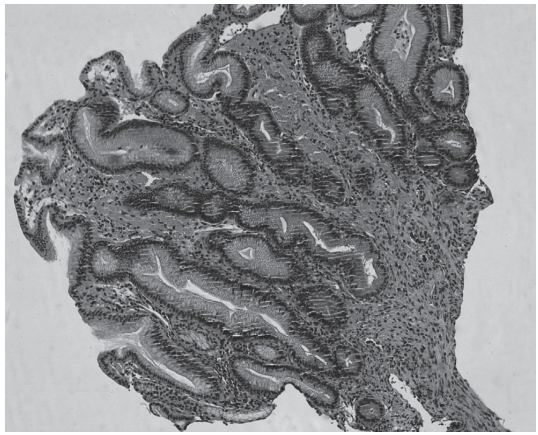


Figure 4: Haematoxylin and eosin stain showing spindle cell proliferation in the submucosa (39)

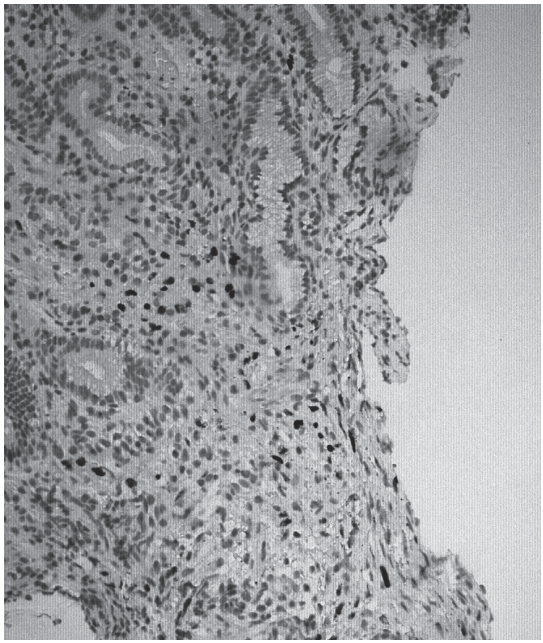


Figure 5: Immunohistochemical stain for human herpes virus 8 showing a diffusely positive latent nuclear antigen staining of the spindle cells, confirming the diagnosis of diffuse visceral Kaposi's sarcoma (39)

Endoscopic evaluation is the best option for AIDS patients who present with GI symptoms (40). If, however, the patient is asymptomatic, the relevance of endoscopy remains a topic of debate. In any case, early endoscopic evaluation allows a proper KS staging and selection of the appropriate therapeutic options, preventing complications associated with the progression of the disease (39).

2. Non-Hodgkin's lymphoma (NHL)

HIV-associated non-Hodgkin's lymphoma (NHL) has been described by Kaplan (31) as the most commonly diagnosed lymphoma in patients with advanced HIV, a low CD4 count (often <100 cells/μL), a high HIV viral load, and a prior diagnosis of AIDS. The advent of antiretroviral therapy (ART) has reduced the incidence of HIV-associated NHL (41, 42, 43, 44, 45, 46). The risk of NHL has continued to be directly related to the CD4 count (47). Hodgkin's lymphoma (HL) is a non-AIDS-defining malignancy associated with severe immunosuppression (48).

Conclusion

The introduction of HAART has drastically reduced opportunistic aetiologies, along with HIV enteropathy (49). HAART not only improves the systemic immune system but also the local cellular immunity of the GIT.

References

1. Patel DN, Pradeep P, Surti MM, Agarwa SB. Clinical Manifestations of Complicated Malaria – An Overview. *JIACM* 2003; 4(4): 323-31
2. Alvarez-Ordonez A, Begley M, Prieto M, Messens W, Lopez M, Bernardo A. Salmonella spp. CH. survival strategies within the host gastrointestinal tract. *Microbiology* 2011; 157: 3268-3281.
3. Ofusori DA, Komolafe OA and Adewole OS. Ethanolic Leaf Extract of Croton zambesicus (MÜll. Arg.) Improves Gastric Emptying Capacity and Gastric Mucosa Integrity in Streptozotocin-induced Diabetic Rats. *International Journal of Diabetes Research* 2012; 1(4): 58-67.
4. Crum-Cianflone NF. HIV and the Gastrointestinal Tract. *Infect Dis ClinPract* (Baltim Md). 2010; 18(5): 283-285.
5. Kotler DP. HIV infection and the gastrointestinal tract. *AIDS*. 2005; 19: 107-117.

6. Koch J, Kim LS, Friedman S. Gastrointestinal Manifestations of HIV. HIV in site knowledge base chapter http://hivinsite.ucsf.edu/ InSite?page=kb-04-01-11 retrieved 26-03-2018.
7. Kotler DP, Gaetz HP, Lange M, Klein EB, Holt PR. Enteropathy associated with the acquired immunodeficiency syndrome. *Ann Intern Med*. 1984; 101(4): 421-8.
8. Maresca M, Mahfoud R, Garmy N, et al. The virotoxin model of HIV-1 enteropathy: involvement of GPR15/Bob and galactosylceramide in the cytopathic effects induced by HIV-1 gp120 in the HT-29-D4 intestinal cell line. *J Biomed Sci*. 2003; 10: 156-166.
9. Schmitz H, Rokos K, Florian P, et al. Supernatants of HIV-infected immune cells affect the barrier function of human HT-29/B6 intestinal epithelial cells. *AIDS*. 2002; 16: 983-991.
10. Sestak K. Chronic diarrhea and AIDS: insights into studies with non-human primates. *Curr HIV Res*. 2005; 3: 199-205.
11. Zeitz M, Ullrich R, Schneider T, et al. HIV/SIV enteropathy. *Ann N Y Acad Sci*. 1998; 859: 139-148.
12. Clayton F, Snow G, Reka S, et al. Selective depletion of rectal lamina propria rather than lymphoid aggregate CD4 lymphocytes in HIV infection. *ClinExpImmunol*. 1997; 107: 288-292.
13. Cappell MS, Geller AJ. The high mortality of gastrointestinal bleeding in HIV-seropositive patients: A multivariate analysis of six factors and warning signs of mortality in 50 consecutive patients. *Am J Gastroenterol* 1992; 87: 815-824.
14. Cello JP, Wilcox CM. Evaluation and treatment of gastrointestinal tract hemorrhage in patients with AIDS. *GastroenterolClin North Am* 1988; 17: 639-648.
15. Balderas V, Spechler SJ. Upper gastrointestinal bleeding in a patient with AIDS. *Nat Clin Pract Gastroenterol Hepatol*, 2006; 3: 349-53.
16. Bernardo S, Fernandes SR, Ribeiro LC. Kaposi's Sarcoma – An Unusual Cause of Upper Gastrointestinal Bleeding Sarcoma Kaposi. *GE Port J Gastroenterol*. 2016; 23(5): 267-269.
17. Burke EC, Orloff SL, Freise CE, et al. Wound healing after anorectal surgery in human immunodeficiency virus-infected patients. *Arch Surg*. 1993; 126: 1267-1271.
18. Schmitt SL, Wexner SD, Nogueras J. Is aggressive management of perianal ulcers in homosexual HIV-positive men justified. *Dis Colon Rectum* 1993; 36: 240-246.
19. Safavi A, Gottesman L, Dailey TH. Anorectal surgery in the HIV-positive patient: An update. *Dis Colon Rectum* 1991; 34: 299-304.

20. Potter DA, Danforth DN, Macker AM, et al. Evaluation of abdominal pain in the AIDS patient. *Ann Surg* 1984; 199: 332-339.
21. Wexner SD, Smithy WB, Trillo C, et al. Emergency colectomy for cytomegalovirus ileocolitis in patients with the acquired immunodeficiency syndrome. *Dis Colon Rectum* 1988; 31: 755-761.
22. Dietrich DT, Rahmin M. Cytomegalovirus colitis in AIDS: Presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr Hum Retrovirol* 1991; 4: S29-S35.
23. Zalar AE, Olmos MA, Piskorz EL, Magnanini FL. Esophageal motility disorders in HIV patients. *Dig Dis Sci*. 2003; 48(5): 962-7.
24. Lebovics E, Dworkin BM, Heier SK, Rosenthal WS. The hepatobiliary manifestations of human immunodeficiency virus infection. *Am J Gastroenterol*, 1988, 83: 1-7.
25. Lefkowitch JH. Pathology of AIDS-related liver disease. *Dig Dis*, 1994;12:321-30.
26. Cappell MS. Hepatobiliary manifestations of the acquired immune deficiency syndrome. *Am J Gastroenterol*, 1991; 86: 1-15.
27. Pol S, Lebra P, Vallet-Pichard A. HIV Infection and Hepatic Enzyme Abnormalities: Intricacies of the Pathogenic Mechanisms. *Clinical Infectious Diseases*. 2004; 382(1): S65–S72, https://doi.org/10.1086/381499.
28. Lipsky JJ. Antiretroviral drugs for AIDS. *Lancet*, 1996; 348: 800-3.
29. Keaveny AP, Karasik MS. Hepatobiliary and pancreatic infections in AIDS: Part one. *AIDS Patient Care STDS*. 1998; 12(5): 347-57.
30. Chung CJ, Sivit CJ, Rakusan TA, Chandra RS, Ellaurie M. Hepatobiliary Abnormalities on Sonography in Children with HIV Infection. *J Ultrasound Med.* 1994; 13: 205-210.
31. Kaplan LD. AIDS-related lymphomas: Clinical manifestations, diagnosis, and staging of systemic lymphoma. https://www.uptodate.com/contents/aids-related-lymphomas-clinical-manifestations-diagnosis-and-staging-of-systemic-lymphoma retrieved 25-02-18.
32. Levine AM. AIDS-related malignancies. *Curr Opin Oncol*. 1994; 6: 489.
33. Conant MA. Management of human immunodeficiency virus-associated malignancies. *Recent Results Cancer Res*. 1995; 139: 423.
34. Rabkin CS. Epidemiology of AIDS-related malignancies. *Curr Opin Oncol*. 1994; 6: 492.
35. Levine AM, Pieters AS. Non-AIDS defining cancer. In: *The First National AIDS Malignancy Conference*, National Cancer Institute, Bethesda, MD 1997: 18.

36. Imrie KR, Sawka CA, Kutas G, Brandwein J, Warner E, Burkes R. HIV-Associated Lymphoma of the Gastrointestinal Tract: The University of Toronto AIDS-Lymphoma Study Group Experience. *Leukemia & Lymphoma*. 1995; 16(3-4): 343-349.
37. Cardona Diana M, Layne Amanda, Lagoo An and S. Lymphomas of the gastro-intestinal tract. *Pathophysiology, pathology, and differential diagnosis*. 2012; 55(1): 1-16.
38. Rezende RE, Kahwage RL, da Costa TV, Machado AA, Brunaldi MO, Kemp R, Módena JL. Upper gastrointestinal Kaposi's sarcoma in HIV-infected patients: ten years of endoscopy observation at a single Brazilian center. *Int J Infect Dis*. 2015; 39: 110-5. doi: 10.1016/j.ijid.2015.09.006. E-pub 2015 Sep 14.
39. Silva M, Maia T, Macedo G. Upper Gastrointestinal Kaposi's Sarcoma in an HIV-Infected Patient. *GE Port J Gastroenterol.* 2016; 23(6): 316-318.
40. Bower M, Palfreeman A, Alfa-Wali M, Bunker C, Burns F, Churchill D, et al. British HIV Association guidelines for HIV-associated malignancies 2014. *J Clin Oncol.* 2010; 28: 250-251.
41. International Collaboration on HIV and Cancer (ICHC). Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* 2000; 92: 1823.
42. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood* 2001; 98: 2339.
43. Diamond C, Taylor TH, Aboumrad T, Anton-Culver H. Changes in acquired immunodeficiency syndrome-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: incidence, presentation, treatment, and survival. *Cancer* 2006; 106: 128.
44. Levine AM, Seneviratne L, Espina BM, et al. Evolving characteristics of AIDS-related lymphoma. *Blood* 2000; 96: 4084.
45. Stebbing J, Gazzard B, Mandalia S, et al. Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol* 2004; 22: 2177.
46. Seaberg EC, Wiley D, Martínez-Maza O, et al. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. *Cancer* 2010; 116: 5507.
47. Bower M, Fisher M, Hill T, et al. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. *Haematologica* 2009; 94: 875.

48. Biggar RJ, Jaffe ES, Goedert JJ, et al. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood* 2006; 108: 3786.
49. Kearney DJ, Steuerwald M, Koch J, et al. A prospective study of endoscopy in HIV-associated diarrhea. *Am J Gastroenterol*. 1999; 94(3): 556-9.

RENAL DISEASES IN HIV/AIDS

OYEKUNLE OLAYANJU OYEBISI
MBBS, FMCP
AND OLUTAYO CHRISTOPHER ALEBIOSU
BSC, MBCHB, FWACP

Nigeria has the second highest burden of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the world with a national HIV prevalence of 3.4%. Two-thirds of all new HIV infections worldwide in 2015 were in sub-Saharan Africa. There has been a rise in the scourge of HIV in the last 20 years but mortality has reduced considerably due to the advent of anti-retroviral drugs (ARD), which were introduced in 1985.

Renal involvement can occur at all stages of HIV infection and can be the initial clue to the presence of HIV infection in an undiagnosed patient but HIV-associated nephropathy (HIVAN) is one of the syndromes directly caused by HIV infection. However, recent studies suggest that the spectrum of chronic kidney disease in HIV-infected patients is changing with less HIVAN and more comorbid kidney disease, such as that caused by hypertension and diabetes. Renal involvement in HIV disease can also occur due to other causes as seen in the non-HIV-infected population like exposure to nephrotoxic medications, haemodynamic changes during an acute illness, and obstruction. HIVAN is associated with rapidly deteriorating renal function with a high rate of progression to end-stage renal disease (ESRD). These patients usually have poorly controlled HIV infection characterized by a low CD4 count and a high HIV RNA load.

The pharmacologic agents used for the treatment of HIVAN include highly active antiretroviral therapy (HAART), steroids, and angiotensin-converting enzyme inhibitors. The introduction of HAART was shown to be associated with a reduction in HIVAN incidence.

HIV is a lentivirus of a subgroup of the retrovirus family. It causes HIV infection and acquired immunodeficiency syndrome in humans (1). There has been a rise in the scourge of HIV in the last 20 years but the number of mortalities has reduced considerably due to the advent of anti-retroviral drugs which were introduced in 1985. HAART has increased survival and physicians are left to deal with more chronic, non-AIDS complications emerging from multiple organ system affectations (2).

The kidney is one of the most vulnerable organs affected by HIV and various forms of renal complications are now seen due to this prolongation of life of people living with HIV (3). Renal involvement can occur at all stages of HIV infection and can be an initial clue to the presence of HIV infection in an undiagnosed patient. Renal involvement in HIV disease can also occur due to other causes as seen in the non-HIV infected population like exposure to nephrotoxic medications, haemodynamic changes during an acute illness, and obstruction. The renal syndromes that occur in HIV patients range from Acute Kidney Injury (AKI) to chronic kidney diseases (CKD) leading to end-stage renal disease (ESRD). Various other forms of electrolyte imbalance could also occur in HIV.

Epidemiology

Thirty-three million people globally are living with HIV and about two-thirds are in sub-Saharan Africa (4). The prevalence varies widely across Africa. The highest prevalence is in South African countries at about 15% and the lowest is in North Africa, about 1% (4). Nigeria accounts for 9% of people with HIV globally despite a low prevalence of 3.2%. The population of Nigeria has put the country on the global map of HIV and thus has more chronic complications such as renal syndromes to deal with.

Acute Kidney Injury (AKI)

Prior to the advent of HAART, acute kidney injury (AKI) was common and mostly due to opportunistic infections, often leading to a poor outcome. AKI is defined as a precipitous drop in renal function. Consensus guidelines for the management of kidney disease in patients with HIV recommend a definition of acute renal failure based on an increase in serum creatinine >1.5 mg/dl or 1.3 times the upper limit of normal that returns to baseline values within three months (6). AKI increases the morbidity and mortality in HIV patients (7). The incidence of AKI defined as the peak serum creatinine level of ≥2 mg/dl was reported

to be 20%. The consequences of AKI are electrolyte derangement, metabolic acidosis, pulmonary oedema, and encephalopathy.

Causes of AKI in HIV

In HIV-infected patients, immunodeficiency may be the greatest risk factor for AKI (8). However, many of the common risk factors for AKI are similar in both the HIV-infected and non-HIV-infected populations, such as older age, diabetes, and exposure to nephrotoxic agents, pre-existing CKD, and hepatitis co-infection or liver diseases. Risk factors specific to HIV are advanced stages of HIV infection (e.g., a CD4 cell count of < 200 cells/mm^3 and an HIV RNA level of >10,000 copies/mL) and the use of antiretroviral medications.

The causes of AKI can be divided into pre-renal, renal, and post-renal causes. Pre-renal azotaemia and acute tubular necrosis (ATN) remain the most common causes of AKI in HIV-infected individuals (38% and 35% respectively). Patients with AIDS are at high risk of pre-renal azotaemia which results from vomiting, fever, and poor oral intake due to underlying illness. ATN results from sepsis causing ischaemic ATN in up to 50% of cases. Nephrotoxic medications are used in the treatment of opportunistic infections, such as antibiotics (aminoglycosides), antifungals (amphotericin B), antivirals (acyclovir, ganciclovir), anti-tuberculosis drugs, pentamidine, and anti-inflammatory drugs (9).

Less common causes include immune restoration inflammatory syndrome, direct infectious insults from parenchyma fungal infections and granulomatous nephritis from Mycobacterium. Rhabdomyolysis, especially in association with the use of heroin, cocaine and statin, is a rare cause of AKI and obstruction should be considered when the underlying process is not obvious (11).

Chronic kidney disease

The National Kidney Foundation has endorsed the term “chronic kidney disease” (CKD), defined as evidence of kidney damage that persists for >3 months. CKD is defined as either proteinuria, a marker of kidney damage, or a glomerular filtration rate (GFR) <60 mL/min for ≥3 months (12). The prevalence of HIV-related renal diseases is on the increase; they are associated with proteinuria and progress rapidly to end-stage renal failure (7). This is associated with the worst outcome. A cross-sectional study

from South Africa revealed HIVAN in 83%, membranoproliferative nephropathy in 7% and interstitial nephritis in 10% of patients (17).

HIV-Associated Nephropathy

HIV-associated nephropathy (HIVAN) is one of the chronic kidney diseases directly caused by HIV infection (12). It is a common phenomenon in HIV-infected individuals. It was observed from the early 1980s that some specific form of glomerular disease is associated with HIV. Reports from Miami and New York described a characteristic renal lesion named HIVAN, with histological features of focal and segmental glomerulosclerosis that was associated with nephrotic range proteinuria and rapidly progressive renal failure (13).

HIVAN is commoner among blacks (Afro-Americans) and rare among white American homosexuals (10-12). This is the most common cause of CKD, occurring in 12% to 15% of HIV-infected black patients. Classically this is a late manifestation of HIV infection associated with low CD4 counts and high viral loads and characterized by nephrotic-range proteinuria, increased kidney echogenicity on ultrasound, lack of hypertension, or oedema and progressive kidney failure. Histological examination of the kidneys reveals collapsing focal and segmental glomerulosclerosis, tubular epithelial atrophy with microcystic dilatation of the tubules and lymphocytic interstitial infiltration. HIV viral replication in kidney cells is a prerequisite for disease development, circulating viral RNA is associated with kidney disease progression, and effective inhibition of viral replication improves kidney function and prolongs kidney survival. An allele that confers protection against infection by *Trypanosomabrucei*, a parasite commonly found in Africa, has been linked to greater susceptibility to non-diabetic kidney disease among blacks (16). Other known risk factors include hepatitis C virus (HCV) co-infection, family history, increased viral load levels (>4000 copies/mL) and reduced CD4 cell count.

Non-HIVAN renal lesions are becoming increasingly more common in HIV, likely due to both a change in the natural course of the disease and to the nephrotoxic effects of antiretroviral medications, such as Tenofovir and Indinavir e.g., HIV-specific immune-complex mediated glomerulonephritis, thrombotic microangiopathy, membranoproliferative glomerulonephritis, and membranous nephropathy are becoming increasingly common (14, 15).

HIV Immune Complex Mediated Kidney Diseases

The term HIV immune complex mediated kidney disease (HIVICK) represents a variety of histological entities with common aetiological features including deposited immune complexes containing HIV antigens, characteristic cytokine expression profiles, genetic factors, inflammatory infiltrates, and the development of kidney scarring. Among the many reported pathologies, immunoglobulin A (IgA) nephropathy is relatively common and believed to result from immune complexes that contain HIV antigens. Lupus-like nephropathy typically presents with microscopic haematuria, proteinuria and renal impairment with relatively rapid progression to kidney failure. Histologically there may be diffuse or focal proliferative changes, membranous nephropathy, crescent formation, and tubule-interstitial scarring. Optimal management is unclear and some series have failed to show that HAART influences progression to ESRD (17).

The prevalence of HIVICK is highly variable in the different studies. A study of 60 biopsies found that some form of HIVICK was present in 37% of biopsy specimens. HIVICK may present as post-infectious glomerulonephritis and includes membranous nephropathy, IgA nephropathy, lupus-like glomerulonephritis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and membranoproliferative glomerulonephritis (19).

Thrombotic microangiopathy, haemolytic uraemic syndrome, and thrombotic thrombocytopenic purpura present a spectrum of diseases characterized by haemolytic anaemia, thrombocytopenia, renal insufficiency, and clinical features, such as fever and neurological manifestations. Several reports have linked thrombotic microangiopathy to HIV infection, suggesting that HIV proteins may mediate endothelial dysfunction, leading to platelet deposition in the microvasculature.

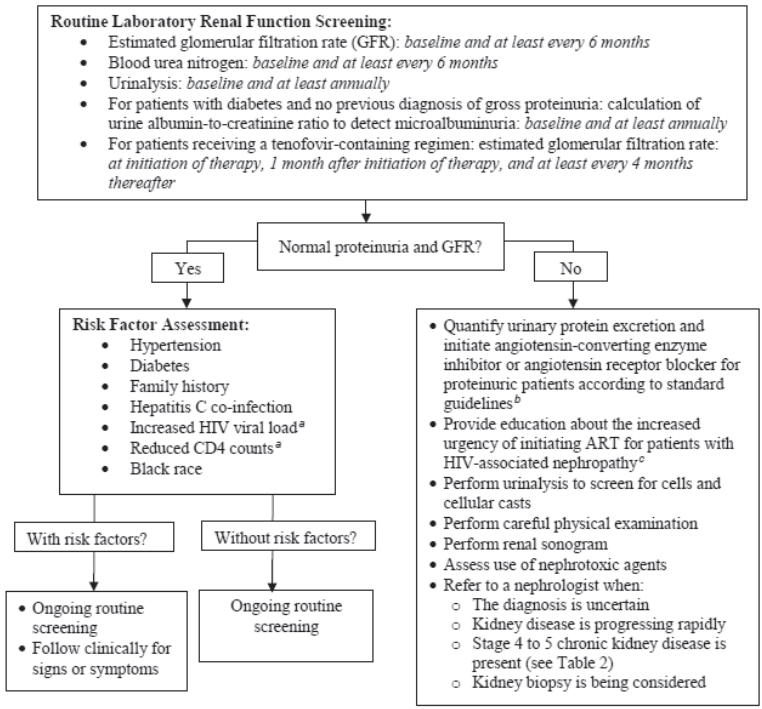
Therapeutic options consist of plasma infusion and plasmapheresis, which have had variable success. Other attempted therapies include glucocorticoids, immunoglobulin infusions, antiplatelet drugs, vincristine, and splenectomy. However, general treatment recommendations are lacking (7, 20).

CKD is defined by KDIGO and is divided into groups based on confirmed eGFR levels (≥ 3 months) (21). The stages of CKD are as shown in the table below.

Staging of Chronic Kidney Disease

Stage	Description	GFR(mL/min)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 (or dialysis)

Figure 1. Steps for screening and initial management of kidney disease.



[a] The Infectious Disease Society of America indicates viral load levels of >4000 copies/mL and CD4 counts of <350 cells/mm^3 as risk factors for kidney disease.[11]

[b] See Section VI. B. *Management of Comorbid Hyperglycemia, Dyslipidemia, Anemia, and Hypertension.*

New York State Department of Health AIDS Institute: www.hivguidelines.org

Changing spectrum of CKD

It was observed in 2004 that nearly half the cases of CKD in HIV-infected patients were caused by HIVAN. Smaller proportions of CKD were caused by immune complex disease, membranous/membranoproliferative glomerulonephritis in association with viral hepatitis, and diabetes or hypertension is implicated. An even smaller proportion was caused by acute interstitial nephritis (22). However, recent studies suggest that the spectrum of CKD in HIV-infected patients is changing with less HIVAN and more comorbid kidney disease, such as that caused by hypertension and diabetes (23).

Clinical Features

Patients with HIVAN typically present with proteinuria. This proteinuria is variable in magnitude, usually heavy in the nephrotic range (>3 gm/day), but can be mild and sometimes present only as microalbuminuria. HIVAN is associated with rapidly deteriorating renal function with a high rate of progression to ESRD. These patients usually have poorly controlled HIV infection characterized by a low CD4 count and a high HIV RNA load. Besides heavy proteinuria, many patients with HIVAN do not exhibit significant oedema or hypertension. A recent study noted that 43% of patients with biopsy-proven HIVAN did not have hypertension. The serum albumin levels remain above 3 gm/dl besides heavy proteinuria. On the contrary, patients with early HIVAN lesions may have normal renal function, microalbuminuria or mild proteinuria. Renal function may remain stable for many years in these patients. Urinalysis usually shows bland sediment with a varying number of proteinaceous casts, oval fat bodies, and renal tubular epithelial cells. Abdominal ultrasound reveals relatively large, echogenic kidneys. Ultrasound findings have limited predictive value. Serologic markers are usually negative in these patients on work up. A diagnostic renal biopsy is usually indicated for diagnosis.

Glomerular Filtration Rate

A glomerular filtration rate (GFR) of <60 mL/min meets the criteria for CKD; this threshold is supported by epidemiologic data linking a low GFR to an increased frequency of hospitalization, cardiovascular events, or death (18). The GFR should be calculated in all the patients with HIV whether on ART or not using one of the following three equations:

1. *Chronic Kidney Disease Epidemiology Consortium (CKD-EPI):* Estimates the GFR based on age, race, and serum creatinine.
2. *Modification of diet in renal disease (MDRD)*: Estimates the GFR based on age, race, sex, and serum creatinine.
3. *Cockcroft-Gault*: Calculates creatinine clearance based on serum creatinine, age, weight, and sex.

Urine Protein Excretion

The most sensitive indicator of kidney damage is elevated urinary protein excretion, measured qualitatively using a urine dipstick or quantitatively using a spot urine protein-to-creatinine ratio or a 24-hour urine collection.

For patients with ≥1+ by urinary dipstick, urinary protein excretion should be quantified using the protein-to-creatinine ratio from a random sample of urine or a 24-hour urine collection. Patients with heavy proteinuria and an apparently normal GFR may have worse clinical outcomes than those with a moderately reduced GFR and normal proteinuria (20).

Diagnosis and Evaluation of Kidney Disease

It is recommended that all patients with a borderline glomerular filtration rate, regardless of age, should undergo the following diagnostic evaluation of kidney function:

a) Urinalysis to screen for cells and cellular casts;
b) Quantification of urinary protein excretion;
c) Renal sonogram;
d) Careful physical examination.

Renal Ultrasound Scan

This gives information about kidney size and structure and can demonstrate obstructive uropathy or small, echogenic kidneys diagnostic of chronic disease. The test is readily available, non-invasive, and inexpensive.

Kidney Biopsy

Biopsies have the greatest clinical utility in patients with acute glomerulonephritis or unexplained CKD, especially in the setting of heavy

proteinuria (defined as 24-hour urinary protein excretion of >2000 mg or a protein-to-creatinine ratio >2000 mg/g creatinine) or in patients with relatively rapid decreases in GFR, because they are at high risk for progression to ESRD. Most nephrologists would treat a proteinuric patient (e.g., 24-hour urinary protein excretion of >300 mg/g or a protein-to-creatinine ratio of >200 mg/g creatinine) with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), regardless of whether or not a biopsy is obtained. However, a definitive diagnosis of HIVAN cannot be made without a biopsy. Other indications for biopsy are not different from the general population without HIV.

Management

Pharmacologic agents used for the treatment of HIVAN include HAART (24), steroids, and angiotensin-converting enzyme inhibitors. The introduction of HAART was shown to be associated with a reduction in HIVAN incidence (24).

Therapeutic options for HUS consist of plasma infusion and plasmapheresis, which have had variable success. Other attempted therapies include glucocorticoids, immunoglobulin infusions, antiplatelet drugs, vincristine, and splenectomy, although general treatment recommendations are lacking (7, 25).

HIV and ESRD

HIVAN is the third leading cause of ESRD despite the stabilization of the incidence of HIVAN-related ESRD that has occurred with the wide use of antiretroviral therapy. This may be due to the prevalence of ESRD from non-HIV causes. Haemodialysis, peritoneal dialysis, and kidney transplantation are all options for managing ESRD in HIV-infected patients. Survival rates are very similar with haemodialysis and peritoneal dialysis in HIV-infected patients with ESRD. Early referral is essential to prepare the patient for renal replacement therapy. Antiretroviral drug regimens and doses should be monitored in patients who are on dialysis and a dose and regimen appropriately adjusted. A National Institute of Health-sponsored study assessed outcomes of kidney transplantation in 150 HIV-infected patients with an undetectable viral load, a CD4+ cell count greater than 200/μL, and stable antiretroviral therapy (11). Patient and graft survival rates were acceptable, being somewhat poorer than rates in the overall transplant population and somewhat better than those among

HIV-uninfected transplant recipients older than 65 years. No increase in frequency of opportunistic infections was observed, and the 5 AIDS-defining illnesses that occurred can also be observed in HIV-uninfected kidney transplant recipients. However, substantial drug interactions occurred, particularly with protease inhibitors and non-nucleoside analogue reverse transcriptase inhibitors. It is crucial that any potential changes in antiretroviral regimens in the post-transplantation period could affect the trough level of immunosuppression and it should be discussed with the transplant team. This is to avoid graft loss.

References

1. Weiss RA. How does HIV cause AIDS? *Science* 260(5112): 1273-9.
2. Lima VD, Hogg RS, Harrigan PR, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS* 2007 Mar; 21(6): 685–92.
3. Krentz HB, Kliewer G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Med*. 2005 Mar; 6(2): 99–106.
4. Joint United Nations Programme on HIV/AIDS (UNAIDS) 2008. 2008 Report on the global AIDS epidemics.
5. USAIDS. Epidemiological Fact Sheet on HIV and AIDS in Nigeria, 2014.
6. Hilton R. Acute renal failure. *BMJ*. 2006; 333: 786-790.
7. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005 Jun; 40(11): 1559–85.
8. Ibrahim F, Naftalin C, Cheserem E, et al. Immunodeficiency and renal impairment are risk factors for HIV-associated acute renal failure. *AIDS* 2010; 24: 2239–2244.
9. Choi, et al. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int*. 2010 Sep; 78(5): 478-85.
10. Rao TK, Friedman EA. Outcome of severe acute renal failure in patients with acquired immunodeficiency syndrome. *Am J Kidney Dis* 1995; 25: 390–398.
11. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39: S1–266.

12. Herman ES, Klotman PE. HIV-associated nephropathy: epidemiology, pathogenesis, and treatment. *SeminNephrol.* 2003; 23: 200–8.
13. Gardenswartz MH, Lerner CW, Seligson GR, et al. Renal disease in patients with AIDS: a clinicopathologic study. *Clin Nephrol.* 1984; 21: 197–204.
14. Pardo V, Aldana M, Colton RM, et al. Glomerular lesions in the acquired immunodeficiency syndrome. *Ann Intern Med* 1984 Oct; 101(4): 429-34.
15. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease, and antiretroviral drug use in HIV-positive patients. *AIDS* 2010 Jul 17; 24(11): 1667–78.
16. Genovese G, Tonna SJ, Knob AU, et al. A risk allele for focal segmental glomerulosclerosis in African Americans is located within a region containing APOL1 and MYH9. *Kidney Int* 2010; 78: 698–704.
17. Hilton R, Coll JR. *Physicians Edinb.* 2013; 43: 236–40.
18. Han TM, Naicker S, Ramdial PK, et al. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int* 2006; 69: 2243–50.
19. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS* 2008 Nov; 22(18): 2409–18.
20. Lundgren JD, Battegay M, Behrens G, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med*. 2008 Feb; 9(2): 72–81.
21. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). *Kidney Int.* 2005 Jun; 67(6): 2089–100.
22. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int.* 2004; 66(3): 1145-1152. 9.
23. Berliner AR, Fine DM, Lucas GM, et al. Observations on a cohort of HIV-infected patients undergoing native renal biopsy. *Am J Nephrol.* 2008; 28(3): 478–486.
24. Yahaya I, Uthman OA, Uthman MM. Interventions for HIV-associated nephropathy. *Cochrane Database Syst Rev.* 2013 Jan; 1: CD007183.
25. Lundgren JD, Battegay M, Behrens G, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med*. 2008 Feb; 9(2): 72–81.

HIV and Diabetes Mellitus

Adebimpe Olukemi Yusuf
MBChB, FMCP
and Babatope Kolawole
MBChB, FWACP, FACP, FACE

The occurrence of diabetes mellitus (DM) in Human Immunodeficiency Virus (HIV)-infected patients doubles the challenge of managing such individuals. Diabetes mellitus and HIV are global health issues that can lead to grave complications in the absence of medical intervention. The increasing prevalence of DM in HIV-infected patients has been majorly attributed to the use of HAART (Highly Active Antiretroviral Agent), and the inflammatory process of viral replication is also contributory. Inadequate management of these conditions can lead to a reduction in quality of life, poor adherence to therapy and increased risk of mortality. Therefore, a high index of suspicion, prompt diagnosis and proper management are necessary to avoid preventable complications and death. This chapter therefore reviews the prevalence and the risk factors, together with clinical features, diagnosis and management of DM in HIV-infected individuals.

Human immunodeficiency viral infection is a pandemic and remains a global medical challenge as the cure is still obscure. Millions of people across the globe are hosts to the virus (1) and the prevalence is on the increase majorly because of better management strategies. Another dimension to this global challenge is the increasing prevalence of metabolic abnormalities such as diabetes mellitus (DM) and dyslipidemia in patients infected with Human Immunodeficiency Virus. Most of the metabolic abnormalities became noticeable after the introduction of HAART. Although earlier antiretroviral agents that caused severe glucotoxicity (e.g., pentamidine) have been removed, some of the available ones do have potentials to precipitate glucose intolerance and can increase morbidity in HIV-infected patients.

Diabetes mellitus independently gives rise to lethal complications and its co-existence in HIV-infected patients definitely worsens the prognosis. The prevalence of DM varies across populations all over the world. An increased risk of DM has been observed in elderly patients, males, as well as patients with a high viral burden and a long duration of HIV infection. In addition to features of immunosuppression like recurrent opportunistic infections, classic symptoms of DM may be present together with features of its acute complications or long-term complications such as visual impairment. Untreated diabetes mellitus worsens immunosuppression. Early diagnosis of DM is paramount and the institution of appropriate therapy is vital to a good outcome. Therapy involves lifestyle modification and the use of pharmacologic agents. Different classes of antidiabetic agents can be employed provided there are no contraindications for such, however insulin appears to be the safest medication in HIV-infected diabetic patients irrespective of the comorbidity. Early recognition of glucose intolerance and prompt management go a long way to improve quality of life, boost societal relevance and promote longevity in HIV-infected patients.

Prevalence of Diabetes Mellitus in HIV Patients

The prevalence of diabetes mellitus in HIV-infected patients is variable and dependent on the population being studied. Various studies have recorded prevalence rates in the range of 1.2% to 6.7% before commencement of HAART (2, 3, 4, 5, 6, 7, 8, 9, 10). It stands to reason that in a population with a high prevalence of DM in the general population, the pre-HAART prevalence of DM will be relatively on the higher side compared to the population in which the incidence is low. However significant increases in prevalence rates were observed after the commencement of HAART (compared to pre-HAART baseline values) in various studies carried out in different parts of the world (2, 3, 4, 5, 6, 7, 8). A study carried out by Jyothi et al., reported a baseline prevalence of DM in pre-HAART HIV patients, increasing from 6.7% to 20% after the commencement of HAART (6). Another study from the Women's Interagency HIV Study reported an incidence of DM to be 2.8% in patients treated with protease inhibitor vs. 1.2% in HAART-naive patients and 1.4% in the HIV-negative controls (8).

Risk Factors for Diabetes Mellitus in HIV Patients

There are many factors that can predispose people living with HIV to developing abnormalities in glucose metabolism and diabetes. Some of

these are known (traditional) risk factors for DM and others are related to HIV infection (11).

Age: The risk of developing DM has been found to be higher in patients who are sixty-five years and above in the general population and a similar trend was obtained in the HIV-infected population according to the reports of some researches carried out in these group of patients (10, 12, 13).

Sex: Female patients on HAART have a lower risk of developing diabetes according to studies in developed and developing countries (13, 14, 15, 16).

Obesity: Diabetes tends to occur more commonly among obese HIV-infected patients than patients who are neither overweight nor obese. In earlier research on HIV-infected individuals, the prevalence of diabetes mellitus doubled in obese participants, compared with those having a normal body mass index (16).

HIV infection: Infection with HIV induces a chronic inflammatory state that results in the significant lowering of adiponectin levels, and this lowering favours the development of insulin resistance. This occurs more often in patients with a low CD4 count, a high viral burden, and chronic HIV infection (17).

"Return to health phenomenon" (11): A positive response to treatment with HAART promotes weight gain, improves appetite, and increases caloric intake. However, excessive caloric intake can lead to obesity. Obesity promotes insulin resistance and can result in diabetes in genetically predisposed individuals (11).

Hepatitis C co-infection: The co-existence of Hepatitis C Virus (HCV) infection with HIV infection can potentiate the development of DM. This is because the inflammatory process from HCV replication promotes increased levels of intrahepatic tumour necrosis factor as well as hepatic steatosis with the resultant development of insulin resistance in the liver. An abnormality in glucose metabolism will eventually lead to glucose intolerance and diabetes (18).

Antiretroviral therapy: HAART, especially protease inhibitors (PIs), contributes significantly to abnormal glucose metabolism in HIV-infected individuals (19). This development has been referred to as antiretroviral-associated diabetes (18).

Pathogenesis of Diabetes Mellitus in HIV Patients

Glucose intolerance occurs secondary to insulin resistance in HIV-infected patients. Insulin resistance develops from the interplay of various factors that promote insensitivity to insulin action. These factors include an elevation of tumour necrosis factor and a reduction in adiponectin levels. Hypoadiponectinemia favours a reduction of glucose uptake in peripheral tissue and promotes hepatic glucose production (20, 21). There is also an increased free fatty acids level due to a reduction in fatty acid oxidation thereby increasing insulin resistance (20, 21). Other factors include increased intra-abdominal fat deposition with a loss of peripheral subcutaneous fat (secondary to HIV infection and HAART use), an increased rate of lipolysis and proteolysis (20, 21).

Intra-abdominal adipocytes are resistant to the anabolic effect of insulin and thus generate an increased level of free fatty acids which hinder insulin action and thus contribute significantly to the development of glucose intolerance (21). Elevated levels of 11 B-hydroxysteroid dehydrogenase type 1 are found in mesenteric fat and this enzyme is responsible for the conversion of cortisone to cortisol. Cortisol is one of the counter-regulatory hormones that inhibit insulin action. Another independent factor is antiretroviral therapy (ART) especially the PIs. At the cellular level, protease inhibitors have been shown to reduce insulin secretion and increase insulin resistance through interference with GLUT-4 mediated glucose transport. PIs also contribute to insulin resistance by indirectly inhibiting peroxisomal proliferator-activated receptor (PPAR)γ (22). Inhibition of this receptor facilitates the inflammation of adipocytes with the generation of increased levels of free fatty acids which inhibit insulin action (22). Discontinuation of PIs has been found to correct this abnormality in most cases (22). Nucleoside reverse transcriptase inhibitors (NRTI) especially stavudine, have been observed to play some role in the development of insulin resistance in HIV patients. This class of ART has been found to increase the risk of diabetes mellitus with long-term use (22).

Opportunistic infections commonly affect the pancreas during the course of HIV infection, and structural abnormalities of the pancreas have been reported in post-mortem examinations of AIDS patients (23). Pancreatic dysfunction can occur in the advanced disease where pancreatic tissue has been grossly replaced by the infiltrative/inflammatory process (23). Highly active antiretroviral therapy was also observed to cause beta cell dysfunction with a reduction in the amount of insulin secreted from beta

pancreatic cells in some individuals (24, 25).

Clinical Features of Diabetes Mellitus

At the initial stage, diabetes mellitus may reveal no obvious symptoms and elevated blood glucose or the presence of glucose in urine may be discovered only during routine screening (26, 27). The classic triad of symptoms of diabetes mellitus is polyuria, polydipsia and weight loss. Other additional features are usually related to the acute and chronic complications of DM. Acute complications may present with restlessness, confusion, lethargy and symptoms of precipitating illness such as fever and loss of appetite. Chronic complications are common and can be grouped into two main classes:

(a) Macrovascular complications.
(b) Microvascular complications.

Macrovascular complications majorly affect the coronary arteries, cerebral arteries and peripheral arteries. Therefore patients can present with chest pain (angina or silent myocardial infarction), sudden weakness or paralysis of some parts of the body (stroke), pain in the lower limbs during ambulation (intermittent claudication) or non-healing foot ulcers.

Microvascular complications majorly affect the eyes (retina), the kidneys (nephrons) and the arteries supplying the nerves. Thus damage to these structures can present as impaired vision, frothy urine and facial or pedal swelling. Others are numbness in the feet or hands, a tingling sensation, erectile dysfunction and nocturnal diarrhoea.

Evaluation of HIV Patients with Diabetes Mellitus

Once an individual has been confirmed as HIV positive, the preliminary tests should include fasting blood glucose, oral glucose tolerance test or post prandial glucose levels estimation among others. These investigations are very pertinent to the overall management of HIV patients. The tests are used to classify patients with abnormal results into two categories; (a) the prediabetic category; and (b) the diabetic category (see the diagnosis of diabetes mellitus below). They are also to be repeated just before the commencement of HAART and rechecked from the third to the sixth month of therapy (23, 25). Further screening with an oral glucose tolerance test and a postprandial glucose assessment is necessary for

patients with normal fasting glucose. This is because of the pathogenesis of diabetes in this group of patients, as there would have been a preceding period of hyperinsulinaemia with impaired glucose tolerance, or postprandial hyperglycaemia before fasting hyperglycaemia becomes apparent. Postprandial hyperglycaemia contributes to the longstanding complications that are seen when diabetes eventually becomes diagnosed.

Criteria for Diagnosis of Diabetes Mellitus (WHO) (28)

a) Random* blood glucose concentration ≥11.1 mmol/L or 200 mg/dL in addition to the presence of classic symptoms of diabetes mellitus; or
b) Fasting** plasma glucose ≥7.0 mmol/L (126 mg/dL); or
c) 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) after a 75 gram oral glucose load;
d) HbA1c*** ≥6.5%.

Criteria for Diagnosis of Pre-Diabetes (Impaired Fasting Glucose, Impaired Glucose Tolerance) (WHO) (28)

Impaired Fasting Glucose:

a) Fasting plasma glucose ≥6.1–<7 mmol/L (110-126 mg/dL)

Impaired Glucose Tolerance:

b) 2-hour plasma glucose ≥7.8–<11.1 mmol/L (≥140–<200 mg/dL) after a 75 gram oral glucose load

*Note: * Random signifies disregarding the time the last meal was taken. **Fasting is taken as no caloric intake for at least 8 hours. In asymptomatic patients, the test is expected to be repeated at least once on another day. HbA1c-glycated haemoglobin.*

Management of Diabetes Mellitus in HIV Patients

Adequate management of DM in HIV patients is key to ensuring the maintenance of good quality of life and promoting longevity in this group of individuals. Adequate management of insulin resistance and diabetes in HIV patients will prevent or delay complications, and encourage adherence to antiretroviral therapy. The pathophysiologic pattern seen in the development of HIV entertains insulin resistance as the major disorder preceding the development of glucose intolerance, thus the aim of

treatment should target improving insulin sensitivity, controlling blood glucose levels and reversing/limiting further progression of complications.

Using the guideline for HIV/AIDS Clinical Care, HRSA HIV/AIDS Bureau June 2012, treatment is as follows (21): Management strategy using this criterion is similar to the guideline used for diabetic patients in the general population. Therefore treatment modality can still be grouped into two broad groups;

a) **Lifestyle modification**: This is the main recommendation for patients with insulin resistance or with no biochemical evidence of hyperglycaemia [as well as those with prediabetes] and is aimed at preventing progression to the development of diabetes mellitus. These measures include dietary modification, weight loss (overweight/obese patients), exercise and prevention of obesity.
b) **Pharmacologic agents**;
   This involves the use of medications, which act at different levels to restore elevated glucose levels to normal levels. However, lifestyle modification is also added to this therapy for better treatment outcome.

Therapeutic agents are used with the aim of achieving euglycaemia without precipitating hypoglycaemia. Glycated haemoglobin is aimed at values below 7%. An antiretroviral agent that induces hyperglycaemia is discontinued and replaced with agents that have a good glycaemic profile, as well as maintaining the viral suppression desired in such patients. Metformin is the first drug of choice usually used for type 2 diabetes mellitus. It also improves BMI in overweight patients. However, this drug can aggravate lipoatrophy and increase the risk of developing lactic acidosis. Therefore, it is contraindicated in patients:

a) when serum creatinine levels are >1.5 mg/dL in males and >1.4 mg/dL in females;
b) with severe lipoatrophy;
c) with liver failure;
d) with cardiac failure;
e) taking drugs that potentiate the risk of lactic acidosis; and
f) with infections such as tuberculosis (29).

Thiazolidinedione is another class of antidiabetic agents that can be used to manage diabetes in HIV patients. It improves lipodystrophy and thus is preferable in patients with such a condition (25). It is contraindicated in

patients with hepatic impairment or heart failure. Side effects include fluid retention, cardiovascular morbidity, and reduction in haematocrit level (25).

Sulphonylurea, for example glimepiride can be used, but they may not adequately lower glucose to desirable levels in the presence of severe insulin resistance (30).

Insulin (especially insulin analogues (31, 32)) is considered the safest drug for patients with the classical symptoms of diabetes: excessive urination, thirst and weight loss. Insulin analogues are preferable because they have a lower risk of hypoglycaemia compared to earlier types of insulins. It should be borne in mind that patients can occasionally have constitutional symptoms like reduced appetite and nausea, all of which can increase the risk of hypoglycaemia. Insulin also has additional benefits over other antidiabetic agents and these advantages are:

a) It reduces inflammatory markers.
b) It does not cross-react with antiretroviral medications.
c) It is not contraindicated in individuals with renal or hepatic dysfunction.
d) It does not worsen cardiovascular disease.
e) It can be used in insulin deficient/resistant states.

Other oral agents, e.g., drugs like saxagliptin, are under evaluation for the possibility of their use in patients with HIV and diabetes mellitus (33).

In conclusion, diabetes coexisting with HIV infection is quite challenging but manageable and the outcome is good if promptly diagnosed and properly managed. Adequate overall care will promote good quality of life and longevity.

References

1. UNAIDS. The Gap Report. 2014.
2. El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naive cohort. *HIV Med*. 2005; 6: 114-121.
3. Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clinic: preexisting versus drug-associated diabetes mellitus. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998; 17: 46-50.
4. Manuthu EM, Joshi MD, Lule GN, Karari E. Prevalence of

Dyslipidaemia and Dysglycaemia in HIV-infected patients. *East Afr Med J* 2008; 85: 10-17.
5. Yinzhong Shen, Zheyan Wang, Lilia, Refang Zhanga, Hongzhou Lu. Prevalence of hyperglycaemia among adults with newly diagnosed HIV/AIDS in China. *BMC Infect. Dis*. 2013; 13: 79.
6. Jyothi I, Ravindra'a n G, Jason D'Souza, Givija Singh, Sultana Furruqh. Diabetes Mellitus, Insulin Resistance and Metabolic Syndrome in HIV positive patients in South India. *Int J. Gen Med*. 2011; 4: 73-78.
7. Feleke Y, Fekade D, Mezegebu Y. Prevalence of HAART-associated metabolic abnormalities and Lipodystrophy in HIV infected patients. *Ethiop Med J*. 2012 July; 50(3): 221-230.
8. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr*. 2003; 32: 298-302.
9. Reng R, Uloko AE, Puepet FH, Onwugbuezie GA, Ramalan MA. Prevalence and determinants of Glucose Intolerance among HIV/AIDS patients in North-central Nigeria. *Nigerian Journal of Medicine*, 2016; 25(2): 128-133.
10. Ogeneh BO, Umezinne NC, Udoh IP, Eleazar C. Concomitant prevalence of diabetes and tuberculosis in HIV/AIDS patients in Enugu, Nigeria. *International Journal of Medicine and Medical Science Research*. 2015; 3(1): 001-005.
11. Reid M, Tsima B, Kirk B. HIV and diabetes in Africa. *African Journal of Diabetes Medicine* 2012; 20: 28-32.
12. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011; 53: 1130-1139.
13. L Galli, S Salpietro, G Pellicciotta A Galliani, PM Piatti, H Hasson, et al. Prevalence of type 2 diabetes mellitus and its predictive factors in Italy: a comparison between HIV-infected and uninfected subjects. *Journal of the International AIDS Society*. November 2010; 13: P230.
14. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005; 165: 1179-1184.
15. Salami AK, Akande AA, Olokoba AB. Serum Lipids and Glucose Abnormalities in HIV/AIDS Patients on Antiretroviral Therapies. *West African Journal of Medicine* 2009; 28(1): 300-305.
16. De Wit S, Sabin C, Weber R, Worm SW, Reiss P, Cazanave C, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the data collection on adverse events of anti-HIV drugs

(D:A:D) study. *Diabetes Care* 2008; 31: 1224-1229.
17. Fichtenbaum CJ, Hadigan CM, Kotler DP, et al: Treating morphologic and metabolic complications in HIV-infected patients on antiretroviral therapy. *IAPAC Monthly*. 2005, 38-46.
18. Dagogo-Jack S. HIV therapy and diabetes risk. *Diabetes Care*. 2008, 31 (6): 1267-1268.
19. Fisac C, Fumero E, Crespo M, Roson B, Ferrer E, Virgili N. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine**.** *AIDS* 2005; 9: 917-925.
20. Sheng T, Yang K. Adiponectin and its association with insulin resistance and type 2 diabetes. *J Genet Genomics*. 2008 Jun; 35(6): 321-326.
21. Aberg JA, Kaplan JE, Libman H,. et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49(5): 651-681.
22. Lee GA, Rao M, Greenfeld C. The effects of HIV Protease inhibitors on carbohydrate and lipid metabolism. *Curr Infect Dis Resp*. 2004, 6: 471-482.
23. Sanjay K, Bharti K, Navneet A, Unnikrishnan AG. Understanding diabetes in patients with HIV/AIDS. *Diabetol Metab Syndr* 2011; 3: 2.
24. Woerle HJ, Mariuz RR, Meyer C, et al. Mechanisms for the deterioration in glucose tolerance associated with HIV protease inhibitor regimens. *Diabetes*. 2003; 52: 918-925.
25. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *J Acquir Immune Defic Syndr*. 2002; 33: 257-275.
26. Gale EAM, Anderson JV. Diabetes mellitus and other disorders of metabolism. In: *Kumar and Clark's Clinical Medicine.* 7th ed. Spain: Saunders Elsevier, 2009, 1029-1076.
27. Alvin C. Powers. Diabetes Mellitus. In: *Harrison's Textbook of Internal Medicine*. 17th ed. USA: McGraw-Hill Inc, 2008, 2275-2304.
28. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation. Geneva: World Health Organisation, 2006, 21.
29. Kohli R, Shevitz A, Gorbach S, Wanke C. A randomized placebo-controlled trial of metformin for the treatment of HIV lipodystrophy. *HIV Medicine*. 2007, 8: 420-426.
30. Agency for Healthcare Research and Quality. Clinician Summary Guide: Comparing Oral Medications for Adults with Type 2 Diabetes.

Rockville, Maryland, 2007.
31. Kalra S, Kalra B, Sharma A. Ketonuria and ketonemia in type 2 diabetes mellitus patients attending an Indian endocrine clinic. *Ind J Endocr & Metab.* 2007, 11: 7-10.
32. Agency for Healthcare Research and Quality: Clinician Summary Guide: Comparing Oral Medications for Adults with Type 2 Diabetes. Rockville, Maryland, 2007.
33. Gadsby R. Efficacy and safety of sitagliptin in the treatment of type 2 diabetes. *Clinical Medicine. Therapeutics*. 2009, 1: 53-62.

HIV AND REPRODUCTIVE HEALTH

ESTHER OLUFUNMILAYO ASEKUN-OLARINMOYE
BSC, MD, FWACP
AND ELIZABETH BUNMI ADEDIRE
MBBS, MPH, FWACP

HIV/AIDS remains a significant cause of mortality among women of reproductive age and adolescents. The challenges encountered in the provision of reproductive health services are similar to those worsening the HIV/AIDS epidemics; these include poverty, women's lack of power to take decisions by themselves and for themselves over their sexual and reproductive lives, and gender-based violence and discrimination. Girls, especially in the adolescent period are most affected due to related issues among adolescents such as teenage pregnancy, sexually transmitted infections (STIs), HIV and sexual violence. HIV/AIDS affect all aspects of women's sexual and reproductive health including conception, delivery, infant feeding and nutrition, contraceptive use, methods of termination of unwanted pregnancies, transmission and management of sexually transmitted infections and vulnerability to gender-based violence. Reproductive health services and HIV/AIDS prevention programs share a common target audience, especially in countries with generalized epidemics with the youth especially women and girls of reproductive age as the target audience. Therefore, this chapter aims to discuss the inter-relationships between HIV/AIDS and reproductive health services.

Women of reproductive age and young adolescents are disproportionately vulnerable to HIV infection and AIDS and it is a significant cause of death amongst them (1). In sub-Saharan Africa, women constitute about 60 per cent of those living with HIV/AIDS, and three-quarters of this proportion consists of 15 to 24 year-olds living with HIV virus (1). Factors responsible for delaying the realization of the rights of people living with HIV/AIDS include stigma, discrimination, and access to essential information and services to

prevent and treat HIV (1). The challenges encountered in the provision of reproductive health services are similar to those worsening the HIV/AIDS epidemic, including poverty, gender-based violence and discrimination, and the fact that women do not have the power of decision over matters concerning their sexual and reproductive lives. Sexual problems affecting adolescent girls disproportionately include teenage pregnancy, sexually transmitted infections (STIs), HIV, and gender-based violence (2).

Globally, young people account for 41% of new infections among those aged 15 years or older (3). Adolescent girls are especially vulnerable to HIV acquisition (4).

HIV directly or indirectly affects all aspects of women's reproductive health which are affected by HIV directly or indirectly (5, 6, 7). For example, HIV infection worsens the prognosis and outcomes of most reproductive conditions and illnesses. Evidence from studies in both developed and underdeveloped countries has shown that HIV adversely affects the ability to become pregnant, and infection with HIV also affects the sexual health and well-being of women as well as men.

Sexual and reproductive rights should be accessible to all individuals irrespective of HIV status. Gender inequality and some social and cultural practices often tightly restrict and sometimes control women's and girls' decision-making attitude, freedom and power concerning their sexual and reproductive choices. Poverty, HIV-related stigma, and discrimination are barrier factors to the access of critically needed information and services by HIV-positive women and adolescent girls resulting in dire consequences. Reproductive health services and HIV/AIDS prevention programs share a common target audience, especially in countries with a generalized epidemic with the youth especially women and girls of reproductive age as the target audience.

Access to reproductive health services for HIV-positive women is pivotal to ensure their reproductive needs are addressed and their reproductive rights are protected. Therefore, a strong linkage between reproductive health and HIV policies, programs and services has been advocated by several international organizations (8).

Reproductive Health

Health has been defined as a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity (8).

Reproductive health can therefore be defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes" (8). This means that people are able to enjoy a healthy sex life and that they have the ability to conceive and the freedom to decide on the choice of ways and means by which they will achieve it. This connotes that men and women need to be well informed of and to have access to the different methods of modern contraception available. The principle of primary health care (PHC) of universal accessibility, affordability and acceptability should be employed in the provision of these services. Reproductive and sexual health focuses on overall improvement of life and inter-personal relationships.

Core Elements of Sexual and Reproductive Health (9)

1. Family planning (FP) services;
2. Provision of Antenatal care, skilled attendance at delivery, and postnatal care;
3. Management of obstetrical and neonatal complications and emergencies;
4. Management of abortion complications and provision of post-abortion care;
5. Prevention and management of all infections of the reproductive tract including HIV/AIDS;
6. Early diagnosis and treatment of breast cancer and reproductive tract cancers (men and women);
7. Promotion, education, and provision of support for exclusive breastfeeding;
8. Prevention and appropriate treatment of sub-fertility and infertility;
9. Prevention of harmful practices, such as female genital cutting;
10. Adolescent sexual and reproductive health;
11. Gender-based violence prevention and management.

Health Impact of Reproductive and Sexual Health

Reproductive and sexual health is an important element of people's existence. Reproductive and sexual health services can:

1. Prevent unintended pregnancies: About 50% of all pregnancies are unintended. Low birth weight, postpartum depression, delays in receiving prenatal care, and family stress are among risks associated with unintended pregnancy.

2. Prevent adolescent pregnancies: Over 400,000 teenage girls age 15-19 years give birth each year in the United States (10).
3. Early detection of health issues: Proper prenatal care can identify high risk conditions thereby preventing complications.
4. Improve diagnosis and management of STDs. Complications in adulthood could be as a result of STDs during adolescence that were neglected or not properly treated.
5. Lower the occurrence of infertility. In the United States of America, neglected or improperly managed STDs are the cause of infertility in about 24,000 women every year.
6. Reduce the transmission of HIV through the provision of testing and antiretroviral treatment (ART) (11). ART makes HIV-positive persons nine times less likely to transmit the virus to other people (12).

Interrelationships between core components of reproductive health and HIV/AIDS

According to the United Nations Convention on the Elimination of All Forms of Discrimination against Women (CEDAW), irrespective of their HIV status, all women have the right to decide to control the size of their family, choose the interval at which to bear children and to have access to the information, education and empowerment to exercise their rights (13). In taking a decision on sexual and reproductive issues, HIV seropositive women are usually faced with a dilemma between the desire for pregnancy and the possible outcome of such pregnancy, the choices of contraceptive methods available, decisions on actions to be taken about an unwanted and or an unintended pregnancy and the care options and choices necessary for reducing peri-natal HIV transmission. For women who are HIV seropositive, integration between reproductive health and HIV services should address the following distinct reproductive health circumstances and guide their choices (Fig. 1):

a) Those who do not wish to become pregnant and are sexually active should be offered family planning services.
b) Those who want to conceive should be assisted to conceive and to be able to access prenatal care including the prevention of mother-to-child transmission of HIV PMTCT.
c) For those in a serodiscordant relationship, methods of HIV prevention of infection transmission to the partner when trying to conceive and during infertility treatment should be available to her if required.

d) Those currently pregnant and who wish to continue the pregnancy should be given the opportunity to access antiretroviral therapy, which reduces the risks of HIV transmission through the PMTCT program.
e) Postpartum contraception should be made available for those who have completed their desired family size.

Reproductive health and HIV linkages at policy, program and service delivery levels are very important to ensure that the sexual and reproductive health needs of HIV-seropositive women are met. These connections will reduce the impacts of the HIV epidemic by ensuring women with HIV who do not want to become pregnant have access to effective contraception. Preventing unintended pregnancies in HIV-positive women will improve both maternal and child health and prevent new HIV infections in infants.

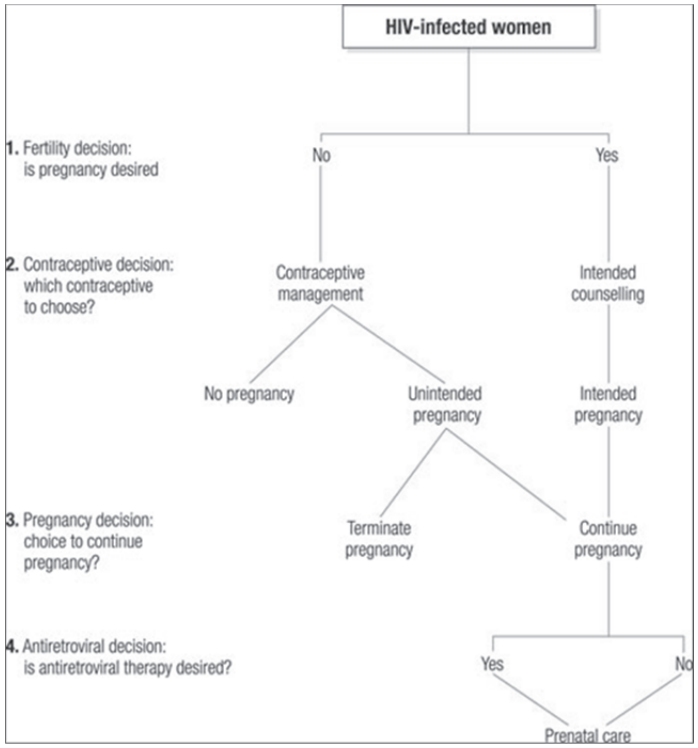


Figure 1: Reproductive Choices for HIV-positive women (14)

Integration of Reproductive Health and HIV/AIDS programs

The integration of reproductive health and HIV/AIDS programs ensures the achievement of multiple key goals such as prevention of new HIV infections; prevention of mother-to-child transmission [PMTCT]; prevention of more AIDS orphans; and support for HIV-positive women's reproductive rights and fertility choices. Reproductive health and HIV services are usually considered separately and operate vertically; this means that clients see a different provider for each health service. The majority of HIV infections are sexually transmitted in sub- Saharan Africa (8), therefore tackling reproductive health problems and HIV together would offer a comprehensive approach to better serve the needs of clients and healthcare providers alike. As a public health issue of importance and priority, it is vital that essential sexual and reproductive health care be provided in HIV/AIDS prevention, care and treatment programs and also that prevention and treatment of HIV/AIDS be included in sexual and reproductive health services.

Need for strengthening integration/linkages in reproductive health and the HIV/AIDS Program

Integration of RH and the HIV/AIDS program can increase access to HIV prevention, care, and treatment services for vulnerable women and girls, and also reduce the stigma and discrimination associated with vertical HIV programs. Although reaching populations such as sex workers, adolescent girls, and injection drug users (IDUs) remains a challenge, integrated services have the potential to reach larger numbers of target groups in need of both HIV and RH services. Promoting integration between HIV/AIDS programs and reproductive health services for women can help to focus on the new resources available for HIV/AIDS and the limited funding for reproductive health services thereby making better use of scarce resources. Integration helps to address the shortages of healthcare workers to cater for these needs especially in resource limited settings. New training requirements for staff may make the initial cost seem higher; however, the investment will pay off in the long run in terms of cost-effectiveness. Integration brings heavier duties for staff but this can be overcome by the proper organization of the work schedule through efficient and effective supervision by program managers. Integration may be more effective at achieving both HIV and reproductive health objectives because

RH/FP providers and non-governmental organizations already have the capacity to offer these services, and reach the high-risk target populations.

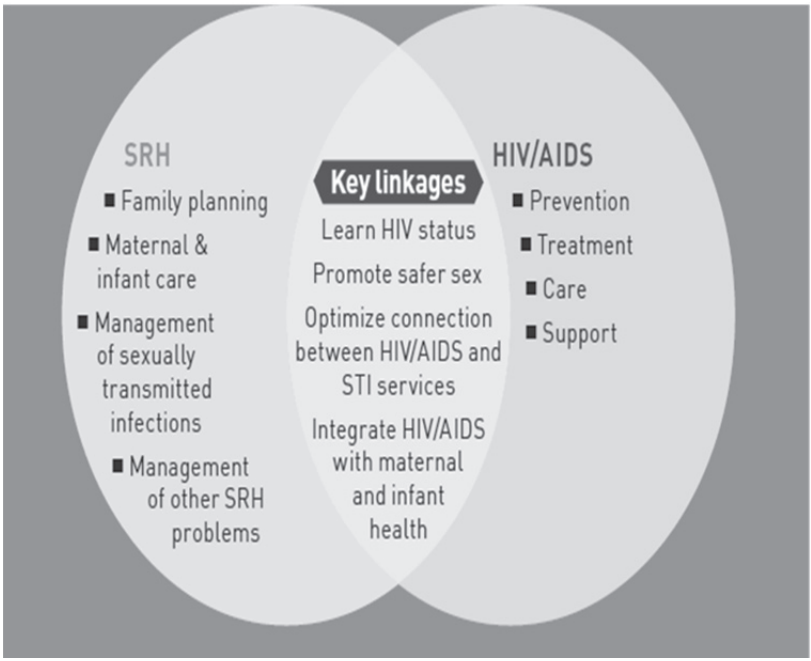


Figure 2: Linkage between Sexual and Reproductive Health Services and HIV/AIDS (15)

Family Planning Services and HIV/AIDS

Family planning reduces the number of unplanned pregnancies and abortions, enhances maternal and infant well-being and diminishes the likelihood of the vertical transmission of HIV. Family planning services which include the provision of family planning information, counselling, and a family planning method, have proven to be a cost-effective addition to prevent mother-to-child transmission (PMTCT) (16). Integrating family planning services with HIV services provides the opportunity to promote male and youth involvement in reproductive health and HIV services. The integration of family planning and HIV services also acts to facilitate the prevention of unwanted and unintended pregnancies among HIV-positive clients (17). Some of the advantages of

integrating the programs are increasing access to both reproductive health and HIV services, a reduction in HIV-related stigma and discrimination, and an extension of the programs to previously marginalized populations. HIV service providers should be well-equipped with the skills and knowledge to discuss fertility desires and contraceptive methods for women and couples who are HIV positive. Likewise, linking family planning services with HIV testing and counselling (HTC) services also improves access to both HIV services as improved access to one service reinforces the other (18).

Sexual Health Vulnerability and HIV/AIDS

HIV/AIDS-infected individuals usually have weakened immune systems; they are biologically more vulnerable to certain sexually transmitted infections than others. Additionally, they may be at risk of re-infection with another strain of HIV. "Safer sex" practices connote the correct and consistent use of barrier methods (male and female condoms). Safer sex practice can reduce an individual's risk of HIV and other STIs. Although some sexual behaviours (such as non- penetrative sex) can also reduce risk, total abstinence and fidelity between couples remain the best strategy (19). There is evidence demonstrating positive sexual and reproductive health outcomes when marriage is delayed. For example, findings from a recent study from developing countries show that early marriage is associated with many more pregnancy- and delivery-related complications, poor foetal outcomes and gender-based violence with the partner (20).

Pregnancy and HIV/AIDS

HIV and pregnancy are intertwined, studies have shown that HIV-positive women and girls are more prone to pregnancy complications, and are at higher risk of maternal death (21). A higher mortality ratio in HIV-infected pregnant women than uninfected women has been documented; non-obstetric causes are the most prevalent causes of maternal death among HIV-infected pregnant women, however, HIV-infected pregnant women were also at higher risk of dying from pregnancy-related complications (22, 23). Accessing family planning services and other reproductive health services would empower women living with HIV to prevent health complications related to unintended pregnancies and to plan pregnancies based on their child-bearing desires and health needs.

HIV and Breastfeeding

The World Health Organization (WHO) had previously recommended that HIV-positive mothers should avoid breastfeeding if they were able to afford, prepare and store formula milk safely; however, it has recently recommended that HIV-positive mothers should exclusively breastfeed their children for six months and both the mother and their infants should be given antiretroviral drugs throughout the period of breastfeeding and until the infant is 12 months old (8). This would suggest that breastfeeding the child for the longer period of time under this circumstance will proffer the maximum benefit to the child with little risk of transmission of the virus. Previous researchers had demonstrated that exclusively breastfed infants are three to four times less prone to HIV transmission through the feeding route compared to infants who were not exclusively breastfed (8).

Traditional Birth Attendants/Home Deliveries and HIV/AIDS

In resource-poor countries, TBAs assist between 60% and 90% of deliveries in rural areas (24). The preference for home births is affected by cultural norms and religious beliefs. The ability to speak the local language, being a trusted community member and able to provide psychosocial support during delivery are some special characteristics of the TBAs. TBAs play a crucial role in maternal and child health; they help bridge the gaps in supporting women with deliveries especially in communities where the closest health centre is many miles away. Deliveries with TBAs have been associated with the use of unsterilized tools, unskilled personnel, poor environmental conditions, and little or no knowledge of the prevention of mother-to-child transmission of HIV (PMTCT), thus contributing to high maternal and infant mortality and MTCT of HIV rates. PMTCT is one of the key HIV prevention strategies in Nigeria's National HIV/AIDS response. The uptake of PMTCT remains low despite the efforts and rapid scale-up of the national PMTCT program. TBAs must be encouraged by all public health programs to participate in PMTCT programs in order to expand the reach to otherwise underserved areas (25).

HIV and Female Genital Cutting (FGC)

According to the WHO, FGC is defined as "all procedures involving the partial or total removal of the external female genitalia or other injury to the female genital organs for non-medical reasons" (26). Traditionally, it is believed to reduce sexual desire and feelings on the part of women and thereby discouraging prostitution. Female genital cutting has no known health benefits rather, it is known to be harmful to girls and women in many ways. Female genital cutting (FGC) practices are liable to lead to recurring trauma, bleeding, open sores and open wounds, which would increase the risk of HIV infection during unprotected sex. Although empirical evidence may still be lacking for the direct association between FGC and HIV, the repeated utilization of unsterilized instruments is likely to increase the risk for transmission of HIV between consecutive clients (26, 27). Likewise, the increased prevalence of herpes in women subjected to female genital cutting may also increase the risk for HIV infection, as genital herpes is a risk factor in the transmission of HIV (28).

HIV and Male Circumcision

Male circumcision is the surgical removal of the foreskin from the penis. Scientific literature has documented the fact that circumcised men are more than twice less likely to acquire HIV infection in heterosexual relationships (29). Voluntary male medical circumcision (VMMC) has been recommended by the WHO/UNAIDS as a useful intervention for HIV prevention in certain settings (30, 31). However, VMMC's public health benefit is limited among certain male high-risk populations like male sex workers, drug injection users and men who have sex with men (MSM). It is an evidence-based fact that male circumcision can partially protect men from HIV transmission, therefore it should be included as part of a comprehensive HIV prevention strategy.

References

1. UNFPA2015; http://www.unfpa.org/hiv-aids#sthash.E6Y1qrn7.dpu accessed 19 November, 2015.
2. WHO Reproductive health http://www.who.int/topics/reproductive_health/en/ accessed 20 November, 2015.
3. Global report. UNAIDS report on the global AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010.

4. Leclerc-Madlala S. Age-disparate and intergenerational sex in southern Africa: The dynamics of hypervulnerability. *AIDS* 2008; 22(Suppl. 4): S17e25.
5. Massad LS, Springer G, Jacobson L, Watts H, Anastos K, Korn A, Cejtin H, et al. Pregnancy rates and predictors of conception, miscarriage, and abortion in US women with HIV. *AIDS* 2004, 18(2): 281–286.
6. Ross A, Van der Paal L, Lubega R, Mayanja BN, Shafer LA, Whitworth J. HIV-1 disease progression, and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda. *AIDS* 2004; 18(5): 799–804.
7. Hunter SC, Isingo R, Boerma JT, Urassa M, Mwaluko GM, Zaba B. The association between HIV and fertility in a cohort study in rural Tanzania. *Journal of Biosocial Sciences*, 2003, 35: 189–199.
8. WHO. HIV/AIDS and Sexual and Reproductive Health Linkages. March 2009.
9. UNFPA. Reproductive health services: offering essential services, 2006. www.unfpa.org/rh/services.htm.
10. Centers for Disease Control and Prevention. Preventing teen pregnancy in the U.S. CDC Vital Signs. Atlanta, GA, 2011. Available from http://www.cdc.gov/VitalSigns/pdf/2011-04-vitalsigns.pdf.
11. Centers for Disease Control and Prevention. HIV testing in the U.S. CDC Vital Signs. Atlanta, GA, 2010. Available from http://www.cdc.gov/nchhstp/newsroom/docs/Vital-Signs-Fact-Sheet.
12. National Prevention Council, Office of the Surgeon General, U.S. Department of Health and Human Services. National Prevention Strategy. Washington, DC, 2011, 45.
13. UNFPA. The Human Rights of Women, Convention on the Elimination of All Forms of Discrimination against Women (CEDAW), United Nation Population Fund (UNFPA) 2006, https://www.unfpa.org/resources/human-rights-women.
14. Rose Witcher & Willard Cates. Bulletin of the World Health Organization 2009; 87:833-839. doi: 10.2471/BLT.08.059360.
15. UNAIDS. Sexual and Reproductive Health & HIV/AIDS, Framework for Priority Linkages, 2005. http://data.unaids.org/pub/agenda_linkages_evidence_review_en.pdf.
16. John Stover. Are Cost Savings Incurred by Offering Family Planning Services at Emergency Plan HIV/AIDS Care and Treatment Facilities? Policy Project, Washington, D.C., March 2006,

http://www.policyproject.com/abstract.cfm/2741.
17. Kennedy CE, Spaulding AB, Brickley DB, Almers L, Mirjahangir J, Packel L, et al. Linking sexual and reproductive health and HIV interventions: a systematic review. *Journal of the International AIDS Society* 2010, 13: 26.
18. Chabikuli NO, Awi DD, Chukwujekwu O, Abubakar Z, Gwarzo U, Ibrahim M, et al. The use of routine monitoring and evaluation systems to assess a referral model of family planning and HIV service integration in Nigeria. *AIDS* Nov. 2009;, 23 (suppl. 1): S97-S103.
19. NIH. Sexually transmitted diseases and infections (STDs and STIs) and HIV/AIDS research: HIV/AIDS in female populations. Rockville, MD, United States National Institute of Child Health and Human Development (NICHD), 2005 (http://www.nichd.nih.gov/womenshealth/STDHIV.cfm, accessed 1 October 2005).
20. Santhya KG and Shireen J Jejeebhoy. Sexual and reproductive health and rights of adolescent girls: Evidence from low- and middle-income countries. *Global Public Health* 2015; Vol. 10, No. 2, 189, 221, http://dx.doi.org/10.1080/17441692.2014.986169.
21. World Health Organization Trends in Maternal Mortality: 1990 to 2008 Geneva: WHO; 2010. Available from http://whqlibdoc.who.int/publications/2010/9789241500265_eng.pdf Accessed Feb. 2018.
22. Landes M, van Lettow M, Bedell R, Mayuni I, Chan AK, Tenthani L, Schouten E. Mortality and health outcomes in HIV- infected and HIV-uninfected mothers at 18-20 months postpartum in Zomba District, Malawi. *PLoS One.* 2012; 7(9): e44396.
23. Moran NF, Moodley J. The effect of HIV infection on maternal health and mortality. *Int J Gynaecol. Obstet*. 2012 Oct; 119 (Suppl. 1): S26-9.
24. Bulterys M, Fowler MG, Shaffer N, Tih PM, Greenberg AE, Karita E, Coovadia H, De Cock KM. Role of traditional birth attendants in preventing perinatal transmission of HIV. *BMJ* 2002; 324: 222-224. 10.1136/bmj.324.7331.222.
25. Wanyu B, Diom ED, Mitchell P, Tih PM, Meyer D. Trained birth attendants provide "prevention of mother-to-child HIV transmission" care in rural Cameroon, Africa. *J Midwifery Women's Health*. 2007; 52: 334-41. 10.1016/j.jmwh.2006.12.018.
26. WHO. Female Genital Mutilation, 2013. Available from http://www.who.int/mediacentre/factsheets/fs241/en/ accessed Feb. 2018.

27. Monjok E, Essien E, Holmes L. Female genital mutilation: Potential for HIV transmission in sub-Saharan Africa and prospect for epidemiologic investigation and intervention. *African Journal for Reproductive Health*, April 2007, 11(1): 33-42.
28. UNAIDS 2008. Interagency Statement on Eliminating Female Genital Mutilation.
29. WHO. Voluntary medical male circumcision for HIV prevention in 14 priority countries in eastern and southern Africa; progress brief, 2017.
30. UNAIDS Joint United Nation Programme on HIV/AIDS: 2008 Global report On HIV Epidemics.
31. Lemle M. Circumcised men less likely to get HIV, says study. *Science Development Network* 29 July 2005. Available: http://www.scidev.net/content/news/eng/circumcised-men-less-likely-to-get-hiv-says-study.cfm.

HIV/AIDS AND MUSCULOSKELETAL DISORDERS

DARE, BABATUNDE JOSEPH, PHD

Complications that involve the nerves, tendons, cartilages, muscles, and supporting structures of the body and compromise their functions describe musculoskeletal disorders. These are the initial manifestation of the viral illness. Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) eliminates $CD4^+$ T-helper lymphocytes permitting opportunistic infections and tumours. Musculoskeletal disorders in HIV/AIDS are aided by complex environmental and genetic interactions, and are categorized into infectious musculoskeletal disorders (Cellulitis, Soft-tissue Abscesses, Pyomyositis, Osteomyelitis, and Septic Arthritis), non-infectious (neoplasm) musculoskeletal disorders (non-Hodgkin's lymphoma and Kaposi's sarcoma), arthropathies including Arthritides (Articular pain syndrome, Reiter syndrome, psoriatic arthritis, and the syndromes of oligo-arthritis and polyarthritis), Arthropathies (Osteonecrosis, Osteoporosis, Rhabdomyolysis, Hypertrophic and Osteoarthropathy), Polymyositis and Myopathies (necrotizing non-inflammatory myopathy, nemaline (rod) myopathy, myositis ossificans and subclinical myopathy). This chapter gives step-by-step details of the clinical conditions associated with musculoskeletal systems observed in HIV/AIDS individuals. This is necessary for adequate knowledge of the existence and characteristic pathological appearance of the conditions affecting osseous, articular cartilages, and muscle (soft tissues) in HIV/AIDS individuals. Radiological imaging techniques that are specific for each pathological condition (valuable for diagnosis, detection and for the appropriate treatment regimen) are also explained.

Human Immunodeficiency Virus (HIV) causes Acquired Immunodeficiency Syndrome (AIDS) through the progressive destruction of the cell-mediated immune (CMI) system by eliminating $CD4^+$ T-helper lymphocytes (1) which permit opportunistic infections and tumours ($CD4^+$ cells are helper cells that recognize a specific target antigen and activate B

cells, killer cells, and macrophages). HIV/AIDS directly damages specific organs including bones and muscles. The time range for HIV infection leading to death is an average of 6 months to 15 years. HIV and AIDS are retroviruses belonging to the family of lentiviruses which can use self RNA and host DNA to make viral DNA that enhances decreased immunity, destroying the T cells that secrete cytokines (chemicals that kill cells), such as interferon, which bind to target cells and activate the inflammatory process, also by eliminating phagocytes (monocytes and macrophages) that are important in immune response regulation and inflammation, leading to opportunistic infections that compromise the musculoskeletal system. Opportunistic infections are caused by organisms that do not cause infections in healthy individuals (2). The musculoskeletal system comprises connective tissues such as the bone that aids movement, provides support, stores calcium, produces red blood cells and protects delicate organs in the body; the cartilage that serves as a template for bone formation during foetal life and forms the articular end of bone around the joints; the tendons that connect muscles to bone; and the ligaments that connect bone to bone and the muscles (3).

The musculoskeletal system has three (3) principal components; the joint (cartilages, tendons and ligaments), the muscle (soft tissue) and the bone (osseous tissue). Complications that involve the nerves, tendons, cartilages, muscles, and supporting structures of the body and compromise their functions are referred to as musculoskeletal disorders (4). The immunosuppressant property and viral actions of HIV/AIDS aided by complex environmental and genetic interactions enhance the susceptibility of individuals diagnosed with HIV/AIDS to disorders of musculoskeletal system functions.

Musculoskeletal disorders affect about 72% of HIV/AIDS infected individuals and about 35% of the affected individuals had arthralgia, 10% had Reiter's syndrome, 2% had psoriatic arthritis and myositis while about 1% had vasculitis (5, 6). Infectious musculoskeletal disorders include, but are not limited to the following: cellulitis, necrotizing fasciitis, soft tissue abscess, pyomyositis, osteomyelitis, septic arthritis, septic bursitis, and bacillary angiomatosis (7). Among other forms of infectious musculoskeletal disorders are the mycobacterial infections consisting of tuberculous spondylitis and spondylodiskitis, arthritis, osteomyelitis, and tenosynovitis, as well as infections caused by atypical mycobacteria (8).

Non-infectious (neoplasm) musculoskeletal disorders elicited by increased activity of a number of cytokines and chemokines in joint tissues drive the

production of matrix-degrading enzymes. Non-infectious (neoplasm) musculoskeletal disorders include osteoarthritis, polymyositis, and non-Hodgkin's lymphoma and the Kaposi's sarcoma form of neoplasm (3).

HIV/AIDS has myriad effects on the joint (cartilages), the muscle (soft tissue) and the bone (osseous tissue) (9). However, propagation of musculoskeletal disorders in HIV/AIDS virus infection involves multifactorial conditions which are explained in three (3) major processes, each process expressing different pathological conditions (10). Adequate knowledge of the existence and characteristic pathological appearance of the conditions affecting osseous, articular cartilages, and muscle (soft tissues) in HIV/AIDS individuals is valuable for diagnosis, detection and for the appropriate treatment regimen. This chapter tends to elucidate appropriately, alterations in the musculoskeletal system as a complication regarding HIV/AIDS individuals.

Aetiopathogenesis of Musculoskeletal Disorders in HIV/AIDS

Several factors play roles in disorders that compromise components of the cells, tissues, and organs involved in the musculoskeletal system, including the respective functions of these components to the general body and in isolation in parts. The pathogenesis of HIV/AIDS is basically between HIV replication and the immune responses via cell-mediated and immune-mediated reactions. The HIV/AIDS infection mediates mature $CD4^+$ T-cell destruction; progenitor cells in the bone marrow, thymus, and peripheral lymphoid organs as well as microglia within the nervous system. This results in the failure of T-cell production and the depletion of $CD4^+$ cells consequently leading to immune suppression in HIV/AIDS infection.

HIV/AIDS mediates direct cytopathic effects such as single-cell killing and cell fusion, or syncytium formation (11). The syncytium is a fusion of multiple uninfected $CD4^+$ cells with one HIV-infected $CD4^+$ cell via the interaction of CD4–gp120 (major viral glycoproteins together with gp41 in the HIV-viral lipid bilayer, which function to mediate the recognition of $CD4^+$ cells and chemokine receptors by HIV/AIDS). This fusion results in a multinucleated syncytium, or giant cell, which ultimately serves as a means to produce many virions. The host immune responses play a role in $CD4^+$ cell depletion through cytotoxic $CD8^+$ T-cells (antibody-dependent cellular cytotoxicity, and natural killer cells). Autoimmune responses,

super-antigen-mediated activation of T-cells, and programmed cell death (apoptosis) are another mechanism by which HIV/AIDS compromises the musculoskeletal system. HIV/AIDS progresses through a more severe immunosuppression and depletion of $CD4^+$ cells. An increase in the $CD8^+$ count yields an overall decrease in the $CD4^+$:$CD8^+$ ratio. $CD4^+$ and $CD8^+$ T-lymphocytes elicit the immunogenic response and promote an inflammatory reaction within the muscle.

HIV and AIDS equally infect many types of cells outside lymphoid organs including the brain, spinal cord, lung, colon, liver, and kidney, usually occurring during late illness.

A. Infectious musculoskeletal disorders

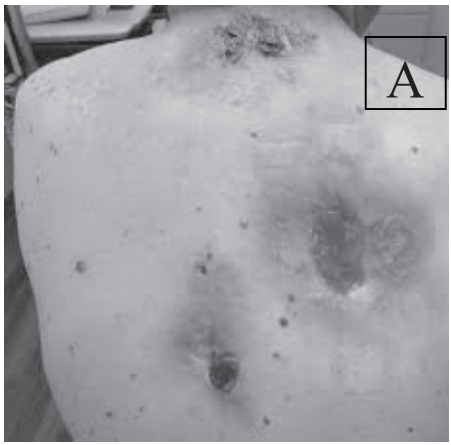
The complication in patients with HIV/AIDS is aided and enhanced by infections usually caused by Streptococcus aureus bacterium. Others pathogens include Streptococcus pyogenes, Mycobacterium tuberculosis, Mavium-intracellulare, Nocardia asteroids, Cryptococcus neoformans, and Toxoplasma. HIV/AIDS infection affects soft tissues (muscles and skin) and bone and joint (osseous and cartilages) integrity (12), and reduces the body's defence mechanisms by impairing the T-lymphocyte response which forms the gateway for various opportunistic infections and a non-opportunistic mode of infection in immunosuppressed HIV/AIDS individuals. Therefore, infectious musculoskeletal disorder in HIV/AIDS clinically presents in two forms: superficial infection and deep infection.

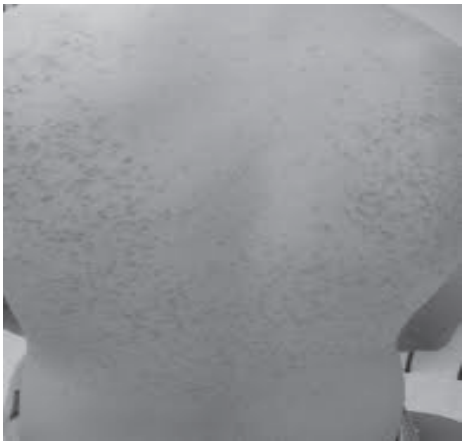
It occurs in cellulitis, necrotizing and non-necrotizing fasciitis, soft-tissue abscesses and pyomyositis in direct soft tissue (muscles) infection while the cytopathic effect and muscle necrosis or degeneration occur in the direct invasion of the muscle by HIV/AIDS viral infections. The presence of HIV/AIDS virus in skeletal muscle can be determined through the polymerase chain reaction (PCR) (4).

I. **Cellulitis:** is an acute inflammatory condition of the skin that is characterized by swelling, erythema, calor and localized pain in the affected area. Cellulitis is caused by S. aureus or S. pyogenes bacterial infection in the nerves, tendons, muscles, and the supporting structures of the body (7). In S. aureus the infection spreads from a centrally localized infection such as an abscess, an infected foreign body, or folliculitis (infection of hair follicles). In S. pyogenes rapid spread through a process associated with lymphangitis and fever is implicated (13, 14). Also, in superficial

cellulitis, inflammatory changes only involve subcutaneous fat in the superficial fascia, characterized by a thickening of the skin and superficial fascia, and septation of the subcutaneous fat (15, 16). In the deep soft tissues such as the deep fascia and muscles a deep cellulitis, fasciitis and myositis with or without necrosis occur with clinical manifestations of disproportionate muscles without affecting subcutaneous tissue in the case of bacterial myositis (8). Fasciitis, an inflammation of the fascia present with necrosis (necrotizing fasciitis) and without (non-necrotizing fasciitis) of the muscles surrounding soft tissues, manifests trauma in immunosuppression HIV/AIDS infection (12).

Features of cellulitis include extensive necrosis of the superficial and deep fascia usually with systemic complications, necrotizing fasciitis manifest as brawny oedema and tenderness, local coagulopathy, and thrombosis of the blood vessels with necrosis of the deep soft tissue fascia (7, 17). Magnetic Resonance imaging is useful in differentiating necrotizing fasciitis from severe cellulitis with or without secondary abscess formation and pyomyositis. This is because imaging features in necrotizing fasciitis and cellulitis are similar, however, thickening of the fascia, fluid collections in the deep fascia sheaths, and inter-muscular septa are specific for the necrotizing fasciitis in muscles. MR imaging and CT are useful in the medical examination of osseous tissues (18).





Plates 1A and B: Show spreads of infection from a centrally localized area as seen in Folliculitis usually caused by S. aureus and the rapid spread of skin infection observed in lymphangitis caused by S. pyogenes

II. **Soft-tissue Abscesses** are a localized bacterial infection that extends and develops into an abscess in direct proportion to the level of the depressed immunologic status of HIV/AIDS. An increase in the bacteria density/population in the soft tissues causes the body to form a ring wall around the infected area as a defence mechanism to prevent further spread to other parts of the body. However, bacteria in the abscess multiply and the area becomes more swollen. In other cases, the bacteria get through the ring wall and cause an infection of the tissues around the abscess and the blood. Clinical signs and symptoms observed include: a well-demarcated fluid collection surrounded by pseudo capsule sequences, and a peripheral rim.

Magnetic resonance imaging and gadolinium-based contrast administration are useful radiological imaging techniques in diagnosis. Needle aspiration for percutaneous drainage is necessary for the relief of swelling and pain (18).

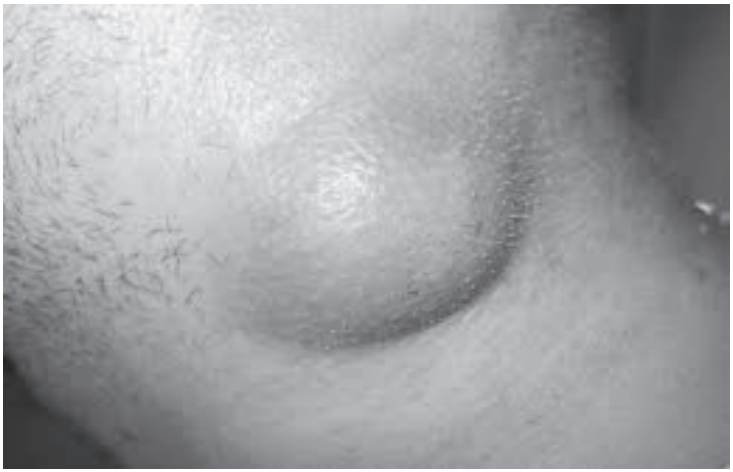


Plate 2: Collection of pus (abscess) round the soft tissue, present with swelling, redness and localized pain

III. **Pyomyositis** (bacterial myositis): characterized by pyogenic inflammation of the muscle commonly associated with HIV/AIDS symptomatic expression. It is endemic in warm, humid environments through opportunistic infection obtained in the prevalence of intravenous drug abuse, rhabdomyolysis and repetitive trauma among HIV/AIDS. Pyomyositis (bacterial myositis) is characterized by

a) Pain localized in the infected muscle group and an increased white blood cell (WBC) count.
b) Escalating pain, fever, and oedema of the infected muscle.
c) Abscess with necrosis of the muscle and septic.
d) Muscle enlargement leading to secondary oedema.
e) Intramuscular intense fluid collections result in oedema, hyperaemia, and myonecrosis (18, 19)

IV. **Osteomyelitis:** is inflammation of the bone caused by an infection from haematogenous seeding, the spread of infection to bone, from adjacent soft tissues and joints, and infection into the bone from trauma or surgery usually caused by pathogens *Bartonella Quintana* and *B. henselae* (*Rochalimae Quintana* and *R. henselae*) (7). Osteomyelitis in HIV/AIDS tends to affect the tibia bone, wrist bones, femoral heads, ribs, and thoracolumbar spine, and erythema

of the overlying soft tissues is indicated by elevated erythrocyte sedimentation rate. However, Scintigraphy is a sensitive method for the diagnosis and detection of early osteomyelitis (7) and a definitive diagnosis is usually established with a bone needle biopsy in osteomyelitis. Among HIV/AIDS patients, osteomyelitis has been commonly diagnosed with tuberculosis infection and bacillary angiomatosis. The infection spreads from the anterior aspect of the vertebral body into the vertebral disk space, sub-ligamentous area, adjacent soft tissues and epidural matter (8, 20).

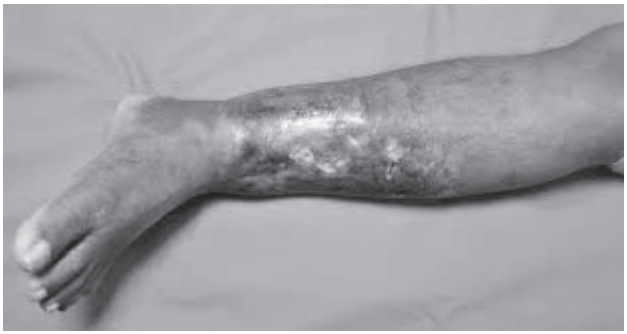


Plate 3: Inflamation of bone from the adjacent soft tissues (osteomyelitis)

Erosion of the anterior vertebral bodies with deformity of the adjacent soft-tissue mass and destructive changes involving the cortical bone of the vertebral bodies, and calcifications in the paravertebral soft tissues with a fluid collection (abscess formation) are usually associated with osteomyelitis. Deformity of the spinal cord and thickened nerve roots (Arachnoiditis) had been observed with the use of magnetic resonance imaging.

However, in the HIV-infected population bacillary angiomatosis is a rare form of osteomyelitis but anaemia, hepatomegaly and splenomegaly can manifest as the associated complications of HIV/AIDS musculoskeletal disorder (20). Osteolytic bone lesions diagnosed in bacillary angiomatosis distinguish bacillary angiomatosis infection from Kaposi's sarcoma (Mesenchymal tumour of the lymphatic and vascular system) in an inflammatory condition which involves vascular neoplasm that compromises the functional integrity of mucocutaneous tissues, lymph nodes, and visceral organs.

V. **Septic Arthritis:** is a joint infection that usually begins as a haematogenous spread or contiguous extension from a neighbouring soft-tissue infection or osteomyelitis. *S. aureus*, *N. gonorrhoeae*, *Candida albicans*, and *M. tuberculosis* are pathogens implicated in immunosuppressed HIV/AIDS patients (21). Septic Arthritis is characterized by erythema, soft-tissue swelling, and decreased joint movement. Joint effusion, bone erosion, osteoporosis, indistinct margins of the joint with joint space narrowing, septic bursitis of the olecranon, pre-patellar, sub-deltoid bursitis and oedema have been observed in HIV/AIDS patients.

B. Non-infectious (neoplasm) musculoskeletal disorders:

Non-Hodgkin's lymphoma (NHL) and Kaposi's sarcoma are the two most common neoplasms observed in HIV/AIDS patients and are responsible for musculoskeletal disorder (22). The incidence of non-Hodgkin's lymphoma (NHL) is 60 times greater in HIV/AIDS patients with $CD4^+$ counts <200 cells per microlitre. Non-Hodgkin's lymphoma (NHL) is characterized by primary lymphoma of bone (affecting the lower extremity, spine, pelvis, and skull without periosteal reaction) and permeative of a soft tissue mass often in the psoas muscle, pelvis or lower limb.

While Kaposi's sarcoma (KS) involves the manifestation of a local extension of a soft tissue mass, permeative and erosive lesions (periosteal reaction) and red blood cell pooling result from a mesenchymal tumour of the lymphatic and vascular system (7).

Musculoskeletal complications in non-Hodgkin's lymphoma (NHL) include lower extremity, spinal, pelvis, skull and extranodal sites. Bone marrow lesions are observed in one-third (1/3) of the HIV/AIDS patients; osseous extension fever, painful unilateral limb swelling, weight loss, pathologic limb fracture, lytic lesions, sclerotic lesions and lytic changes have been observed in HIV/AIDS patients (23). Musculoskeletal disorders in NHL are not associated with a periosteal reaction among the HIV/AIDS patients and are more commonly diagnosed in non-Hodgkin's lymphoma (NHL) than in those associated with Kaposi's sarcoma (24). However, Kaposi's sarcoma begins with multiple hyper-vascular lesions and progresses to form a tumour in about 20% of HIV/AIDS patients worldwide, but severe osseous complications have been observed in the African population (25).

C. Inflammatory Processes

Musculoskeletal inflammatory processes in HIV/AIDS patients exist in two (2) forms: arthritides and polymyositis. Rheumatic arthralgia is associated with an inflammatory process in HIV/AIDS infection. Articular pain syndrome, Reiter's syndrome, psoriatic arthritis, and the syndromes of oligo-arthritis and polyarthritis are the common manifestations of arthritides associated with HIV infection. Arthritis in HIV/AIDS patients is associated with unusual manifestations of rheumatologic disease (23).

Polymyositis is the most common muscular manifestation of HIV/AIDS infection and different from pyomyositis (musculoskeletal infection). Arthritides in the HIV/AIDS population is expressed in the form of arthritis caused by complex and multifactorial factors including:

i. localization of P-24 antigen synovial tissue, activation of the immune system;
ii. genetic factors such as human leukocyte antigen–B27;
iii. environmental factors such as infection with arthritogenic micro-organisms;
iv. molecular mimicry; and
v. decreased helper T-cell depletion allows immune regulated arthritides to occur.

Reiter syndrome in HIV/AIDS infected patients is usually caused by *Yersinia*, *Salmonella*, and *Shigella* species and human leukocyte antigen–B27 plays a role (70% to 80%) in the pathogenic expression of Reiter syndrome present (7, 20). Progressive $CD4^+$ cell depletion in HIV/AIDS infection (bacterial, viral, and parasitic infections caused by micro-organisms with atherogenic potential) permits a persistent gut infection and decreases the elimination of streptococcal and staphylococcal bacteria from the gut which results in spondyloarthropathies and psoriasis respectively. Reiter's syndrome is characterized by urethritis, arthritis, and conjunctivitis and usually affects the lower extremity (articulations of the foot, calcaneus, ankle, knee, and sacroiliac joints). Asymmetric alterations of synovial joints, symphyses, enthuses (bone erosion with adjacent bone proliferation) and paravertebral ossification are equally associated complications.

Psoriatic arthritis presents as the major assessment of musculoskeletal disorder in HIV/AIDS infection. This can express in the form of

I. Psoriatic rash characterized by a dermatological eruption of circumscribed, discrete and confluent reddish silver-scaled maculo-papules on the elbows, knees, scalp, and trunk. Psoriatic arthritis and Reiter's syndrome express similar rheumatologic features; however, Reiter's syndrome commonly affects the lower limb while Psoriatic arthritis is poly-articular and asymmetric and the infection of the sacroiliac joint and spine rarely occurs. Acute symmetric polyarthritis involves the small joints of the hands, characterized by rheumatoid arthritis, osteopenia, soft-tissue swelling, joint effusions and deformities (flexion contractures, ulnar deviations, and swan neck deformities), marginal erosions and periosteal reaction. Proliferative bone formation and periostitis are the major features that differentiate symmetric polyarthritis from classic rheumatoid arthritis (8, 20).

Therefore, HIV/AIDS-associated arthritis in musculoskeletal disorder caused by inflammatory processes is expressed in the form of oligoarticular, asymmetric, and involvement of the peripheral joints, particularly the knees, ankles, elbows, and shoulders. Furthermore, joint effusion (with or without periarticular osteopenia), arthralgia, painful articular syndrome (arthropathy), undifferentiated spondyloarthropathy (seronegative arthritis, osteoporosis, soft-tissue swelling, bone erosion, periosteal reaction), systemic lupus erythematosus, rheumatoid arthritis, and psoriasis are associated with musculoskeletal disorder caused by inflammatory processes in HIV/AIDS infection (11, 26).

Polymyositis: the HIV/AIDS antigens observed in endomysial macrophages exert an immunologic response that leads to muscle invasion by inflammatory elements (cytokines that bind to target cells and activate the inflammatory process) and it is distinguished from pyomyositis by bilateral symmetric proximal muscle weakness and elevated serum creatine kinase levels. In Myositis the inflammation occurs from opportunistic infections such as toxoplasmosis and virus (zidovudine, azidothymidine AZT). Mitochondrial DNA polymerase activities are altered by the presence of AZT, and this alteration results in myopathy (8, 27).

D. Arthropathies: include but are not limited to the following: osteonecrosis, osteoporosis, rhabdomyolysis, abnormal bone marrow and its related anaemia and hypertrophic osteoarthropathy form of skeletal disorders. These are referred to as miscellaneous processes.

I. **Osteonecrosis:** osteonecrosis in HIV/AIDS occurs mostly at the femoral head and bone marrow of the long bone diaphysis, both the distal and proximal, and is usually asymptomatic with an incidence of about 4.4%. Radiation exposure in the treatment of neoplasms among HIV/AIDS individuals has been implicated in osteonecrosis as well as alcohol intake, the use of steroids, and septic hip necrosis. Trauma and haemoglobinopathies also initiate osteonecrosis in HIV/AIDS individuals. Hyperlipidaemia (caused by inhibition of protease) associated with the use of antiretroviral therapy can result in osteonecrosis; this is because protease inhibitors impair the metabolism of corticosteroids. For example; multifocal osteonecrosis had been observed in high serum levels of antiphospholipid antibodies caused by arterial and venous thrombosis and thrombocytopenia (3, 18) which increase intra-osseous platelet aggregation and fibrin platelet thrombosis produces intravascular coagulation, ischaemia, and bone necrosis.

II. **Osteoporosis** results from the depletion of mineral density in the bone affecting about 46% of HIV/AIDs individuals. Protease inhibitors, nucleoside-related mitochondrial toxicity or lactic acidosis, the development of lipodystrophy, immune reconstitution, nutritional and hormonal factors have been implicated in the decrease of bone mineral density followed by the wasting of muscle and bone.

III. **Rhabdomyolysis** is a nonspecific clinical and laboratory syndrome which involves muscle cell injury. It is caused by the direct infection of muscle cells or by an imbalance between the energy metabolism of muscle cells, resulting in the abnormal release of creatine kinase and myoglobin from the affected cells into the circulation. Rhabdomyolysis is characterized by

a) The presence of pigments in urine in association with myalgia, secondary renal insufficiency, and renal failure;
b) Muscle swelling, weakness, and pain;

c) Elevated creatine kinase levels, along with some degree of haematuria;
d) Calcification of muscles in the back, thighs, and pelvis; and
e) Observed renal enlargement, persistent nephrogram, and perinephric fluid (13).

The usual causes of rhabdomyolysis in HIV/AIDS infection include alcohol abuse, trauma, drugs and seizures, electrolyte disorders and infections.

IV. **Hypertrophic Osteoarthropathy** is a musculoskeletal systemic disorder that primarily affects the bones, joints, and soft tissues and is associated with pulmonary neoplasm in HIV/AIDS with *P. carinii* pneumonia**.** Hypertrophic osteoarthropathy is characterized by leg pain, arthralgia and periarticular soft-tissue swelling around the ankles, knees, and elbows. An initial pericortical inflammatory reaction with round cell infiltration and proliferation of vascular connective tissue occurs, followed by osteoid formation and calcification. A smooth periosteal reaction involves the diaphysis of the long bones and as the disease progresses, the periosteal reaction becomes irregular and extends to involve the metaphysis and epiphysis (27).

E. Myopathies: are referred to as the weakness of the skeletal muscles that affects particularly the ocular muscles, facial muscles, upper and lower limbs, the trunk, swallowing, and breathing muscles. This muscular disorder is not related to innervation or neuromuscular junction diseases. Infection caused by HIV/AIDS, metabolic disorders, inflammatory, endocrine disturbance, toxins (even drug-induced toxins), genetics, and idiopathy play major roles in the weakening, atrophy, and dystrophies of skeletal muscles and myoglobinuria (dark urine colouration) noticed in myopathy. HIV-associated myopathies develop at any stage of HIV/AIDS infection. Inflammatory myopathy (Polymyositis, Dermatomyosotis and Myositis) is the prevalent form of myopathies among others such as Muscular dystrophies (X-linked recessive, Oculopharygeal and Fasioscapulohumeral) Myotonic Syndromes, Congenital myopathy, Metabolic myopathy (Glycogen storage disorders, Mitochondrial, Periodic paralysis) and Endocrine myopathy (Thyroid, Parathyroid, Adrenal and Pituitary) (3, 16, 28).

F. Image Techniques in Musculoskeletal Disorders in HIV/AIDS Patients

Computerised Tomography (CT) is performed for lymphomas because of its superior spatial resolution. CT gives a more detailed characterization of lytic bone changes, and reveals the calcification of muscles in the back, thighs, and pelvis (psoas muscle). More importantly, renal enlargement, persistent nephrogram and perinephric fluid are observed (13).

Magnetic Resonance imaging (MRI) is the method of choice for evaluating bone marrow changes and adjacent soft tissue. MRI is preferred for pyomyositis, peripheral neuropathy, polymyositis, bone marrow abnormalities (lymphoma or infection), joint effusion (periarticular osteopenia), arthralgia and painful articular syndrome (arthropathy). MRI is outstanding in depicting spondylo-arthropathy in seronegative arthritis, osteoporosis, soft-tissue swelling, bone erosion, periosteal reaction, asymmetric alterations of synovial joints, symphyses and paravertebral ossification.

Computerized Tomography, Magnetic Resonance Imaging, and Scintigraphy have a complementary role in evaluating Kaposi's sarcoma as the cause of focal pain in HIV/AIDS patients showing cortical lesions in bone erosion and osseous destruction, as well as periosteal reaction. They equally reveal osteopenia, soft-tissue swelling, joint effusions, joint space narrowing, joint deformities such as flexion contractures, ulnar deviations, swan neck deformities and proliferative bone formation and periostitis (to differentiate symmetric polyarthritis from classic rheumatoid arthritis) (24).

Scintigraphy forms a potential tool for narrowing the differential diagnosis and shows red blood cell pooling. Bone scintigraphy reveals an increased radiotracer uptake in muscles affected by rhabdomyolysis.

G. Conclusion

Human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) progressively eliminates $CD4^+$ T-helper lymphocytes and permits opportunistic infections and tumours that compromise the three (3) principal components: the joint (cartilages, tendons and ligaments), the muscle (soft tissue) and the bone (osseous tissue) of the musculoskeletal system leading to a variety of disorders involving the

musculoskeletal system that are classified as Infectious, Non-infectious (neoplasm), Arthropathies and Myopathies affecting the three components of this system in HIV/AIDS individuals. Therefore, adequate knowledge of the existence and the characteristic pathological appearance of the conditions affecting osseous tissue, articular cartilages, and muscle (soft tissues) in HIV/AIDS individuals using radiological imaging techniques specific for each pathological condition is valuable for diagnosis, detection, and the appropriate treatment regimen.

References

1) Lucas S. The pathology of HIV infection. 2002; *Lepr Rev.* 73: 64–71.
2) Obioha EE. Exploring the Cultural Context of HIV/AIDS Pandemic in a Nigerian Community: Implication for Culture-Specific Prevention Programmes. 2008; 10(4): 269–276.
3) Damsgaard M. Analysis of musculoskeletal systems in the AnyBody Modeling System. *Simulation Modelling Practice and Theory* 2006; 14(8): 1100–1111.
4) Boyle A. Musculoskeletal Manifestations of HIV Infection. *AIDS Read.* 2003; 13(2): 1–5.
5) Mahajan A, Vishal RT, and Verma S. Rheumatological Manifestations of HIV Infection. 2006; 7(2): 136–44.
6) Pullen S. Musculoskeletal Considerations in HIV Disease : A Critical Review. *Musculoskeletal Medicine* 2014; 17(2(2)): 1–6
7) Odero R. Imaging Findings implications of Aids 1 Objectives. 2004; 1029–1049.
8) Tehranzadeh TO. Musculoskeletal disorders associated with HIV infection and AIDS. *Skeletal Radiol.* 2004; 33(5): 249–59.
9) Bianchi S, Martinoli C. Ultrasound of the Musculoskeletal System. *Radiology* 2007; 252: 346–346.
10) Ireland ML, & Ott SM. The effects of pregnancy on the musculoskeletal system. *Clinical Orthopaedics and related research* 2000; (372): 169–79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10738426.
11) Klatt EC. Pathology Of HIV/AIDS, 2016
12) Templeton PA. *Clinical tests for the musculoskeletal system*. 2010.
13) Gauri, LA. & Fatima Q. Musculoskeletal manifestations of diabetes mellitus. *Journal of the Indian Medical Association.* 2009; 107(11): 810–821.
14) Anandacoomarasamy A, Fransen M & March L. Obesity and the musculoskeletal system. *Current opinion in rheumatology* 2009; 21(1):

71–77.
15) Arkkila PET & Gautier JF. Musculoskeletal disorders in diabetes mellitus: an update. Best practice & research. *Clinical Rheumatology* 2003; 17(6): 945–70. Available at http://www.sciencedirect.com/science/article/pii/S1521694203001244.
16) Chun R. Common malignant musculoskeletal neoplasms in dogs and cats. *Veterinary Clinics of North America – Small Animal Practice* 2005; 35(5): 1155–1167.
17) Shultz SP, Anner J & Hills AP. Pediatric obesity, physical activity, and the musculoskeletal system. *Obesity Reviews*. 2009; 10(5): 576–582.
18) Exhibit E & Sayer C. Musculoskeletal pathology in HIV – A comprehensive case-based radiological review from a specialist HIV institution, 2013.
19) Moriatis WJ, Cameron KL & Owens BD. Impact of joint laxity and hypermobility on the musculoskeletal system. *The Journal of the American Academy of Orthopaedic Surgeons* 2011; 19(8): 463–471.
20) Szymańska J. Disorders of the musculoskeletal system among dentists from the aspect of ergonomics and prophylaxis. *Annals of agricultural and environmental medicine: AAEM*, 2002; 9(2): 169–73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12498585.
21) Jandial S, & Foster HE. Examination of the musculoskeletal system in children – a simple approach. *Pediatrics and Child Health* 2008; 18: 47–55.
22) Anandacoomarasamy. The impact of obesity on the musculoskeletal system. *International journal of obesity* 2008; 32(2): 211–222.
23) LeBlanc KE & LeBlanc LL. Musculoskeletal disorders. *Primary care* 2010; 37(2): 389–406.
24) Gilles B, Moccozet L & Magnenat-Thalmann N. Anatomical modeling of the musculoskeletal system from MRI. Medical image computing and computer-assisted intervention: MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention. 2006; 9(Pt 1): 289–296.
25) Gosselin RA, Phillips JJ, & Coughlin RR. *Diseases of the Musculoskeletal System. 2012* Available at http://dx.doi.org/10.1016/B0-7216-9052-1/50011-9.
26) Naraghi A & White LM. Three-dimensional MRI of the musculoskeletal system. *American Journal of Roentgenology* 20112; 199(3): 283–293.
27) Chang EY, Du J & Chung CB. UTE imaging of the musculoskeletal system. *Journal of Magnetic Resonance Imaging*, 2014; 883: 870–883.
28) Covey DC. Blast and fragment injuries of the musculoskeletal

system. *The Journal of bone and joint surgery.* American volume, 2002; 84-A(7): 1221–1234.

Skin Manifestations of HIV Infection

Olubukunola Omobuwa
MBChB, MPH, FWACP

Skin disorders are quite common and usually more aggressive in human immunodeficiency virus (HIV)-positive patients than the general population. The skin lesions in HIV disease can be of bacterial, viral, parasitic or fungal origin. Kaposi's sarcoma which is a cancerous lesion of tissues can also occur. Cutaneous manifestations are early and easily identifiable markers of HIV infection. They can help in predicting the severity and progress of the disease. Diseases of the skin and mucous membranes were among the first recognized clinical manifestations of acquired immune deficiency syndrome (AIDS) in the early 1980s. In some patients, skin findings may be the earliest and the only sign of HIV presentation, and can thus alert one to an early diagnosis and treatment (1).

The dermatological manifestations increase both in frequency and severity with the progression of HIV with a decline in CD4+ cell counts thus serving as important markers of disease progression especially in countries with poor resources (2). HIV infection can lead to a variety of cutaneous manifestations in approximately 80-95% of those affected. Dermatologic disease in HIV-infected patients may be severe, atypical, and difficult to treat. Because dermatologic manifestations may be the first clue to HIV infection, offering HIV testing to affected individuals can lead to early diagnosis and treatment as well as a decrease in disease progression and transmission (3).

Clinicians should be familiar with the wide variety of mucocutaneous manifestations in HIV-infected persons as they commonly have cutaneous abnormalities; with the prevalence of such mucocutaneous manifestations approaching 100% (4-6). Some of the conditions are unique and actually pathognomonic for HIV disease; a typical example is Kaposi's sarcoma (KS).

Although some dermatologic diseases have decreased markedly in frequency in the potent antiretroviral therapy era, other conditions remain common. Among HIV-positive individuals with low CD4+ cell counts who are not on or not adherent to antiretroviral therapy, notable skin manifestations include psoriasis, photodermatitis, prurigo nodularis, molluscum contagiosum, and adverse drug reactions. Conditions that remain relatively common despite adequate antiretroviral therapy include eczema, xerosis, warts, and Kaposi's sarcoma. Disorders that are associated with immune reconstitution under potent antiretroviral therapy include acne, staphylococcal infections, and erythema nodosum (7). Skin findings are regarded by the World Health Organization as useful in assessing the severity of HIV infection in patients in resource-limited environments (8).

Classification of Dermatologic Manifestations of HIV/Aids

Papulosquamous Dermatoses/inflammatory lesions of HIV/AIDS

Pruritic papular eruption (PPE) is one of the commonest skin manifestations in HIV-infected patients. The lesions appear as small, itchy, red, or skin-coloured papules on the head, neck, and upper part of the trunk. The cause is unknown. According to Boonchai et al., 81.25% of patients with PPE tend to have advanced immunosuppression (9).

Eosinophilic folliculitis manifests as an idiopathic, highly pruritic, papulopustular eruption of sterile pustules involving the face, neck, trunk, and extremities (10). Acquired ichthyosis may start to appear on the lower extremities and disseminate in advanced HIV disease. Acquired ichthyosis may be a marker of concomitant infection with HIV-1 and human lymphotropic virus II in persons who use intravenous drugs and have profound helper T-cell depletion (11).

Other lesions which have been reported include seborrhoeic dermatitis, xerosis (dryness of the skin), ichthyosis, lichenoid eruption, psoriasis, and cutaneous drug eruptions (12).

Bacterial infections

Impetigo and folliculitis may occur in a recurrent and persistent fashion in HIV disease, especially in children. Disseminated furunculosis, gingivitis, gangrenous stomatitis, as well as abscess formation can also occur in

patients with HIV infection. Bacillary angiomatosis, which is caused by *Bartonella henselae,* and much less commonly by *Bartonella quintana,* usually presents as red papules and nodules (13).

Mycobacterial infections

Mycobacterium tuberculosis; M. avium-intracellulare complex (MAC); and occasionally *M. kansasii,* may present as acne-like papules and indurated crusted plaques.

MAC, a common opportunistic pathogen among patients with AIDS, usually causes disseminated disease involving the lungs, lymph nodes, and gastrointestinal tract. Primary cutaneous infections with MAC are extremely rare; most cutaneous lesions are caused by dissemination. Cutaneous manifestations reported thus far include the scaling plaques, crusted ulcers, ecthyma-like lesions, verrucous ulcers, inflammatory nodules, panniculitis, pustular lesions, and draining sinuses. Localized skin involvement resembling sporotrichosis is unusual. Primary cutaneous MAC infection presenting as sporotrichosis-like lesions has been described in an AIDS patient (14).

The possibility of co-infections, which may be multiple, should be borne in mind. Co-infection with *B. quintana*, MAC, and cytomegalovirus (CMV) has been reported in a patient with AIDS (15).

In individuals with HIV infection, *M. haemophilum* can also present as violaceous draining nodules and superficial ulcers on the extremities (upper and lower limbs), trunk, head, and genitalia.

Syphilitic skin lesions in HIV infection

Co-infection with syphilis (as well as other sexually transmitted diseases) may occur in HIV-infected patients, particularly among homosexuals or bisexuals or illicit drug users. Syphilitic ulcers are believed to enhance HIV transmission.

Most cases of syphilis that occur in HIV infection are clinically and serologically typical (16) whereas some are not (17). A high rate of re-infection was observed in one French study, with less severe cutaneous manifestations (16). However, syphilis seroconversion may be delayed, and standard serologic tests that help in diagnosing syphilis may not be reliable. Also, in primary syphilis, presentation with multiple ulcers has

been found to be commoner in HIV-infected patients. Rapid progression of secondary syphilis to tertiary syphilis and syphilis maligna has been reported in HIV-infected patients. An appropriate serologic follow-up to ensure an adequate response to treatment is important in patients with HIV infection.

Staphylococcus aureus infection

Patients with HIV have been found to have higher rates of cutaneous colonization by *Staphylococcus aureus,* and sepsis and deep tissue infection can be common in those with advanced disease. Methicillin-resistant *S. aureus* (MRSA) soft-tissue infection is also an increasing problem (18). Pyoderma has been reported as a fairly common skin lesion in HIV disease (12).

Viral infections

In patients infected with HIV, several viruses of the Herpesviridae family may lead to cutaneous disease, including chronic perianal and perioral herpetic ulcers caused by the herpes simplex virus (HSV), recurrent typical dermatomal zoster caused by the herpes zoster virus (HZV), and disseminated CMV infection.

Herpes simplex and herpes zoster viruses

Recurrent oral and anogenital HSV infection is common in patients infected with HIV, and may lead to chronic ulcerations. In paediatric patients, HSV stomatitis is more common than varicella zoster virus (VZV) and may become chronic and ulcerative. Patients with VZV may develop chronic ecthymatous VZV. Acute disseminated HZV infection and the following atypical manifestations have also been described:

- Hyperkeratotic papules;
- Folliculitis;
- Verrucous lesions;
- Chronic ulcerations; and
- Disseminated ecthymatous lesions.

Chronic VZV infections associated with HIV-1 infection begin as vesicles and progress into necrotic, nonhealing ulcers (19, 20). Chronic VZV infection may resemble basal cell carcinoma (21).

Epstein-Barr virus

Epstein-Barr virus (EBV) has been found to be associated with the pathogenesis of oral hairy leukoplakia, which may develop in HIV-infected persons, particularly men. Oral hairy leukoplakia is characterized by filiform white papular lesions localized on the sides of the tongue. This condition does not undergo malignant transformation but may be the initial sign of progressive immunosuppression. White plaques caused by EBV may be confused with oral candidiasis, lichen planus, and geographic tongue.

Cytomegalovirus

CMV is a DNA virus in the herpesviridae family. Ulcers in the perineal region are the most common presentation of CMV infection in patients infected with HIV-1. The concurrent involvement of other infectious agents, such as HSV, in the same lesions confounds the role of CMV in cutaneous lesions. HSV is proposed to be the initiating infection leading to ulcer formation, with CMV secondarily localizing in the granulation tissue.

CMV infection of the eccrine ducts resulting in squamous metaplasia has been described in a patient with HIV. Diagnosing skin CMV infection in individuals infected with HIV is important. The presence of CMV infection is considered a poor prognostic sign in HIV disease (22).

Other viral infections reported in HIV infection include molluscum contagiosum and warts.

Parasitic infestations

Scabies

In HIV-infected patients the most common ectoparasitic skin infestation is scabies. Presentations may vary from classic crusted papules to severe keratotic, crusted and pruritic dermatitis (23).

Fungal infections

Candida infections

Recurrent and persistent mucocutaneous candidiasis is common in individuals with HIV infection. Oral thrush, particularly if extending to the oesophagus has been widely reported to be synonymous with severe immunosuppression (24). Vaginal candidiasis has also been reported, being found to occur concomitantly with oral candidiasis and AIDS-defining medical conditions (25).

Tinea infections

In adults, generalized dermatophytosis, or tinea capitis, which is typically caused by *Trichophyton rubrum,* may suggest HIV infection.

Neoplastic skin manifestations in HIV infection

Kaposi's sarcoma (KS) is a type of cancer that develops in connective tissues like bone, cartilage, fat, blood vessels, and muscle tissues. For decades, KS was considered a rare disease; however, in the last two decades, with the advent of HIV/AIDS, more people are being diagnosed with KS. The disease usually causes tumours to form in the subcutaneous tissues, which appear as raised blotches or lumps that may be purple, brown, or red in colour. Researchers believe a type of herpes virus causes HIV-related KS. The herpes virus is usually dormant in healthy individuals whereas people with compromised immune systems including people with HIV/AIDS, may develop KS as a result of the infection (22).

Conclusion

Cutaneous manifestations can therefore be considered as good clinical indicators to predict and assess the underlying immune status in resource-poor countries. Furthermore, HIV infection should be suspected when a cutaneous lesion tends to be chronic, severe, bizarre, or involving more than one dermatome.

Physicians caring for People Living with HIV should be familiar with the diagnosis and management of common cutaneous lesions because prompt and appropriate management of these conditions will reduce morbidity.

References

1. Goldstein B, Berman B, Sukenik E, Frankel SJ. Correlation of skin disorders with CD4 lymphocyte counts in patients with HIV/AIDS. *J Am Acad Dermatol.* 1997; 36: 262-264.
2. Vasudevan B, Sagar A, Bahal A, Mohanty AP. Cutaneous manifestations of HIV – a detailed study of morphological variants, markers of advanced disease, and the changing spectrum. *Medical Journal Armed Forces India (MJAFI)*. 2012; 68(1): 20-27.
3. Uthayakumar S, Nandwani R, Drinkwater T, Nayagam AT, Darley CR. The prevalence of skin disease in HIV infection and its relationship to the degree of immunosuppression. *Br J Dermatol* 1997; 137: 595-598.
4. Koehler JE, Quinn FD, Berger TG, et al. Isolation of Rochalimaea species from cutaneous and osseous lesions of bacillary angiomatosis. *N Engl J Med* 1992; 327: 1625-1631.
5. Schwartzman WA. Infections due to Rochalimaea: The expanding clinical spectrum. *Clin Infect Dis.* 1992; 15: 893-900.
6. Slater LN, Min KW. Polypoid endobronchial lesions: A manifestation of bacillary angiomatosis. *Chest.* 1992; 102: 972-974.
7. International AIDS Society – USA. Dermatologic Manifestations of HIV Infection. *HIV Med.* 2005; 13(5): 149-154.
8. World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. Geneva, Switzerland: World Health Organization, 2006. Available at http://www.who.int/hiv/pub/vct/hivstaging/en/. Accessed on 22 August, 2015.
9. Boonchai W, Laohasrisakul R, Manonukul J, Kulthanan K. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. *Int J Dermatol*. 1999; 38(5): 348-50.
10. Puig L, Pradinaud R. Leishmania and HIV co-infection: dermatological manifestations. *Ann Trop Med Parasitol*. 2003; (97 Suppl. 1): 107-14.
11. Kaplan MH, Sadick NS, McNutt NS, Talmor M, Coronesi M, Hall WW. Acquired ichthyosis in concomitant HIV-1 and HTLV-II infection: a new association with intravenous drug abuse. *J Am Acad Dermatol*. 1993; 29(5: 1): 701-8.
12. Shittu et al. Dermatological Lesions in HIV Patients. *World J Life Sci. and Medical Research* 2013; 3(1): 26.
13. Plettenberg A, Lorenzen T, Burtsche BT, Rasokat H, Kaliebe T,

Albrecht H, et al. Bacillary angiomatosis in HIV-infected patients – an epidemiological and clinical study. *Dermatology* 2000; 201(4): 326-31.
14. Kayal JD, McCall CO. Sporotrichoid cutaneous Mycobacterium avium complex infection. *J Am Acad Dermatol*. 2002 Nov.; 47(5 Suppl): S249-50.
15. Rovery C, Rolain JM, Lepidi H, Zandotti C, Moreau J, Brouqui P. Bartonella quintana coinfection with Mycobacterium avium complex and CMV in an AIDS patient: case presentation. *BMC Infect Dis*. 2006; 6: 89.
16. Courjon J, Hubiche T, Dupin N, Grange PA, Del Giudice P. Clinical Aspects of Syphilis Reinfection in HIV-Infected Patients. *Dermatology*. 2015; 230: 302-307.
17. Balagula Y, Mattei PL, Wisco OJ, Erdag G, Chien AL. The great imitator revisited: the spectrum of atypical cutaneous manifestations of secondary syphilis. *Int J Dermatol*. 2014; 53(12): 1434-41.
18. Rodgers S, Leslie KS. Skin infections in HIV-infected individuals in the era of HAART. *Curr Opin Infect Dis*. 2011; 24(2): 124-9.
19. Leibovitz E, Cooper D, Giurgiutiu D, Coman G, Straus I, Orlow SJ, et al. Varicella-zoster virus infection in Romanian children infected with the human immunodeficiency virus. *Pediatrics* 1993: 92(6): 838-42.
20. Leibovitz E, Kaul A, Rigaud M, Bebenroth D, Krasinski K, Borkowsky W. Chronic varicella zoster in a child infected with human immunodeficiency virus: case report and review of the literature. *Cutis*. 1992: 49(1): 27-31.
21. Tsao H, Tahan SR, Johnson RA. Chronic varicella zoster infection mimicking a basal cell carcinoma in an AIDS patient. *J Am Acad Dermatol*. 1997: 36(5): 831-3.
22. Schwartz RA. Cutaneous Manifestations of HIV. Available at www.medscape.com. Accessed on 1 December, 2015.
23. Hamann ID, Barnetson RS. Non-infective mucocutaneous presentations of human immunodeficiency virus infection. *Australasian Journal of dermatology.* 1997; 38(3): 105-14.
24. Obuekwe ON, Onunu AN. Gender and oral manifestations of HIV infection among adult Nigerians. *African Journal of Reproductive Health*. 2006; 10(2): 81-89.
25. Mawenzi RL, Oguttu OR, Williams HC, Joash A. Epidemiology and clinical spectrum of cutaneous diseases manifesting among newly diagnosed HIV seropositive adults in Nakuru County-Kenya. *Continental Journal of Medical Research*. 2013; 7: 1-9.

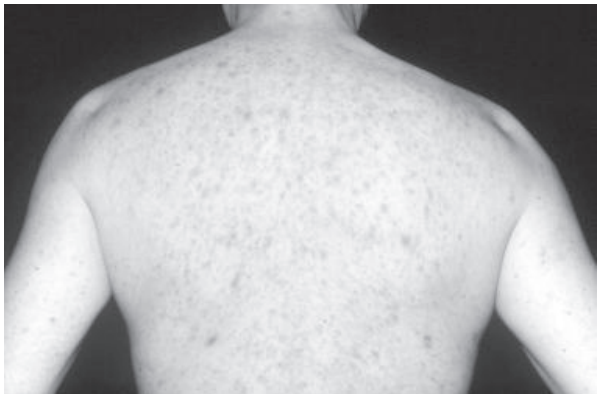


Fig. 1: PPE: Dull red, bluish-purple, maculopapular lesions on the upper part of the trunk (back) in a 49-year-old man with primary HIV-1 infection (Source: Schwartz RA. Cutaneous Manifestations of HIV, available at www.medscape.com)

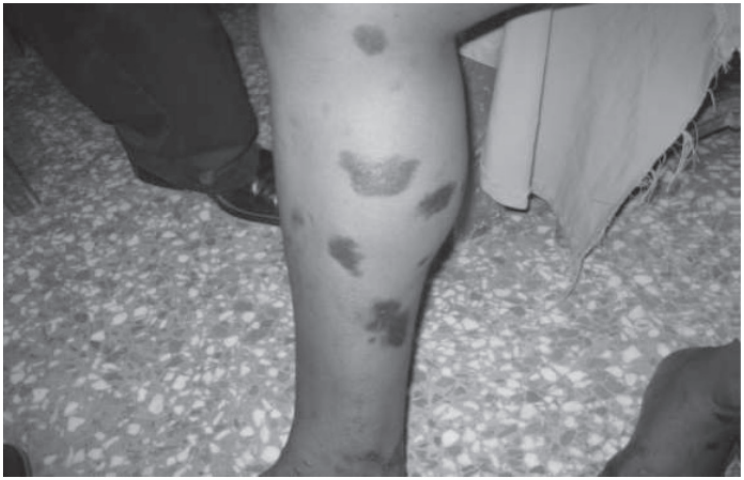


Fig. 2: AIDS patient with pruritic popular eruption – PPE (Source: *World J Life Sci. and Medical Research* 2013; 3 (1): 30)

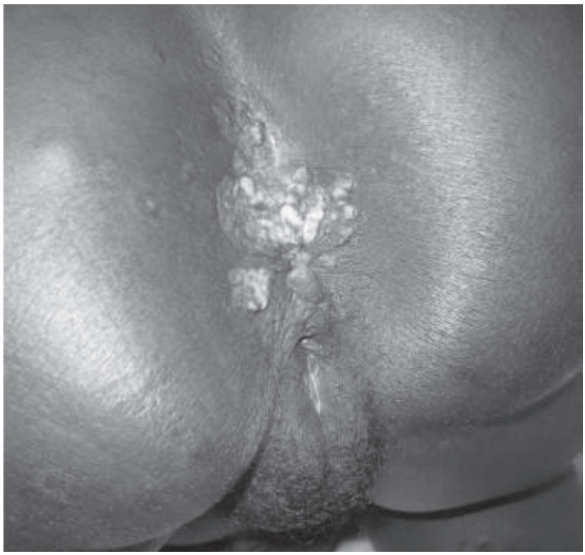


Fig. 3: Genital wart in an HIV positive patient (Source: *World J Life Sci. and Medical Research* 2013; 3 (1): 30)

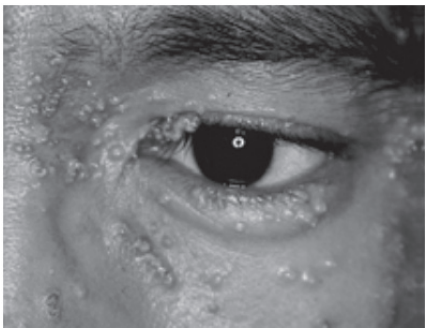


Fig. 4: Molluscum contagiosum (Source: Ansary MA, Hira SK, Bayley AC, et al., *A Colour Atlas of AIDS in the Tropics*. London, Wolfe Medical Publications, 1989)

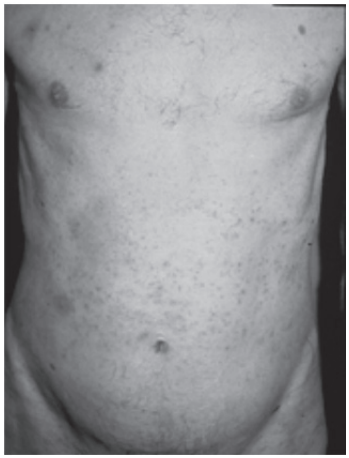


Fig. 5: Scabies (Source: The Prn Notebook™ • Volume 2, Number 4 • August 1997)

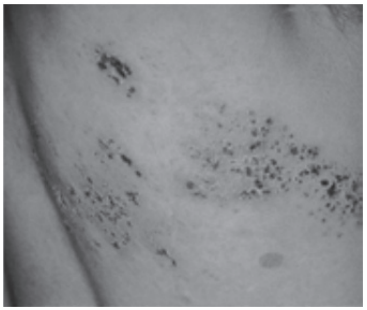


Fig. 6: Herpes zoster: lesions are dermatomal
(Source: The Prn Notebook™ • Volume 2, Number 4 • August 1997)

ORAL MANIFESTATION OF HIV/AIDS

AKINGBOLA ALEXANDER OJO, BDS
AND OLUBAYO ABIODUN FASOLA
BDS, MSC, DIP ETHICS, FWACS, FICD

Human Immunodeficiency Virus (HIV) is a lentivirus; a C-type retrovirus that causes HIV infection which subsequently leads to Acquired Immune Deficiency Syndrome (AIDS). It was first reported in 1981 in the United States of America among homosexuals and a report was first published by the Centers for Disease Control and Prevention, CDC in 1993. It was however reported to have originated from Africa (1). The virus attacks the human body by binding to CD4 molecules found on T-Helper cells (T_H cells), which helps in the maturation of plasma cells into memory B-cells, the activation of cytotoxic T-cells and the activation of macrophages – the dominant cell in chronic inflammation; as well as monocytes. The attack on CD4 molecules on these cells leads to the depletion of these cells, resulting in a reduced immune response and subsequently the susceptibility of infected individuals to opportunistic infection which may manifest in the head and neck region of the body. The Acquired Immune Deficiency Syndrome which is a constellation of diseases, usually typical of opportunistic infection and tumours, is the late stage progression of the Human Immunodeficiency Virus infection as the virus causes the dysfunction and depletion of the immune cells.

In 2016, about 36.7 million people were living with HIV and 1 million deaths were recorded (2). Most of the infected cases live in sub-Saharan Africa (3). HIV is however transmitted through unprotected sexual intercourse with an infected individual, a breach in the integrity of the protective mucosa by infective sharp objects, transfusion by infected blood, from mother to child during pregnancy and through breastfeeding a child by an infected mother.

Oral lesions are one of the early clinical presentations of HIV infection (4). They can help in the prediction of the severity of immunodeficiency

and the disease (5-6). Studies have shown that more than 90% of patients are presenting with at least one oral disease during the course of the disease (7). These lesions may be present in up to 50% of cases of HIV and about 80% of those with a diagnosis of AIDS (8). Hence the presence of these oral lesions in patients is a strong indication of the presence of HIV infection, hence the need for a retroviral screening for confirmation (9). Some of the areas mostly affected in the orofacial regions include the tongue, the palate, the buccal mucosa, the periodontium, the floor of the mouth, and the skin covering of the head and neck region (10). The affectation of the tongue has been involved in the death of up to 75% of patients with AIDS (8). An early study conducted by Berberi and co-workers on 50 patients documented the commonest oral lesion to be Pseudomembranous candidiasis (11).

A viral load greater than 3000 copies/ml, a CD4 count less than 200 cells/mm^3, smoking and poor oral hygiene are reported to be additional predisposing factors towards developing HIV/AIDS-related oral lesions. Generally, oral lesions in HIV patients were found to be prevalent: 39% German population (12), 78% South Africans (13) and 36.4% to 84% in various studies in different geopolitical zones (14-19).

Classifications

A. Aetiological factors (20)

Bacteria Periodontal diseases Necrotizing ulcerative periodontitis Linear gingival erythema Granulomatous lesions related to Mycobacterium infection
Fungi Oral Candidiasis Cryptococcus Neoformans Histoplasmosis
Viral Herpes Simplex Herpes Zoster Human Papilloma Virus Cytomegalovirus
Tumours/Neoplasia Kaposi’s Sarcoma Lymphoma

Others Oral ulcers – Aphthous ulcer Idiopathic – Thrombocytopenic Purpura Salivary Gland Disease Side effects/adverse effects of Anti-retroviral Drugs

B. Strength of the association with HIV/AIDS (21)

Another classification was used by the EC-Clearing House on Oral problems related to HIV infection and the WHO Collaborating Centre on the Oral manifestation of Human Immunodeficiency Virus (21).

1. Lesions strongly associated with HIV
   - Pseudomembranous Candidiasis
   - Erythematous Candidiasis
   - Angular Cheilitis
   - Hairy Leukoplakia
   - Kaposi's Sarcoma
   - Non-Hodgkin's Lymphoma
   - Linear Gingival Erythema
   - Necrotizing Ulcerative Gingivitis
   - Necrotizing Ulcerative Periodontitis.

2. Lesions less commonly associated with HIV
   - Mycobacterium Avium Intracellulare
   - Mycobacterium Tuberculosis
   - Melanotic Hyperpigmentation
   - Necrotic Ulcerative Stomatitis
   - Salivary Gland Diseases
   - Xerostomia due to reduction in salivary flow
   - Unilateral or bilateral major salivary gland swelling
   - Thrombocytopenic Purpura
   - Ulceration Non-otherwise-specified
   - Herpes Simplex Virus
   - Human Papilloma Virus.

3. Lesions seen in HIV infection
   - Actinomyces isreali
   - Escherichia coli
   - Klebsiella pneumoniae
   - Cat-Scratch Disease
   - Drug Reactions (ulceration, Erythema multiforme, lichenoid, toxic epidermolysis)

- Cryptococcus neoformans
- Histoplasmosis
- Mucormycosis
- Aspergillosis
- Geotrichum candidum
- Facial nerve palsy
- Trigeminal neuralgia
- Recurrent aphthous ulcer
- Cytomegalovirus infection.

Pseudomembranous Candidiasis

This is an acute variance of Oral Candidiasis commonly referred to as thrush caused by Candida albicans (mycotic infection). This is the commonest type of oral candidiasis as it accounts for about 55.8% to 69.7% of oral candidiasis cases (22-23). Candida albicans is found in the mouth of 50% of the world's population as normal flora (24). However, it can become an opportunistic infectious disease when the immune system is affected as a result of some local or systemic factors. The characteristics of Pseudomembranous candidiasis include white coatings or individual patches of pseudomembranous white slough which when wiped reveals erythematous and sometimes minimally bleeding, mucosa beneath. This is the *cottage cheese or curdled milk appearance*. The white materials are made up of debris, fibrin and desquamated epithelium, that have been invaded by yeast cells and hyphae that invade the depth of the stratum *Spinosum*. It can involve any part of the mouth, but commonly appears on the tongue, buccal mucosa and palate. The condition is usually acute in nature but may become chronic which is typical of the immunosuppression state or people who use corticosteroids topically or inhalers. Finally, there is a disturbance of taste.

Erythematous Candidiasis

This is also known as atrophic candidiasis and it appears as a red raw-looking lesion. It may be seen usually preceding the pseudomembrane or after the pseudomembrane is removed or at times, it may occur on its own without a prior pseudomembrane. It is usually located in the palate and the dorsum of the tongue but rarely on the buccal mucosa. White spots may be seen which are not conspicuous. It is reported to make up to 25.7% to 50% of all cases of candidiasis (22-23) and can be classified into acute erythematous and chronic erythematous candidiasis. Acute erythematous

candidiasis is commonly painful and associated with prolonged antibiotics or corticosteroid, however, the chronic erythematous candidiasis is associated with prolonged denture wearing. The two subtypes are seen in HIV-infected patients.

Angular Cheilitis

This is an inflammation seen at the corner of the mouth, commonly involved in candida infection. The prevalence ranges from 13.7% to 27.1% of all cases of oral candidiasis in HIV patients (22-23). Candidiasis is responsible for 20% of the cases while the mixture of candida and Staphylococcus aureus causes 60% of the cases. Characteristically, there is soreness, erythema, and fissuring of one or both angles of the mouth, oedema is seen intraorally on the commissures and may also be related to prolonged denture use.

In patients with pseudomembranous candidiasis, the membraneous slough can be wiped off to expose an erythematous surface underneath. This helps to distinguish it from other lesions, which cannot be wiped off such as seen in Lichen planus and hairy leukoplakia. Erythematous candidiasis resembles a geographic tongue. It however has a diffused border that differentiates it from erythroplakia normally seen with sharply defined borders. Swabs or smears can be taken from different areas of the mouth for microscopy. An oral rinse of the mouth with normal saline can be done for a minute followed by the spitting of the solution into a vessel for laboratory investigation. This method helps to differentiate between commensal candida carriage and candidiasis. Smears are usually stained with periodic acid-Schiff which stains the fungal cell walls. Candida is gram-positive (25).

The histologic appearance may be variable depending on the clinical type of candidiasis. Pseudomembranous candidiasis shows hyperplastic epithelium, with a superficial parakeranotic desquamating layer (26). The hyphae penetrate the depth of the stratum spinosum (27) and appear as basophilic structures. Polymorphonuclear cells infiltrate the epithelium while the chronic inflammatory cells infiltrate the lamina propria (24).

Erythematous candidiasis appears as thin, atrophic epithelium, which is non-keratinized. Hyphae are sparse and inflammatory cell infiltration of the epithelium and the lamina propria also occurs. In essence, it appears as the pseudomembranous candidiasis without the superficial desquamating layer (24).

Topical antifungal drugs such as nystatin, miconazole, gentian violet and amphotericin B are the treatment of choice for candidiasis. It may however be necessary to add oral or intravenous doses of antifungal drugs. In HIV/AIDS, prophylactic use of antifungals should be used to prevent Candida infection.

Kaposi's Sarcoma (KS)

This is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. The causative virus is human herpes virus 8 (Kaposi's Sarcoma Associated Herpes Virus) (28), which is either sexually transmitted or via blood or saliva. It is the most common malignant lesion in HIV/AIDS patients (29). The most commonly involved site is the skin but it can affect the mucous membranes, the lymphatic system and viscera, and in particular the lungs and gastrointestinal tract. It is usually severe in patients with a CD4 count less than 200 cells/$mm^{3.}$ Twenty per cent of the lesions present intraorally while 45% of patients present with both skin and oral lesions (30). The prevalence of the oral Kaposi's sarcoma ranges from 0 to 12% in Africans and 0 to 38% in the United States and Europe. Intraoral KS occurs on the heavily keratinized mucosa, the palate being the site in over 90% of cases. KS is particularly seen commonly among homosexual and bisexual males and is rarely found in HIV-infected women.

Characteristically, KS lesions appear as reddish, bluish or purple, single or multiple, flat or raised macules or nodules. Orally, they are found on the palate or gingivae and may ulcerate. Gingival involvement may lead to underlying bone destruction and tooth mobility. Occasionally, lesions may have a yellowish mucosa surrounding them.

The definitive diagnosis is made by histology and its presence in the oral cavity is more pathognomonic of low CD4 counts than those with the skin lesions alone (29). Other differential diagnoses that should be considered include haematomas, haemangiomas, pyogenic granuloma, bacillary angiomatosis and pigmented melanotic macules.

The number, size and location of the lesions determine treatment. The choice of treatment depends on the surrounding mucosa, pain, interference with eating and speech and the patient's preference. It is important to give prophylactic treatment such as the removal of plaque and calculus, and local application of a sclerotic agent to reduce the size of the lesion is necessary. Local lesions can be treated by a surgical incision under local

anaesthesia and chemotherapy with the use of 0.1 mg to 0.2 mg of vinblastine. Radiotherapy may be necessary for large lesions.

Linear gingival erythema (LGE)

This periodontal lesion presents as a persistent, distinct, intense, fiery red band condition extending 2-3 mm apically from the free gingival margin. The severity of the erythematous lesion is disproportionately intense with the amount of plaque seen (31) being unlike what is seen in conventional gingivitis. The erythema may be limited to the marginal tissue, the attached gingiva in a punctate or diffuse form, or could extend into the alveolar mucosa. These erythematous changes are usually generalized but may be confined to a few teeth. The gingiva bleeds easily on tooth brushing or gentle probing or even spontaneously in some cases (32). No ulceration is however present. LGE is commonly first seen early in the course of HIV infection and may or may not serve as a precursor to necrotizing ulcerative periodontitis.

The Candida species is isolated from some LGE lesions which suggests its possible aetiologic role (33-35). LGE has been classified under "Gingival diseases of fungal origin", a separate periodontal disease entity at the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions (36). The use of tobacco has been reported to affect the extent of gingival banding which is measured by the number of affected sites (37). The relationship of LGE to severe immune suppression is variable. This condition may (38, 39) or may not be associated with CD4 counts <200 cells/mm^3 (33, 40).

Diagnosis is made by clinical observation of the lesion as compared to the oral hygiene of the patient. A good clinical history suggestive of an immunosuppressive disease may also help in diagnosis. A major clinical hallmark of LGE is its non-responsiveness to conventional scaling and root planing. Histological examination fails to reveal any significant inflammatory response, suggesting that the lesions represent an incomplete inflammatory response, principally with only hyperaemia present. The differential diagnosis is conventional chronic gingivitis, a plaque-induced gingival condition which responds to conventional periodontal therapy.

The use of chlorhexidine gluconate mouth rinse effectively reduces or eliminates the lesion, hence its use as a prophylaxis in the prevention of the reoccurrence of the disease.

Necrotizing ulcerative gingivitis

Necrotizing ulcerative gingivitis (NUG), also called "trench mouth" because it was first observed in the mouth of frontline soldiers of World War 1, is defined using the presumptive diagnostic criterion (21): the destruction of one or more interdental papillae. It is a common, non-contagious infection of the gums with sudden onset. It starts as an acute onset and may later progress into a chronic disease state if not properly treated. NUG is classified into acute and chronic necrotizing ulcerative gingivitis.

Characteristically, the anterior teeth and lower teeth are most often affected (41), so also is the gingiva. In the acute stage of the disease, there is ulceration of the interdental papilla, which may be limited to one tooth or extend to several areas of the jaw and necrosis and sloughing of the interdental papilla and gingivae. Papillary necrosis is described as "punched out" lesions (42). There is gingival haemorrhage with little or no provocation, severe localized pain, fetor oris and metallic taste. In the chronic state, necrotizing ulcerative gingivitis is painless.

NUG in HIV-associated lesions represents the same spectrum of acute necrotizing ulcerative gingivitis (ANUG) seen in patients without HIV infection but in HIV-infected individuals, it progresses more rapidly (43). It is usually caused by a mixed bacterial infection that includes anaerobes such as Provotella intermedia and Fusobacterium as well as spirochetes such as Treponema (42). Some of the other organisms isolated from NUG lesions include Borrelia, gram-positive cocci, βhemolytic streptococci and Candida albicans [44]. NUG has been associated with depleted CD4 lymphocyte counts in some studies (38). However, others have failed to establish this association (45).

Diagnosis is mainly clinical. Isolation of some of the aforementioned bacteria or candida albicans may be useful in supporting the diagnosis. The differential diagnoses are leukaemia and herpetic stomatitis (42).

Treatment involves copious irrigation and debridement of necrotic areas, good oral hygiene and use of chlorhexidine mouthwash. If there is any systemic involvement, antibiotics such as metronidazole may be used.

Necrotizing ulcerative periodontitis

Necrotizing ulcerative periodontitis (NUP) may be an extension of NUG in HIV-infected individuals. The destruction is progressive and can result in the loss of the entire alveolar process in the involved area. Because the periodontal microflora is not different from that seen in healthy patients, the lesion probably results from the altered immune response in HIV infection. Initially, the lesion manifests with severe, deep-seated jaw pain. There is soft tissue loss resulting from ulceration or necrosis with rapid destruction of the periodontal attachment and interproximal bone (21, 46), interproximal necrosis and cratering. The bone may then be exposed, with subsequent necrosis and sequestration, resulting in loosening of the teeth (18). Few teeth are affected in most cases in either the premolar or molar region, however it can be generalized in severe cases with fetor oris. Deep pockets are not a characteristic feature of NUP because of the extensive gingival necrosis, which often coincides with the loss of alveolar bone. The lesion may bleed on probing with 50% of sites bleeding spontaneously (46).

The risk factors for periodontitis in HIV-positive patients include age, pack-years of a smoker and a high viral load. Fusobacterium nucleatum and Prevotella Human herpes-viruses such as cytomegalovirus have however been identified in some NUP lesions (48), including intermedia, Actinobacillus actinomycetemcomitans, neutrophil elastase and βglucuronidase (49). Periapical radiograph shows severe bone loss.

The treatment of NUP involves the gentle debridement of the affected lesions, followed by sub-gingival scaling, root planing and irrigation with chlorhexidine gluconate (47, 50) or povidone-iodine. Oral hygiene instructions should be emphasized alongside the home use of twice-daily antimicrobial mouth rinses such as 0.12% or 0.2% chlorhexidine gluconate. In severe NUP cases, systemic metronidazole – a 500 mg loading dose and 250 mg four times daily for 5-7 days – is the drug of choice. It has been shown to reduce acute pain and promote rapid healing. Metronidazole should be prescribed with caution in patients with liver alteration or a history of hepatitis (46). Alternatively, penicillin may be prescribed. However, it should be used with caution to avoid the proliferation of opportunistic infections such as candidiasis.

Oral Hairy Leukoplakia

This lesion usually presents as asymptomatic, white, vertical, corrugated, hair-like projections on the lateral borders of the tongue (bilaterally or unilaterally). This white appearance is created by hyperkeratosis and epithelial hyperplasia. OHL is classified as an opportunistic viral disease caused by the reactivation of quiescent Epstein-Barr virus infection in an immunocompromised state causing an uncontrolled lytic infection of the oropharynx. OHL was seen and investigated in 1981 by Greenspan et al., who published the initial report of its existence among homosexual men in San Francisco in 1984 (4). It is slightly less common in women than in men, and it is also rare in children. In HIV positive persons, OHL heralds a more rapid progression of AIDS (4, 51, 52). The incidence of OHL is reported to be 20% in CDC II individuals, increasing as the CD4 count falls and the patient's clinical condition worsens (51, 52). It also appears during the late latency stages of HIV infection. Greenspan et al. in 2000 (53) reported that the presence of OHL was not related to the CD4 count but was associated with a high viral load.

OHL lesions are asymptomatic, white corrugated or thickly furrowed and shaggy in appearance with hair-like projections. It affects mostly the lateral borders of the tongue and can spread to the dorsum of the tongue and on the ventral aspect to the floor of the mouth, occasionally on the adjacent buccal mucosa, soft palate, pharynx and oesophagus. When seen in these areas it is smooth and velvety not hair-like and unlike candidiasis, the lesion cannot be wiped off the mucosal surface (21), unlike pseudomembranous candidiasis.

The histologic features of OHL show surface corrugation, hyperplasia of the prickle-cell layer (acanthosis) with groups or layers of "balloon cells" (lightly staining cells) similar to koilocytes, the absence of atypia, nuclear beading in superficial layers (scattered cells with peripheral margination of chromatine and clear nuclei, created by displaced chromatin to the peripheral nucleus by the EBV replication) and a lack of inflammatory cells infiltration in the epithelium or adjoining connective tissues (4). These features are however not pathognomic of OHL.

The evidence of the presence of EBV is required for a definitive diagnosis of OHL, although a presumptive diagnosis can be made on clinical appearance alone and non-response to antifungal drugs (21).

Treatment of OHL is not necessary since the disease is benign. However, due to an associated aesthetic problem, a high dose of acyclovir or desiclovir helps to clear the lesion rapidly. The lesion may reoccur once the therapy is stopped when the immunocompromised state worsens.

Topical use of podophyllum resin or retinoids has been found to be effective in providing temporary remission. Zidovudine has been found to provide significant regression. In HIV, OHL is a predictor of a bad prognosis.

Non-Hodgkin's Lymphoma (NHL)

This is an uncommon feature of HIV disease. It is however, the second most common malignancy in this condition, with 4% of patients developing NHL during the course of their disease (29). It is usually seen in the late stages with CD4 lymphocyte counts of less than 100/mm^3, hence the Center for Disease Control included it as an AIDS-defining cancer in 1987 (54). NHL of the oral cavity accounts for 3% of all malignant lymphomas, which tend to occur extra-orally (55). Though the presentation varies, the pathogenesis of NHL remains obscure, but there has been much interest in the role of the Epstein Barr virus, with 50% of AIDS-related tumours demonstrating EBV genomes and also the aetiologic role of Human Herpes Virus-8 (HHV-8) (56).

Characteristically, the commonest sites are the palate and the gingivae. There is associated lymph node enlargement, fever, night sweats, weight loss and fatigue. It often clinically presents as a rapidly enlarging mass with associated bony destruction with associated bone pains. There may be associated chest pain and body itches and lumps may also be seen on the patient's skin which are commonly itchy, and red or purple in colour. Prognosis is poor, with a mean survival time of less than 1 year, despite treatment with multidrug chemotherapy.

Management of NHL is with the use of chemotherapy and at times a stem cell transplant. Although there are different regimens, CHOP therapy (Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisolone) has been successful. Bendamustine may also be added.

Oral ulcers

In about 50% of cases, AIDS patients present with oral ulcers (57). Oral ulcerative conditions related to HIV infection and AIDS may include HSV lesions, recurrent aphthous ulcers, and neutropenic ulcers. There is an increase in prevalence with a reduction in CD4 count.

Aphthous ulcer is a common condition characterized by the recurrent formation of benign and non-contagious mouth ulcers (aphthae) in an otherwise healthy individual. Aphthous ulcers are classified as Minor aphthous ulcers, Major aphthous ulcers and Herpetiform aphthous ulcers.

Minor aphthous ulcer occurs in non-keratinized epithelial surfaces of the mouth, however in AIDS-related causes it may involve keratinized surfaces as well. The rate of occurrence in AIDS patients is not significantly different from that of the general population (57). Aphthous ulcers occur for a prolonged period of time in AIDS patients and are more painful and difficult to treat (57). These ulcers are shallow in appearance, about 2-5 mm in diameter, covered with a whitish pseudomembrane and surrounded by erythematous tissues (57). These ulcers are either large and solitary or multiple, chronic, deep, and painful often prolonged as compared to the seronegative population and are less responsive to therapy (58). They often interfere with eating hence leading to weight loss in the patient. These ulcers are generally seen in patients with severe immunodepression as seen in AIDS (median CD4 T-lymphocyte count 100 cells/mm^3 or below) (59). They present in crater-like forms with elevated borders and a white-yellowish pseudomembranous covering, measuring over 1 cm in diameter (57). These lesions are very painful and may be prolonged resulting in difficulty in swallowing and difficulties in speech and mastication. They may be accompanied by regional lymphadenopathy (57).

The diagnosis is basically clinical. The most important diagnostic feature is a history of high frequency of recurrence, with prolonged episodes with severe pain. Relevant blood tests can be done to rule out nutritional deficiencies. Histologic appearance is not pathognomonic (58). However early biopsy shows dense inflammatory infiltrates and mostly T-lymphocytes.

A potent topical steroid such as clobetesol or dexamethasone oral rinse can be used for treatment. Systemic glucocorticosteroid therapy may be required (prednisone 1 mg/kg) in large multiple ulcers and ulcers not

responsive to topical preparations. Dapsone 50-100 mg daily and thalidomide 200 mg daily for 4 weeks can be considered in persistent cases such as unresolving major aphthous ulcers (58). In order to prevent superimposed fungal or bacterial infection, antifungal medications such as fluconazole and itraconazole, and antibacterial medications such as chlorhexidine gluconate mouthwash can be used (58).

Salivary gland diseases

HIV-associated major salivary gland swellings are unilateral or bilateral salivary gland swellings and usually present as lymphoepithelial lesions. They can be caused by:

a) Hyperplastic reactive lymphadenopathy
b) Benign lymphoepithelia cysts
c) Malignant lesions: Kaposi's sarcoma, lymphoma
d) Benign neoplasms
e) Bacterial, mycobacterial or viral infections
f) Drug-induced xerostomia.

Salivary gland diseases such as enlargement of the major salivary glands and xerostomia, were reported to be high in Northern Africa and Thailand (60). Malnutrition, especially in Northern Africa may play a role. Enlargement of the salivary glands due to infiltration by CD8 lymphocytes is seen in both adult and paediatric HIV infection (61). Some of these glands undergo cystic change, and as such benign lymphoepithelial cysts occasionally cause pain. The cause of HIV-related salivary gland diseases is unclear, since no aetiological agents have been identified. It may represent a relatively beneficial host CD8 response known as Diffuse Infiltrative Lymphocytosis Syndrome (DILS) (62). No evidence of Epstein-Barr virus or cytomegalovirus has been found in biopsies of salivary glands (63). One report describes an association between HIV-SGD and HLADR5 and HLA-B35 cell-surface antigens (61). Adults and children with salivary gland enlargement seem to experience a slower progression of HIV disease (64). Oral Mucoceles and ranulas have recently been discovered to be oral manifestations of HIV infection. Several reports considered them as initial symptoms and early manifestations of HIV infection (65-66).

Diffuse Infiltrative Lymphocytosis Syndrome

It manifests similarly to Sjogren's syndrome. Diffuse infiltrative lymphocytosis syndrome occurs in 3% of HIV patients with multiple lymphoepithelial cyst proliferation in the parotid gland associated with the painful enlargement of the gland. The lesion usually involves the entire parotid parenchyma, presenting as a local mass. It is not movable, or tender on palpation. There is reduced salivary gland function (xerostomia, sicca symptoms). A unilateral parotid gland enlargement in diffuse infiltrative lymphocytosis syndrome should prompt suspicion of HIV infection. A CT scan showing multiple hypodense areas is suggestive of diffuse infiltrative lymphocytosis. Histology shows persistent infiltration of CD8 cells that have the ability to destroy HIV-infected cells. Fine needle aspiration can also be helpful in diagnosis (54). The use of highly active anti-retroviral therapy, in addition to steroid therapy helps to effectively resolve the clinical signs and symptoms.

Xerostomia

This is known as dry-mouth syndrome, which is associated with reduced salivary flow. Xerostomia is common in HIV disease and may be associated with salivary gland enlargement as seen in diffused infiltrative lymphocytosis syndrome, as well as side effects of antiviral medications or other medications commonly prescribed for patients with HIV infection (like angiolytics, antifungals, etc.). Cytomegalovirus (CMV) has been demonstrated in the salivary gland of xerostomic patients (67). Xerostomia also can lead to oral candidiasis, mucosal injury, and dysphagia, and is often associated with pain and loss of appetite (58).

Symptomatic relief may be provided by salivary stimulants such as sugarless chewing gums or saliva substitutes. A patient who has residual salivary gland function determined by gustatory challenge or oral pilocarpine, often provides improved salivary flow and consistency. Prevention of dental caries in people with xerostomia is extremely important, hence good oral hygiene measures are important; the use of topical fluoride gels and rinses should be encouraged (68). In addition, management of xerostomia will improve oral comfort, the quality of speech and the use of any prostheses (69).

Herpes virus infections

Herpes simplex virus (HSV) is responsible for both primary and recurrent infections of the oral mucosa. These infections are acquired in childhood, and after the initial pustular lesions, the virus remains dormant; but in later stages of immunosuppression the virus can be activated and can lead to various manifestations. Oral manifestations, seen as diffuse mucosal ulcerations, are accompanied by fever, malaise, and cervical lymphadenopathy. Ulcerations that follow the rupture of vesicles are painful and may persist for several weeks. Recurrent HSV usually appears in keratinizing oral mucosa (i.e., palate, dorsum of tongue, and gingiva) as ulcerations but in most HIV-seropositive patients, this rule does not follow. In these patients, the lesions may show unusual clinical aspects and persist for many weeks.

Varicella zoster (VZV) is a herpes virus, and, like other herpes viruses, it causes both primary and recurrent infection and remains latent in neurons present in sensory ganglia. VZV is responsible for two major clinical infections of humans: chickenpox (varicella) and shingles (herpes zoster [HZ]) (70). Herpes zoster is as a result of the reactivation of quiescent cells of varicella zoster virus which remain in nerve cells and ganglia, after the resolution of the previous manifestation of Varicella zoster infection (chickenpox). Herpes zoster, which occurs on the reactivation of Varicella zoster, travels from the nerve body to the endings in the skin, producing blisters. The process of reactivation is not understood. However, it is seen in immunocompromised patients such as HIV. Herpes zoster usually presents with early non-specific signs such as headache, malaise and fever. Burning pain, paraesthesia and hyperaesthesia then follow these earlier symptoms. Pain ranges from mild to extreme in the affected dermatomes with the sensation described as tingling, stinging, aching, numbing or throbbing and can be interspersed with quick stabs of agonizing pain. Between 2 days to 3 weeks the initial phase is followed by painful rashes similar to hives along the skin supplied by the affected dermatome, resulting in a stripe or belt-like pattern that is limited to one side of the face and does not cross the midline. Later the rashes become vesicular, forming blisters filled with serous exudate as the earlier symptoms continue. The vesicles subsequently become dark and cloudy and filled with blood and crust within 7 to 10 days. The crust subsequently falls off and heals. However, scarification of the affected area may occur. In the head and neck region, the trigeminal nerve (cranial nerve V) is commonly affected, which in addition to the aforementioned symptoms, would cause zoster ophthalmicus as a result of affectation of the ophthalmic branch of

the trigeminal nerve, characterized by conjunctivitis, keratitis, uveitis and optic nerve palsies. Affectation of the mandibular and maxillary branch of the trigeminal nerve will cause skin rashes on the affected side of the face and intra-oral mucosa. The intra-oral vesicles break down and leave ulcers that heal within 10-14 days. Ramsay Hunt syndrome type II is also seen in shingles caused by the affectation of the facial nerve (cranial nerve VII). Disseminated shingles may extend to organs other than the skin such as the brain and liver which may make the condition potentially lethal.

Herpes zoster may indicate a poor prognosis of HIV infection (71). This can be an early complication of AIDS, where it is five times more common than in the HIV-negative population.

Diagnosis is made by clinical presentation. Tzank smear is helpful in the diagnosis of active herpes virus infection, however it does not distinguish between Herpes simplex or Herpes zoster virus. The test for the Varicella zoster-specific IgM antibody in blood can be useful in specific diagnosis. Polymerase chain reaction can also be useful.

The use of antiviral drugs may reduce the severity of the disease, however postherpetic neuralgia is not prevented. Acyclovir is the standard drug of choice at 800 mg 5 times daily for 7 to 10 days. However, new drugs such as valacyclovir and famicyclovir have been found to be more effective.

For mild pain, calamine-containing lotion can be applied over the rash or blisters to provide a soothing effect. In severe pain, potent analgesics can be used. Once the lesions have crusted over, capsaicin cream (zostrix) can be used. Topical lidocaine and nerve block can also be used to reduce pain. Administration of gabapentin (anticonvulsant), along with antivirals may offer relief of postherpetic neuralgia (72). Corticoteroids do not seem to reduce long-term pain (73).

Oral lesions and the relationship with CD4 count and viral load

The hallmark of HIV disease is the progressive loss of CD4+ lymphocytes. Without intervention, an average of 60 to 80 cells/mm^3 is lost every year; this loss is highly variable and occurs in periods of stability and rapid decline. A high viral load is also considered to be one of the main indicators of the progression of HIV-induced immunosuppression. Several studies have shown that the higher the viral load, the quicker is the progression to AIDS. The CD4 count and viral load

measure the progression of HIV disease. Several studies have shown a high prevalence of oral lesions in patients with a low CD4 count, <200 cells/mm^3 and a high viral load: >55,000 copies/ml. A CD4 count <200 cells/mm^3 is used as a criterion for initiating HAART, which is consistent with the guidelines for initiating HAART treatment by the WHO (2003). The presence of multiple lesions in infected HIV patients is also associated with severe immunosuppression and AIDS.

Conclusion

A study in a population of 142 Nigerian patients over a period of 5 months showed a strong decline in the cases of oral infection in the population after the use of HAART (75). In an Indian study (64), oral manifestations of HIV were studied in children treated in a HAART centre: these manifestations were observed in children receiving HAART and they included dental caries (26%), periodontal diseases (23%), candidiasis (19%), hyperpigmentation (17%), ulcerative stomatitis (9%) and one case of mucocele. The authors (64) concluded that HAART had increased the disease-free states in HIV-positive children, promising them a better life span. The authors further reported that the incidence of oral manifestations can come down further with adequate oral hygiene measures in HIV-infected children. The percentage decrease varied from 10% in a USA study on 570 patients (76) to 50% in a Mexican study on a selected 1000 HIV patients over a period of 12 years (77). A Spanish study on 154 subjects (78) reported a 30% reduction of oral lesions, while (79) there was a reduction of 24% in a study on 284 patients in the United Kingdom. Some studies looked at a specific oral manifestation (80) as opposed to a range of oral lesions (77-81). However, studies from the USA (76) and Mexico (77) found no significant change in the occurrence of Kaposi's Sarcoma with HAART. Unlike most other oral manifestations of HIV, studies from the USA and the United Kingdom described an increase in the prevalence of oral warts with HAART (76, 82), which may be of statistical significance (53).

Rapid detection of HIV infection is of great importance as it reduces the patient's morbidity and decreases the risk of transmission of the virus. Various studies have shown that the increase in the CD4 count and the reduction of the viral load via the use of Highly Active Antiretroviral Therapy help in the prevention of HIV/AIDS-related oral diseases and also improve the prognosis of some of the oral diseases when managed. Oral manifestations of HIV infection and AIDS drastically changed after the

advent and clinical use of HAART. The goals of HAART should be maximal and durable viral suppression. The aim is preservation and restoration of the immune system at minimal cost to the patient. As a result of an obvious improvement of the immune system, many opportunistic infections have resolved. The reduction of the viral burden will prevent progressive immunodeficiency, decrease the risk of the emergence of resistant viruses and possibly decrease the risk of viral transmission (74).

References

1. Sharp PM, Hahn BH. Origins of HIV and the AIDS Pandemic. *Cold Spring Harbor perspectives in medicine* 2011; 1(1): a006841. doi:10.1101/cshperspect.a006841. PMC 3234451. PMID 22229120.
2. UNAIDS. Jump up to: a b c d Fact sheet – Latest statistics on the status of the AIDS epidemic | UNAIDS, 2016 www.unaids.org. Archived from the original on July 13, 2017. Retrieved July 21, 2017.
3. WHO. Jump up to: a b c d e f g h i j k l m n HIV/AIDS Fact sheet N° 360. November 2015. Archived from the original on February 17, 2016. Retrieved February 11, 2016.
4. Greenspan D, Greenspan JS, Conant M, Petersen V, Silverman Jr S , de Souza Y. Oral "hairy" leucoplakia in male homosexuals: evidence of association with both papillomavirus and a herpes-group virus. *Lancet* 1984 Oct.; 13 2(8407): 831–834. [PubMed].
5. Nayak SK, Das BK, Das SN, Mohapatra N, Nayak S, Bhuyan L. Oral manifestations of human immunodeficiency virus/acquired immunodeficiency syndrome and their correlation to cluster of differentiation lymphocyte count in the population of North-East India in highly active antiretroviral therapy era. *Contemp Clin Dent* 2016; 7: 539-43.
6. Frimpong P, Amponsah EK, Abebrese J, Kim SM. Oral manifestations and their correlation to baseline CD4 count of HIV/AIDS patients in Ghana. *J Korean Assoc Oral Maxillofac Surg*. 2017; 43: 29–36 [PMC free article] [PubMed].
7. Weinert M, Grimes RM, Lynch DP. Oral manifestation of HIV infection. *Annals of Internal Medicine*, 1996, 125; 6: 485-496.
8. Palmer GD, Robinson PG, Challacombe SJ, Birnbaum W, Croser D, Erridge PL, et al. Aetiological factors for oral manifestation of HIV infection. *Oral Dis*. 1996; 2: 193-197.
9. Maeve MC, Greenspan J, Challacombe SJ. Oral lesions in infection with HIV. *Bulletin of the World Health Organisation* 2005; 83: 700-706.

10. Cawson RA, Odell EW. *Cawson's Essentials of Oral Pathology and Oral Medicine*. 8th Edition. Edinburgh: Churchill Livingstone Elsevier, 350-351. ISBN:9780702060168 ISBN:9780702040016.
11. Berberi A, Noujeim Z, Aoun G. 2015. Epidemiology of Oropharyngeal Candidiasis in Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome patients and CD4+ Counts. *J Int Oral Health*, 7(3): 20-23.
12. Schmidt-Westhausen AM, Priepke F, Bergman FJ, Riechart PA. Decline in the rate of Oral opportunistic infections following introduction of HAART. *J. Oral Pathol/Med* 2000; 29: 336-341.
13. Kaminu HN, Naidoo S. Oral HIV lesions and oral health behavior of HIV Positive patients attending the Queen Elizabeth II Hospital. *SADJ* 2002; 57: 479.
14. Adedigba MA, Ogunbodede EO, Jeboda SO, Naidoo S. Patterns of oral manifestation of HIV/AIDS among 225 Nigerian patients. *Oral Dis.* 2008; 4: 314-316.
15. Anteyi KO, Thacher TD, Yohanna S, Idoko JI. Oral manifestation of HIV/AIDS in Nigerian patients. *Int. J. AIDS* 2003; 14: 395-398.
16. Arotiba JT, Arowojolu MO, Fasola AO, Denloye OO, Obiechina AE. Oral manifestation of HIV/AIDS. *Afr J Med Med Sci*. 2006; (35): 13-18.
17. Onunu AN, Obuekwe ON. HIV related oral disease in Benin-City, Nigeria. *West Afr. J. Med*. 2002; 21(1): 9-11.
18. Taiwo O, Okeke EN, Jalo PH, Danfillo IS. Oral manifestation of HIV in Plateau state indigenes, Nigeria. *West Afr. J. Med*. 2006; (1): 32-37.
19. Wright AA, Agbelusi GA. Group II and III lesions in HIV positive Nigerians attending the general Hospital Lagos, Nigeria. *Odonto-Stomatologie Tropicale* 2005; 112: 19-23.
20. Greenspan D. Oral manifestation of HIV. HIV InSite Knowledge Base Chapter, June 1998, http://hivinsite.ucsf.edu/?page=kb-04-01-14.
21. EC-Clearinghouse on oral Problems Related to HIV Infection and the WHO Collaboration center on oral manifestations of the immunodeficiency Virus (ECC/WHO) (1993): Classification and diagnostic criteria for oral lesions in HIV infection. *J Oral Pathol Med* 2993; 22: 289-291.
22. Bendick C, Scheifele C, Reichart PA. Oral manifestations in 101 Cambodians with HIV and AIDS. *J Oral Pathol Med*. 2002; 31: 1-4.

23. Chidzonga MM. HIV/AIDS orofacial lesions in 156 Zimbabwean patients at referral oral and maxillofacial surgical clinics. *Oral Dis* 2003; 9: 317-322.
24. Kerawala C, Newlands C (editors). *Oral and maxillofacial surgery*. Oxford: Oxford University Press, 2010, 446 - 447. ISBN 9780199204830.
25. Odell EW (editor). *Clinical problem solving in dentistry* (3rd ed.). Edinburgh: Churchill Livingstone Elsevier, 2010, 161, 194, 216. ISBN 9780443067846.
26. Purkait SK. *Essentials of oral pathology* (3rd ed.). New Delhi: Jaypee Bros. Medical Publishers, 2011, 12. ISBN 9789350252147.
27. Samaranayake, LP. *Essential microbiology for dentistry* (3rd ed.). Edinburgh: Churchill Livingstone Elsevier, 2009, 178–180, 247, 293–297.
28. Sturzl M, Konrad A, Alkharsah KR, Jochmann R, Mathias T. The contribution of systems biology and reverse genetics to the understanding of kaposi's sarcoma-associated herpes virus pathogenesis in endothelial cells. *Thomb. Haemot*. 2009; 102: 1117-1134.
29. Iain LC, Hamburger J. The significance of oral health in HIV disease. *Sex Trans infection* 2000; 76: 236-243.
30. Tappero JW, Conant MA, Wolfe SF. Kaposi's sarcoma. *J Am Acad. Dermatol*. 1993; 28: 371-395.
31. Holmstrup P, Westergaard J (1998): HIV infection and periodontal diseases. *Periodontology* 2000; (18): 37-46.
32. Robinson PG, Adegboye A, Rowland RW, Yeung S, Johnson NW. Periodontal diseases and HIV infection. *Oral Diseases* 2002; 8(2): 144-15.
33. Grbic FT, Mitchelle-Lewis DA, Fine JB. The relationship of candidosis to LGE in HIV- infected homosexual men and parenteral drug users. *J. Periodontol*. 1995; 66: 30-37.
34. Lamster IB, Begg MD, Mitchell-Lewis D, et al. Oral manifestations of HIV infection in homosexual men and intravenous drug users. *Oral Surg Oral Med Oral Pathol*. 1994; 78: 163.
35. Velegraki A, Nicolatou O, Theodoridou M, et al. Paediatric AIDS-related linear gingival erythema; a form of erythematous candidiasis? *J Oral Pathol Med*. 1999; 28: 178.
36. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol*. 1999; 4: 1-6.

37. Swango PA, Kleinman DV, Konzelman JL. HIV and periodontal Health: a study of military personnel with HIV *J. Am Dent Assoc*. 1991; 122(8): 49-54.
38. Ceballos-Salobrena A, Aguirre-Urizar JM, Bagan-Sebastian JV. Oral manifestations associated with human immunodeficiency virus infection in a Spanish population. *J Oral Pathol Med*. 1996; 25: 523-526.
39. Holmes HK, Stephen LX. Oral lesions of HIV infection in developing countries. *Oral Disease* 2002; 8(2): 40-43.
40. Davoodi P, Hamian M, Nourbaksh R, Motamayel FA. Oral Manifestations Related to CD4 Lymphocyte Count in HIV-Positive Patients. *J Dent Res Dent Clin Dent Prospect*. 2010; 4(4): 115-119.
41. Robinson PG, Sheiham A, Challacombe SJ, Wren MWD, Zakrzewska JM. Gingival Ulceration in HIV infection. A case series and case control study. *J Clin Periodontol*. 1998; 25: 260-267.
42. Scully, Crispian. *Oral and maxillofacial medicine: the basis of diagnosis and treatment* (2nd ed.). Edinburgh: Churchill Livingstone, 2008, 101, 347. ISBN 9780443068188.
43. Winkler JR, Murray PA. A potential intra-oral expression of AIDS may be rapidly progressive periodontitis. *Journal of the California Dental Association* 1987; 15: 20.
44. Reichart PA, Gelderblom HR, Becker J, Kuntz A. AIDS and the oral cavity. The HIV-infection: virology, etiology, origin, immunology, precautions and clinical observations in 110 patients. *Int J Oral Maxillofac Surg*. 1987; 16: 129-153.
45. Barr C, Lopez MR, Rua-Dobles A. Periodontal changes by HIV serostatus in a cohort of homosexual and bisexual men. *J Clin Periodontol.* 1992; 19: 794-801.
46. Winkler JR, Robertson PB. Periodontal diseases associated with HIV infection. *Oral Med Oral pathol*. 1992; 73: 145-150.
47. Umeizudike KA, Savage KO, Ayanbadejo PO, Akanmu AS. Severe presentation of Necrotizing Ulcerative Periodontitis in a Nigerian HIV Positive Patient – A Case report. *Med Princ Pract*. 2011a; 20: 374-376.
48. Slots J. Update on human cytomegalovirus in destructive periodontal diseases. *Oral Microbiol Immunol*. 2004; 19: 217.
49. Alpagot T, Duzgunes N, Wolff LF, Lee A. Risk factors for periodontitis in HIV positive patients. *J Periodont Res*. 2004; 39: 149-157.
50. Grassi M, Williams CA, Winkler JR, et al. Management of HIV-associated periodontal diseases. In Robertson, PB & GJS, eds.

Perspectives on Oral Manifestations of AIDS. Littleton: PSG Publishing Co., Inc., 1988, 119-130.
51. Glick M, Muzyka BC, Lurie D, Salkin LM. Necrotising Ulcerative Periodontitis: a marker for immune deterioration and a predictor for the diagnosis of AIDS. *J. Periodontol*. 1994; 65: 393-397.
52. Lifson AR, Hilton JF, Westenhouse JL. Time from HIV seroconversion to oral candidiasis or Hairy Leukoplakia among homosexual and Bisexual men enrolled in three prospective cohorts. *J AIDS* 1994; 8: 73-79.
53. Greenspan D, Canchola AJ, MacPhail LA, Cheikh B, Greenspan JS. Effect of highly active antiretroviral therapy on frequency of oral warts. *Lancet* 2001; 357: 1411-1412.
54. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Council of State and Territorial Epidemiologists; AIDS Program, Center for Infectious Diseases (PDF). *Morbidity and Mortality Weekly Report*. 1987; 36 (Suppl. 1): 1S-15S. PMID 3039334. Archived (PDF) from the original on 2017-06-09.
55. Epstein JB, Silverman S. Head and neck malignancies associated with HIV infection. *Oral Surg. Oral Med. Oral Pathol*. 1992; 73: 193-300.
56. Boshoff C, Whitby D, Talbot S. Aetiology of AIDS-related Kaposi's sarcoma and lymphoma. *Oral Dis*. 1997; 3: S129-132.
57. GA Agbelusi, OM Eweka, KA Ùmeizudike and M Okoh. Oral Manifestations of HIV, *Current Perspectives in HIV Infection* April 10th 2013. Shailendra K. Saxena, IntechOpen, DOI: 10.5772/52941. Available from: https://www.intechopen.com/books/current-perspectives-in-hiv-infection/oral-manifestations-of-hiv.
58. Bajpai S, Pazare AR. Oral manifestations of HIV. *Contemp Clin Dent* 2010; 1: 1-5.
59. Ramos-Gomez FJ. Oral aspects of HIV disease in children. *Oral Dis.* 1997; 3: S31-35.
60. Nittayananta W, Chungpanich S. Oral lesions in a group of Thai people with AIDS. *Oral Dis*. 1997; 3: 41-56.
61. Schiodt M, Bakilana PB, Haza FR. Oral candidiasis and hairy leukoplakia correlate with HIV infection. *Oral Surg Oral Med Oral Pathol.* 1990; 69: 591-596.
62. Itescu S, Brancato L, Buxbaum J. A diffuse infiltrative CD8 lymphocytosis syndrome in HIV infection: A host immune response associated with HLA-DR5. *Ann Intern Med.* 1990; 112: 3-10.

63. Soberman N, Leonidas JC, Berdon WE. Parotid enlargement in children seropositive for human immunodeficiency virus: imaging findings. *AJR* 1991; 157: 553-6.
64. Katz MH, Mastrucci MT, Leggott PJ, Westenhouse J, Greenspan JS, Scott GB. Prognostic significance of oral lesions in children with perinatally acquired HIV infection. *Am J Dis Child* 1993; 147(1): 45-48.
65. Syebele K, Munzhelele TI, Syebele K, Munzhelele TI. Oral mucocele/ranula: another human immunodeficiency virus-related salivary gland disease? *Laryngoscope* 2015; 125: 1130-6. doi: 10.1002/lary.25058. CrossRef PubMed Google Scholar.
66. Kamulegeya A, et al. 2012: Ranulas: Possible signs for HIV/AIDS? 1 year Ugandan descriptive study. Kamulegeya A, Okello SM. *Acta odontologica Scandinavica* 70(2): 149-53. DOI: 10.3109/00016357.2011.600709 . PubMed.
67. Greenspan JS, Barr CE, Sciubba JJ, Winkler JR. Oral manifestations of HIV infection. *Oral Surg Oral Med Oral Pathol*. 1992; 73: 142-144.
68. Greenspan D, Greenspan JS. HIV-related oral disease. *The Lancet* 1996; 348: 729-733.
69. Narani N, Epstein JB. Classifications of oral lesions in HIV infection. *J clin Periodontol* 2001; 28: 137-145.
70. Greenburg MS, Glick M (2003). Ulcerative, vesicular and bullous lesions. In *Burkett's oral Medicine. Diagnosis and Treatment*, 10th edition. India: BC Decker Inc. 2008, 50-84.
71. Scully C, McCarthy G. Management of oral health in persons with HIV infection. *Oral Surg Oral Med Oral Pathol.* 1992; 73: 215-225.
72. Tyring SK. Management of herpes zoster and postherpetic neuralgia. *J. Am. Acad. Dermatol.* 2007; 57 (6 Suppl): S136-42. doi:10.1016/j.jaad.2007.09.016. PMID 18021865.
73. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database of Systematic Reviews* March 28, 2013.
74. Fauci AS, Bartlett JG, Goosby EP. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Panel on clinical practices for treatment of HIV infection conveyed by the Department of Health and Human services and the Henry J Kaiser Foundation, 2000.
75. Taiwo OO, Hassan Z. The impact of Highly Active Antiretroviral Therapy (HAART) on the clinical features of HIV-related oral

lesions in Nigeria. *AIDS Res Ther*. 2010; 7: 19 [PMC free article] [PubMed].

76. Patton LL, McKaig R, Strauss R, Rogers D, Eron Jr JJ. Changing prevalence of oral manifestations of human immuno-deficiency virus in the era of protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 89: 299-30.
77. Ramírez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, Anaya-Saavedra G, Gonzalez-Ramírez I, Ponce-de-Leon S. The changing clinical spectrum of human immunodeficiency virus (HIV)-related oral lesions in 1,000 consecutive patients: a 12 year study in a referral center in Mexico. *Medicine (Balt)* 2003; 82: 39-50.
78. Alejandro Ceballos-Salobreña, Luis Alberto Gaitán-Cepeda, Laura Ceballos-Garcia, and David Lezama-Del Valle. Oral lesions in HIV/AIDS patients undergoing highly active antiretroviral treatment including protease inhibitors: a new face of oral AIDS? *AIDS Patient Care and STDs*. Dec 2000. ahead of print http://doi.org/10.1089/10872910050206540.
79. Tappuni AR, Fleming GJ. The effect of antiretroviral therapy on the prevalence of oral manifestations in HIV-infected patients: a UK study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001; 92: 623-628.
80. Cauda R, Tacconelli E, Tumbarelo M, Morace G, De Bernadis et al. Role of protease inhibitor in preventing recurrent oral candidosis in patients with HIV infection: a prospective case-control study. *J AIDS* 1999; 21: 20-25.
81. Eyeson JD, Tenant-Flowers M, Cooper DJ, Johnson NW, Warnakulasuriya KA. Oral manifestations of an HIV positive cohort in the era of highly active anti-retroviral therapy (HAART) in South London. *J Oral Pathol Med* 2002; 31: 169-174.
82. Greenwood I, Zakrzewska JM, Robinson PG. Changes in the prevalence of HIV-associated mucosal disease at a dedicated clinic over 7 years. *Oral Dis* 2002; 8: 90-94.
83. Rachana V Prabhu 1*, Vishnudas Prabhu 2, Laxmikanth Chatra 1 and Prashant Shenai 1. *Journal of Tropical Diseases Oral Manifestations of HIV*: 1-9.

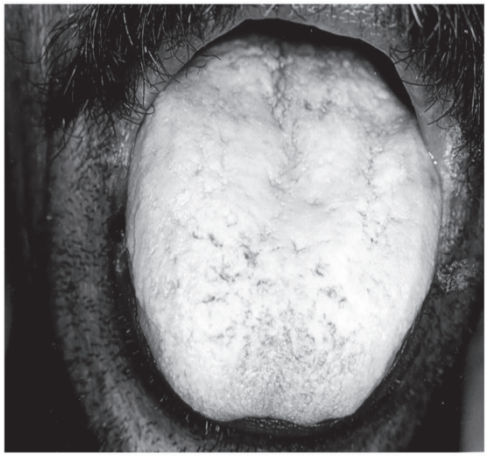


Fig. 1.1. Pseudomembraneous Candidiasis

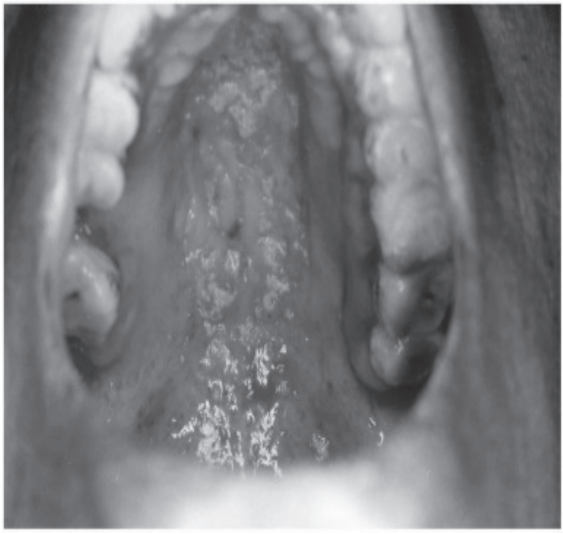


Fig. 1.2. Erythematous candidiasis

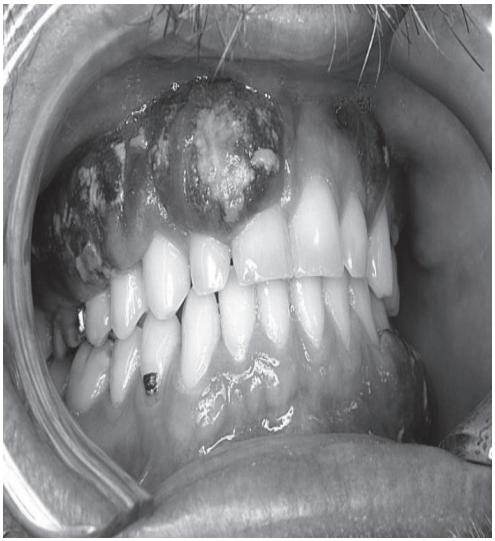


Fig. 2. Kaposi's Sarcoma

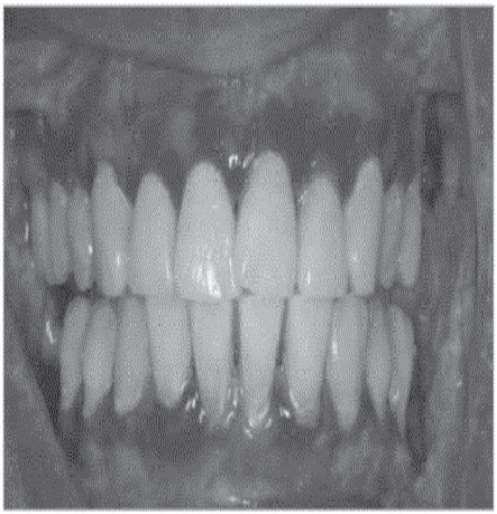


Fig. 3. Linear erythematous gingiva

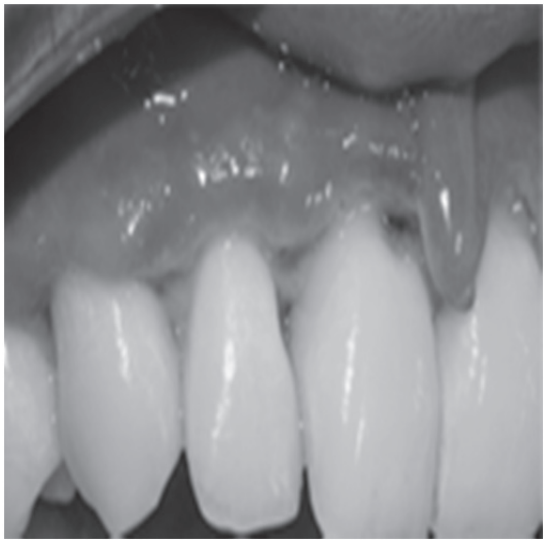


Fig. 4. Necrotizing ulcerative gingivitis

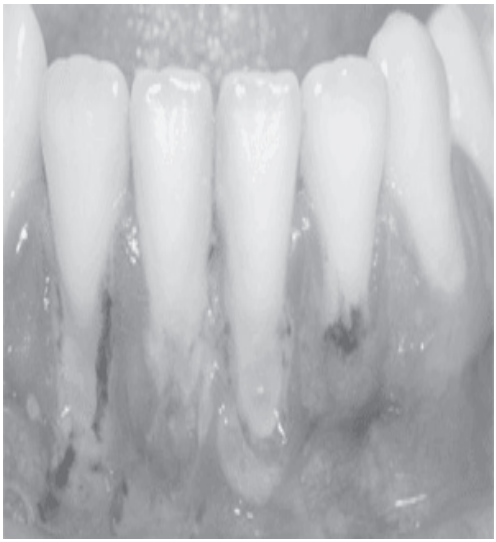


Fig. 5. Necrotizing ulcerative periodontitis

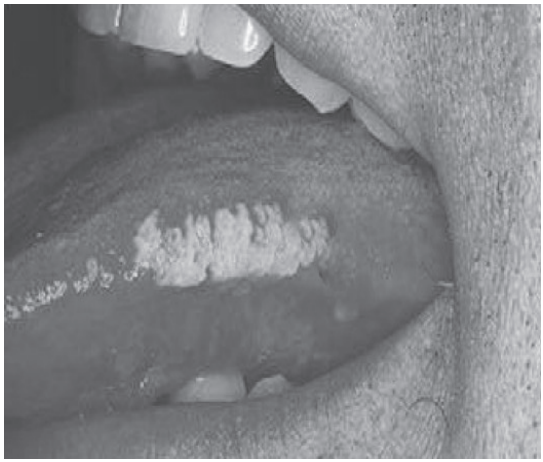


Fig. 6. Oral hairy Leukoplakia

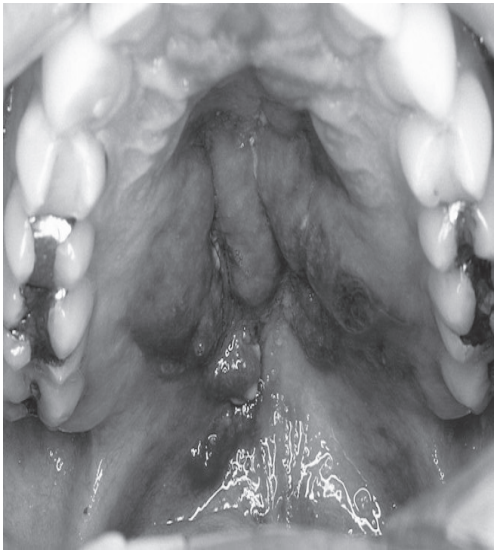


Fig. 7. Non-Hodgkin's Lymphoma

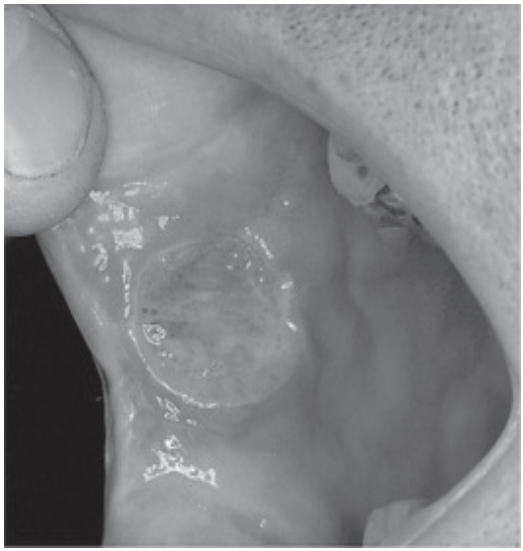


Fig. 8. Major aphthous ulcer

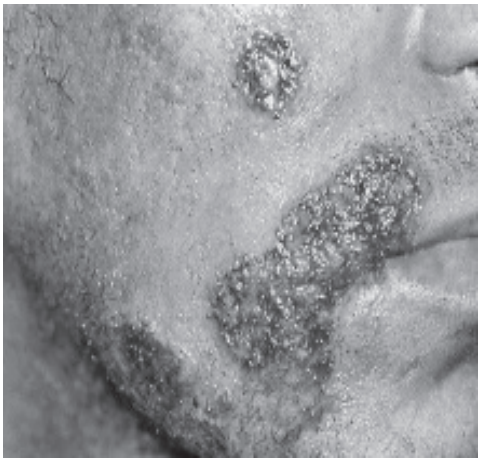


Fig. 9. Herpes simplex virus infection

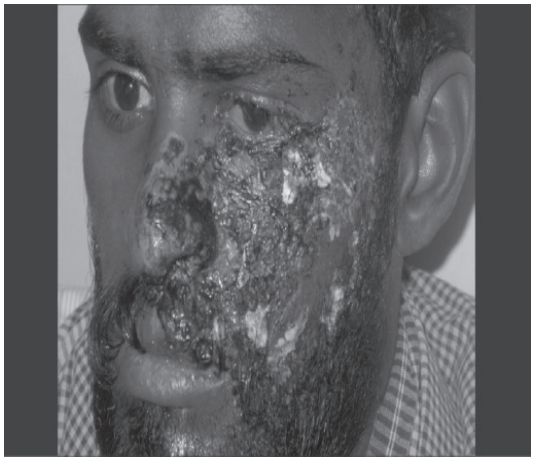


Fig. 10. Herpes Zoster virus infection

Fig. 1: Clinical Appearance of Oral Candida Infection and Therapeutic Strategies: Shankargouda Patil,[1,*] Roopa S. Rao,[1] Barnali Majumdar,[1] and Sukumaran Anil[2] : ncbi.nlm.nih.gov/pmc/articles/PMC4681845/ (2015).

Fig. 2: Kaposi's sarcoma from Wikipedia, the free encyclopedia (March, 2018).

Fig. 3: Recurrent Gingival and Oral Mucosal Lesions: Eric T Stoopler, DMD, FDS RCSEd, FDS RCSEng[1]; Thomas P Sollecito, DMD, FDS RCSEd[1] (March, 2017).

Fig. 4: Managing Patients with Necrotizing Ulcerative Gingivitis: Sylvia Todescan**,** DDS, MSc, PhD; Reem Nizar Atout, BDS, DDS, MS j can dent assoc. 2013; 79: d46 (April, 2018).

Fig. 5: Managing Patients with Necrotizing Ulcerative Periodontitis: Sylvia Todescan, DDS, MSc, PhD; Reem Nizar Atout, BDS, DDS, MS j can dent assoc. 2013; 79: d44 (March, 2013).

Fig. 6: Picture of Hairy Leukoplakia. Image source: *Harrison's Principles of Internal Medicine*.

Fig. 7: medscape.com/slideshow/oral-cav-6003300#14: hellomrdoctor. com/hairy-leukoplakia (September, 2017).

Fig. 8: CHAPTER 13. Diseases of the oral mucosa: non-infective stomatitis TRAUMATIC ULCERS → Summaries pp. 246, 247, Pocket dentistry, fastest clinical dentistry insight (September, 2014).

Fig. 9: Anterior segment manifestations of human immunodeficiency virus/acquired immune deficiency syndrome: PubMed Central –

PubMed: Biswas J, Sudharshan S, *Indian J Ophthalmol* (2008 September-October).

Fig. 10: National HIV Curriculum: Section 2. Basic HIV Primary Care: Cutaneous Manifestations by Rebecca G. Kinney, MD David H. Spach, MD: hiv.uw.edu (May 6th, 2017).

HIV-Associated Malignancies

Wasiu Olalekan Adebimpe
FWACP, PhD

There are many malignancies associated with the occurrence of HIV infections. In the early days of the pandemic, the diagnosis of Kaposi's Sarcoma was solely regarded as a precursor to HIV. Cancer cells have been found to flourish in the presence of immune-suppression which is the hallmark of HIV. In the WHO classification, the occurrence of HIV malignancy is associated with end stage HIV infection otherwise known as AIDS. Kaposi's Sarcoma is a cancer that is common among people living with HIV/AIDS (PLWHA). Other common cancers include non-Hodgkin's lymphoma (NHL), and cervical cancer among HIV-positive women. Cancer prevention among PLWHA is similar to that of HIV-negative clients. While primordial prevention can reduce cancer incidence among the virgin population, primary and secondary prevention can reduce disease progression and prevent the co-morbidity of some communicable diseases that are precursors of malignancies both in HIV-positive and negative individuals.

Compared to individuals who are HIV negative, People Living With HIV/AIDS (PLWHA) are at increased risk of developing some malignancies (1, 2). These AIDS-associated malignancies constitute major complications encountered by HIV/AIDS patients upon immune-suppression. A weak immune system itself may aid carcinogenesis and spread some cancers more rapidly, more so when conventional cancer management methodologies such as chemotherapy and radiation therapy can also weaken the immune system. Susceptibility to cancer development could be related to exposure to risk factors to cancers and their state of health as defined by the CD4 count and the viral load. These diseases could constitute more burdens to the already poor quality of life which is usually exhibited by PLWHA who are not living positively. As the world celebrates World HIV Day annually on the 1st day of December, the author hopes that the magnitude of the problem of HIV-associated cancers will be looked into, through quality research and focused service delivery by stakeholders.

Classification of HIV-associated cancers

HIV-associated neoplasms are numerous and can be broadly divided into two groups:

(1) AIDS-defining malignancies: the appearance of the following malignancies among PLWHA signifies the progression of the disease to AIDS. They include:

Kaposi's sarcoma: (KS);
Non-Hodgkin's lymphoma (NHL);
Cervical cancer.

(2) HIV-associated but not AIDS-defining malignancies: the appearance of malignancies in this category among PLWHA does not necessarily imply progression to AIDS. Cancers in this category include:

Anal cancer;
Hodgkin's disease (Hodgkin's lymphoma);
Melanoma – skin cancer;
Liver cancer;
Lung cancer;
Mouth and throat cancers;
Testicular cancer;
Colorectal cancer;
Squamous cell and basal cell skin cancers.

Occurrences

The three common "AIDS-defining malignancies" have a far higher increased prevalence among PLWHA compared to people of the same age who are not infected with the virus (3). Literatures have reported that PLWHA were several thousand times more likely to be diagnosed with Kaposi's Sarcoma compared to other people who are not infected with the virus. They were also found to be at least seventy (70) and five (5) times more likely to be diagnosed with non-Hodgkin's lymphoma and cervical cancer (among women), respectively (Grulich et al., 2007). Others include anal cancer (25 times), Hodgkin's lymphoma (10 times), lung cancer (3 times), and liver cancer (5 times) when compared with HIV-negative individuals (3).

Risk factors to HIV-Associated cancers

The mechanism of action of HIV is to cause immune-suppression, and it subsequently reduces the body's ability to fight other infections that may be precursors of cancers (4, 5). Viruses acting as precursors of cancers are common (4-6), and listed as follows:

- Human Herpes Virus 8: acting as a precursor of Kaposi's Sarcoma;
- Epstein-Barr Virus: as a precursor of some forms of non-Hodgkin's and Hodgkin's lymphoma;
- Human Papilloma Virus (HPV): as a precursor of cancer of the cervix, some mouth and throat cancers;
- Hepatitis B virus: as a precursor of liver cancers.

The prevalence of documented behavioural risk factors of some cancers such as smoking (for lung cancer) and heavy alcohol use (for liver cancer) is higher among people living with HIV (3, 7) compared to the general population. Older age (>40 years) has also been found to increase the propensity of developing some HIV-associated malignancies (8).

Table 1: Specific description of KS and NHL

	KS	NHL
Description	Related to human herpes virus 8 (HHV-8) infections (also called KSHV) Epidemic Kaposi's sarcoma	Range from lymphoid interstitial pneumonitis to high-grade NHL and Primary CNS lymphoma (PCNSL) Starts in lymphoid tissue and may spread to other organs PCNSL starts in the brain or spinal cord
Presentation	Lesions do occur in multiple sites including the skin, mouth, and lymph nodes. Skin lesions may first appear as erythematous macules, becoming darkened and raised or nodular with time. Lesions appear as dark plaques or	Symptoms of PCNS lymphoma can include seizures, facial paralysis, confusion, memory loss, extra-nodal disease Metastasized to the brain, bone marrow, and gastrointestinal tract to give systemic symptoms

	nodules on dark skin, and reddish-purplish or brownish on light skin	
Diagnosis	Biopsy and cytology Fine needle Aspiration	Diagnosis of NHL is made through biopsy of affected tissue CT-Scan and MRI and CSF analysis for PCNSL
Prognosis	Low CD4+ cell count	Low CD4+ cell count History of opportunistic infections, and a good performance status Older age
Treatment	HAART Chemotherapy Radiotherapy Subcutaneous interferon α (IFN-α) Immunotherapy	HAAART Chemotherapy Radiation with PCNSL Immunotherapy

Prevention and control of HIV-associated cancers

Prevention is perhaps the most cost-effective strategy in cancer prevention. National governments should ensure that they put in place an enabling environment for cancer prevention and reduction policies to thrive. Some of the steps in cancer prevention and control are:

(1) Highly Active Anti-Retroviral Therapy (HAART): Since the introduction of HAART, new developments on the progression of HIV cancers have been reported. The Swiss HIV Cohort Study of AIDS-associated cancers among 9429 PLWHA and subsequent follow-up (9) confirmed this report.

The incidence of KS and NHL has decreased markedly with HAART while such a decrease was not significantly noticed in the environment with poor access to HAART for many reasons such as poor finance or poverty (4, 10).

The importance of both immunologic and virologic responses in immune restoration has been identified, leading to a decrease in the

incidence of opportunistic infections, reducing the risk of developing NHL or KS, and prolonging survival (11,12).

(2) Early diagnosis through cancer screening: this could reduce the incidence and prevalence of HIV-associated cancers. Screening for hepatitis could reduce the incidence of liver cancer, EBV virus screening prevents the occurrence of primary CNS lymphoma while Paps smear prevents the occurrence of cancer of the cervix among women.

(3) Specific treatments: chemotherapy and radiation therapy among other treatment regimens are available and crucial for the survival of PLWHA. Optimal care can only be achieved by the close cooperation of the cancer management team including oncologists and haematologists for highly favourable treatment outcomes. The use of Human Papilloma Virus vaccine and interferon in the management of some cancers is a step towards achieving specific protection against cancers targeting the precursors.

(4) Behavioural Change Communication (BCC) strategy: this could determine the occurrence or otherwise of some other co-infections among PLWHA. For example, sexual pattern could be a determinant for the occurrence of cancer of the cervix, and alcohol and smoking reduction for cancer of the liver. Stakeholders have to improve their frequency and quality of counselling that would bring about positive behavioural change towards cancer prevention and control among PLWHA.

References

1. Rubinstein PG, Aboulafia DM, Zloza A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS*, 2014;28:453.
2. Carbone A, Vaccher E, Gloghini A. Diagnosis and management of lymphomas and other cancers in HIV-infected patients. *Nat Rev Clin Oncol*, 2014; 11: 223.
3. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immune-suppressed transplant recipients: a meta-analysis. *Lancet* 2007; 370(9581): 59–67.
4. Engels EA, Biggar RJ, Hall HI. Cancer risk in people infected with human immunodeficiency virus in the United States. *International Journal of Cancer* 2008; 123(1): 187–194.

5. Powles T, Macdonald D, Nelson M, Stebbing J. Hepatocellular cancer in HIV-infected individuals: tomorrow's problem? *Expert Review of Anticancer Therapy*, 2006; 6(11): 1553–1558.
6. Angeletti PC, Zhang L, Wood C. The viral etiology of AIDS-associated malignancies. *Advances in Pharmacology* 2008; 56: 509–557.
7. Silverberg MJ, Abrams DI. AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. *Current Opinion in Oncology*, 2007; 19(5): 446–451.
8. Spano JP, Costagliola D, Katlama C. AIDS-related malignancies: state of the art and therapeutic challenges. *Journal of Clinical Oncology*, 2008; 26(29): 4834–4842.
9. Franceschi S, Lise M, Clifford GM. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer* 2010; 103: 416.
10. Engels EA, Pfeiffer RM, Goedert JJ. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS,* 2006; 20(12): 1645–1654.
11. Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. *Ann Intern Med,* 2000; 133: 401.
12. Bonnet F, Balestre E, Thiébaut R, et al. Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France. *Clin Infect Dis*, 2006; 42: 411.

HIV/AIDS AND THE PAEDIATRIC POPULATION

HENRY C ANYABOLU
MBBS, FWACPAED
AND JEROME B.E ELUSIYAN
FWACPAED

The children of Nigeria and sub-Saharan Africa have borne a disproportionate burden of the scourge of the pandemic of paediatric HIV infection. Remarkable progress has been made since 1983 when the first paediatric HIV diagnosis was made. The PubMed, African Journals Online (AJOL) and official websites of the National Agency for Control of AIDS (NACA), the United Nations Agency for AIDS (UNAIDS) and the World Health Organization (WHO) were searched for publications between 2000 and December 2017 that related to HIV in children. The epidemiology, clinical presentation, psychosocial aspects, control efforts, recent advances and future directions are highlighted. Enormous gaps remain in the control of paediatric HIV. The global commitment to support the treatment and care of children living with HIV and to fund research in HIV prevention and control efforts should be sustained.

Since 1983 when the first report of children who were perinatally infected with human immunodeficiency virus (HIV) was published (1), HIV/AIDS in children has grown to become a pandemic that has revolutionized the landscape of global public health. The watershed event that turned the tide against the scourge was the Millennium Declaration (2) when it was made one of the targets of the Sixth Millennium Development Goal. Currently, the Sustainable Development Goals (3) seek to build on the momentum gained over the past 15 years to bring an end to the unfinished business of the control of HIV/AIDS in children. This chapter evaluates current global events, research, control efforts and challenges regarding paediatric HIV/AIDS with an emphasis on Nigeria.

History of Paediatric HIV

The first case of paediatric HIV was a teenager from St Louis, USA who died in 1969, of a mysterious illness which was confirmed 18 years later to be acquired immunodeficiency syndrome (AIDS) (4). In 1982, the United States Centre for Disease Control (5) reported four infants who had features of severe acquired immunodeficiency and the first reports of perinatally transmitted HIV in children were made in 1983 (1). The first case of HIV/AIDS in Nigeria was reported in 1986 (6) and it was, incidentally, a 13-year-old child who was a hawker in Lagos. The first sentinel seroprevalence survey among antenatal women was done in 1991 by the Federal Ministry of Health (7) and a prevalence rate of 1.8% was reported. Subsequent surveys showed a peak of 5.8% in 2001 (8). The prevalence rate gradually fell to the most recent value of 3.0% in 2014 (9). The antiretroviral therapy (ART) program in Nigeria commenced in 2002 on 25 sites across 18 states in the country (10) while paediatric ARVs became available in public health facilities for the first time in October 2005. With the introduction of the free ARV treatment policy for all eligible persons in 2006, the number of adults and children on ART increased from 51,000 in 2005 to 636,000 in 2013 (10).

Epidemiology

Globally, 2.1 million children were living with HIV in 2016. In the same year, 160,000 children were newly infected with HIV which is a 47% decline from 2010 figures. In 2016, 120,000 children died of HIV-related causes. With 270,000 HIV-infected children in 2016, accounting for about 30% of the global burden of HIV-infected children (11, 12), Nigeria had the highest number of HIV-infected children worldwide. Nigeria is one of the 22 global priority countries which account for 90% of all children newly infected with HIV worldwide (13). Among these countries, eight countries have reduced new HIV infections among children by more than 50% since 2009, based on the 2013 data, and another 4 are close to that mark. Nigeria has reduced new infections among children by only 16% since 2010 (11). With the increasing availability of highly active antiretroviral drugs, the number of perinatally-infected adolescents who are growing up to become adults living with HIV is also expectedly on the rise. The National seroprevalence of HIV in the Sentinel Survey conducted among antenatal clinic attendees in 2014 was 3.0% (9). Antiretroviral drug coverage for pregnant women living with HIV was 29% in 2014 (10), up from 13% in 2009 using the Option B strategy which is currently

employed as the national policy for preventing mother-to-child transmission. The average national MTCT rate in 2016 is 26% (10) while an estimated 51,000 HIV-infected infants are born in Nigeria annually (10). Currently, the proportion of HIV-exposed children accessing early infant diagnosis is 3.9% while the proportion of eligible children accessing HAART increased from 5% in 2009 to 12% in 2014 (13).

The world has exceeded the AIDS targets of Millennium Development Goal (MDG) 6, halting and reversing the spread of HIV (14), and more countries are getting on the Fast-Track Initiative to end the AIDS epidemic by 2030 as part of the Sustainable Development Goals (SDGs) (3). UNAIDS launched a global Fast-Track Initiative known as the 2016-2021 Strategy on World AIDS Day in 2014 (15). At the core of the Fast-Track Initiative is an intensive effort to build on these achievements and reach the 90–90–90 treatment targets by 2020: 90% of people (children, adolescents, and adults) living with HIV know their HIV status, 90% of people who know their HIV-positive status are accessing treatment and 90% of people on treatment have suppressed viral loads.

Mode of transmission

Mother-to-child transmission (MTCT) accounts for >90% of transmission in children and can occur in-utero, at delivery or during breastfeeding (16). Other routes of transmission include sexual contact (forced or consensual), through transfusion of blood and blood products as well as the use of contaminated sharps such as needles, circumcision or scarification needles. Studies in Nigeria (17, 18, 19, 20), have suggested that the commonest route (93-95%) for paediatric HIV infection remains mother-to-child transmission (MTCT). In the earlier studies (21, 22) MTCT constituted as low as 30% of the routes of transmission with blood transfusion contributing up to 15% (23). In Nnewi (24), MTCT accounted for 79.7% while blood transfusion was the route of HIV transmission in 16.4% of cases. The highest reported proportion of HIV transmission occurring through sexual transmission was 5.0% (23). Currently, the average MTCT rate in Nigeria is estimated at 26% (10). However, in recent PMTCT programs, MTCT rates as low as 1.8% has been reported from Sokoto (25) while 3.6% was reported in Nnewi (26). The rates in these states are similar to reports from PMTCT programs in developed countries and fall within the <5% MTCT rate target of the global elimination of MTCT (eMTCT) (13, 27).

Pathogenesis of HIV in children

Disease progression is faster and prognosis is poorer among children less than five years old (especially infants) compared to adults (28). This manifests in the trend of the viral load (VL). In infants, VL levels are low at birth, increase to levels >100,000 to millions of copies/ml by two months of age and remain at the same level throughout the first year of life before declining slowly over the next few years to a "set point" (29). Three distinct patterns of disease are described in children (30). The pattern with a rapid disease course also known as category 1 constitutes 25-30% of HIV-infected children in developing countries. They are believed to have been infected *in-utero* and test positive to virologic tests at 48 hours of life. They develop symptoms during the first few months of life and have a median survival time of 6-9 months if untreated. The majority (50-60%) of the children belong to the category of slow progressors (category 2) who are believed to have been infected intrapartum and if untreated, die within 3-5 years of life. The last group (category 3) is the long-term survivors who live beyond 8 years with minimal symptoms. They are believed to have been infected by the virus during the postnatal period principally through inappropriate breastfeeding practices. A defective infecting virus and altered immune cell receptors are some other proposed theories to explain the basis for this long-term survivor phenomenon.

HIV exposed uninfected children

In view of the increasing effectiveness of PMTCT programs, the number of HIV exposed but uninfected children (HEU) is increasing and their health is assuming significant public health relevance. Various studies have shown that, compared to HIV unexposed children, HEU have greater low birth weight rates, a higher prevalence of growth, development and immunologic abnormalities and ultimately higher mortality rates (31-35). Theories proffered to explain these outcomes include the side effects of ARVs taken by the mother and the baby, prevalent food insecurity in many HIV-affected households and lately, and coexisting maternal cytomegalovirus infection (maternal HIV-cytomegalovirus co-infection) which was transmitted to the baby (36).

Clinical Features

Various studies have characterized the symptomatology of HIV infection in children. Common presenting symptoms were prolonged fever lasting

for more than one month, persistent diarrhoea lasting 14 days or more, chronic ear discharge, difficult/fast breathing and vomiting; while clinical signs were wasting (<-2 z-score), crepitations in the lungs, pallor, parotid swelling, oral thrush, hepatomegaly, generalized lymphadenopathy, and dehydration.

Features predictive of HIV infection were fever, diarrhoea, cough, weight loss, suppurative otitis media, generalized lymphadenopathy, herpes zoster, parotitis and oropharyngeal thrush. The mean z-scores of the nutritional indices were significantly lower in HIV-infected children as compared to uninfected children (37). Serum levels of micronutrients are not spared as HIV-infected children have been found to have lower mean levels of zinc, selenium, and vitamin C (38) all of which play a vital role in body defence and immunity. The most common presenting laboratory feature was anaemia occurring in 92.9% of HIV-infected children seen in Enugu (22). A Zidovudine-based regimen especially in association with the routine co-trimoxazole preventive therapy has been found to reduce the haematocrit of children progressively following the initiation of HAART.

Opportunistic infections are distinctive features in immunosuppressive conditions. They are infections that ordinarily in immunocompetent people will present with minimal or no symptoms/signs but produce significant illnesses in immunosuppressed people. Common infections among Nigerian HIV-infected children include tuberculosis (especially pulmonary and lymph node tuberculosis), mucocutaneous candidiasis, herpes zoster, chronic protozoal diarrhoeal illnesses, and chronic suppurative otitis media (17, 39). The pattern of infections is virtually unchanged between the pre-HAART (22, 23) and the present HAART era (17). The pattern of infections seen in children is different from adults as Pneumocystis jiroveci and parotitis are rarely seen in adults**.**

Clinical and immunological Stages: Studies from various parts of the country revealed that 60% -82% of children with HIV/AIDS presented for the first time in late clinical stages while as many as 59% were already in severe or advanced immunosuppression (17, 20, 40). These portray the wide prevalence of the problem of late diagnosis of HIV-infected children in Nigeria. The poorer outcome of children diagnosed late was evident in the study by Omoni et al. in Benin (41) which reported slower and suboptimal immunological recovery following HAART initiation in the group of children who were diagnosed late compared to those who were diagnosed earlier and who had higher CD4 counts at initiation. Virologic monitoring is being scaled up in Nigerian paediatric treatment sites as a

routine investigation for monitoring following the WHO recommendation (42) as it is a more accurate reflection of the efficacy of ART in patients. Up till 2015, viral load measurement was used in most paediatric HIV treatment sites strictly for diagnosing virologic failure as a confirmation for treatment failure after clinical features and CD4 counts have shown clinical and immunologic failure. The high cost has been the major constraint hindering the scale-up of viral load measurement in ART treatment facilities but it is expected that with innovation and deployment of point-of-care virologic testing equipment, access to viral load monitoring will be increased.

Antiretroviral treatment in Nigerian children

Antiretroviral drugs first became available in public health facilities in Nigeria in October 2005. They have, since then, been provided at no cost to the patients. The combination of antiretrovirals for the treatment of HIV is known as highly active antiretroviral therapy (HAART). The main objective of ART is to achieve clinical, virologic, immunologic and epidemiologic control of HIV. This leads to the improved growth and development of these children as well as an overall reduction in mortality. Criteria for initiation of ART have evolved over the years as more evidence from myriad researches became available. Currently, the criteria are based on the "Test and Treat Strategy" whereby any child who is confirmed to be HIV positive is commenced on ART ideally within two weeks of diagnosis regardless of the immunologic or clinical stage of the infection. Antiretroviral drugs that are available and are being used for the treatment of HIV-infected children in Nigeria (9) include zidovudine, abacavir, lamivudine, nevirapine, efavirenz, tenofovir and ritonavir-boosted lopinavir. The newest additions are dolutegravir (DTG), an integrase inhibitor and the pellet formulation of ritonavir-boosted lopinavir (LPV/r).

Adherence to ART

Adherence to ART is the most important factor responsible for antiretroviral treatment success (43, 44). The minimum effective adherence is 95% (45). ART adherence among children is dependent largely on the caregiver. In studies that evaluated adherence levels using caregiver reports, an 85% adherence rate was reported in Lagos (46) while 80% of caregivers admitted being adherent three days before the clinic visit in Kano (47). In the study on the large paediatric ART program of the

APIN-Harvard Nigerian program, less than half of the children retained at 12 months reported optimal adherence to ART (48). Reasons given in the studies for nonadherence include the child sleeping through the dosing time, the drug supply running out due to a missed clinic appointment and the caregiver being away (46, 47).

Care of HIV-infected children

The current advocated model of care for HIV generally is the integrated, comprehensive family-centred care model (9, 49). The timeline of care is broadly divided into pre-ART and ART periods. The "integration" involves accessing routine maternal and child health services as well as HIV testing and treatment in the same facility. "Comprehensive" implies a diverse range of multidisciplinary care packages which include prevention services, nutritional support, mental and psychosocial services, orphan and vulnerable children support, adherence counselling and disclosure. The family-centred care model involves providing treatment and prevention services to adults and children from the same family unit in the same setting (50). It improves HIV testing and treatment services uptake and encourages long-term adherence to ART (51).

Retention in care

Retention in care describes the continued engagement of a client along with the entire continuum of care from diagnosis till discharge (for HIV-exposed infants), transfer or death (52). Retention in care, with treatment adherence, is the most important determinant of outcome in any HIV treatment and care program. Retention is calculated based on the aspect of care being evaluated. For example, pre-ART retention rates may be calculated to identify those who remain in care from diagnosis (as HIV-exposed or HIV-infected children) to discharge (for those confirmed HIV negative) or enrolment into the ART program. The ART retention rate evaluates the proportion of children who are alive and remain on ART after a specific period (say 12, 24, 36 or 48 months) following ART initiation.

Diagnosing and retaining HIV-exposed and infected children and adolescents in care present unique challenges. Their vulnerability is heightened by their dependence upon a caregiver. Retention rates at diverse timelines in Nigeria ranged from 64% in Lagos (53) to 81.3% in Nnewi (54) while a large multi-centre study (55) found a retention rate of

76.8% over one year. Barriers to retention in care include site-specific barriers. These sets of barriers include the lack of an age-appropriate comprehensive HIV care package, human resource shortfalls especially of community-based patient trackers, prolonged waiting times in clinic which discourage caregivers, and a lack of adequate counselling and support services which ought to help patients and their caregivers navigate through family, health and social challenges (55). Child level barriers include financial challenges when poor caregivers have to source funds to pay for clinic visits, transportation difficulties where clients live in difficult-to-navigate areas which are far from the facility, an advanced clinical stage of HIV which hampers mobility, orphanhood and social stigma (48, 56).

Disclosure

The process of informing an HIV-infected child of his HIV status is known as disclosure (57). Disclosure of the status of perinatally infected children especially when the mother is still alive and well has long been known to be a sensitive issue for the parents, the child himself and other spheres of the society such as the school (58, 59). Disclosure of the child's serostatus is encouraged as it has been shown to improve adherence to ARV as the child now understands the need for his long-term medications (60, 61). It is done in stages and provided in an age-appropriate manner. Generally, disclosure should begin by 5-7 years and proceed in gradual incremental steps as the child's cognitive and developmental capacities guide the process (43, 44, and 62). HIV serostatus disclosure among HIV-infected Nigerian children by their parents is still low at 13.5% in Ibadan (63) while it was 30.9% in Abuja (64). The Abuja study found age to be the only significant predictor of disclosure. The fears expressed by the mother of the child blaming her for transmitting the infection to him, or the child disclosing his serostatus to other children and an erroneous belief that the children would not understand anything about HIV until they are young adults were given in these studies as the principal reasons for non-disclosure.

Early Infant Diagnosis Program in Nigeria

It is estimated that in the absence of effective treatment, 35 per cent and 52 per cent of all HIV-infected children die by the age of one year and two years respectively (65). The early infant diagnosis program aims to identify these HIV-infected infants and to place them on antiretroviral therapy before they become symptomatic. It involves the use of the HIV

DNA-Polymerase chain reaction (HIV DNA-PCR) method to test dried blood spot (DBS) samples from the HIV-exposed infants first at 6-8 weeks of age and again at 3 months after all forms of breastfeeding are discontinued (that is at the age of 15 months for all babies who stopped breastfeeding at 12 months as recommended in the Nigerian National Guideline) (9). If at either of the two ages a baby tests positive, the baby is confirmed to be HIV infected and commenced on HAART. If the baby tests negative at the two ages, he is confirmed as HIV negative. If the baby tested negative at 6-8 weeks and then tests positive at 15 months, it points to the postnatal acquisition of the infection.

Nigeria's Early Infant Diagnosis (EID) program began in 2007 with two laboratories linked to six facilities where the blood samples of infants were collected for testing (10). There are about 23 EID laboratories in Nigeria with over 1200 health facilities equipped to process blood samples for EID while 8686 health workers have been trained to provide both paediatric and adult ART services (10). The Nigerian EID program aims to provide EID services for at least 90% of all HIV-exposed infants and targets to test more than 158,000 HIV-exposed infants by 2020 in line with the UNAIDS 90-90-90 global target (10). So far, EID coverage has remained low with only 4% of HIV-exposed infants receiving a virologic test within two months of birth (10).

Co-infections

Tuberculosis-HIV co-infection is a major threat to the control of either disease. Both diseases are twin pathologies that synergistically drive the progression and spread of each other. The long existing challenge of diagnosis of Tuberculosis (TB) in HIV-infected children is currently being addressed by the roll out of the Xpert TB diagnostic test across the country as recommended by the World Health Organization (66). GeneXpert MTB/RIF testing is a fully automated nucleic acid amplification test that diagnoses tuberculosis and also tests for resistance to rifampicin (67). It is a fast test with results being available in 90 minutes. Its much lower limit of detection (131 colony-forming units/ml as compared to 10,000 colony-forming units/ml for sputum smear microscopy) is particularly useful in HIV-infected children who commonly have paucibacillary tuberculosis (68). Moreover, the detection of rifampicin resistance is an added benefit that enables the diagnosis of multidrug resistant tuberculosis. The implementation of isoniazid prophylaxis for HIV-infected children is still low with rates as low as 0.8% in a nationwide survey (69) for eligible

children. Adduced reasons for the low implementation rate are the widespread unavailability of the lower milligram (100 mg) child-friendly dispersible formulation as well the low awareness of indications for INH prophylaxis among paediatric healthcare providers. TB was the commonest opportunistic infection in Lagos (40) seen in 25.8% of patients. In hospital-based studies in paediatric HIV clinics, TB was found in 15.4% of children in Nnewi (70) and 19.5% in Gwagwalada, Abuja (64).

Hepatitis B and C co-infections were reported among 1.9% and 3.3% of the HIV-infected children respectively in Enugu (20) and Ibadan (17). The prevalence of HBV and HCV were 7.5% and 5.2% respectively in Benin-City among Nigerian children in an antiretroviral treatment program (71, 72).

Kidney disease

There have been reports of kidney affectation in HIV-infected children. In the pre-ART era, HIV-associated nephropathy (HIVAN) was clearly the commonest renal pathology in every country affected by HIV (73). However, in countries where access to HAART is high, for instance in the US, toxic nephropathy from HAART and other drugs for opportunistic infections have assumed prominence. Serum cystatin levels have been found to provide a better assessment of kidney functions than a creatinine-based estimation of glomerular filtration rate in HIV-infected children and adults due to the prevalent muscle wasting in these patients (74) Esezobor et al. in Lagos evaluated the serum cystatin levels and estimated glomerular filtration rates in stable HIV-infected children and HIV-negative controls (75). They found that more HIV-infected children had eGFR less than 60 ml/min than the controls. Also, more HIV-infected children than the controls had a serum cystatin level greater than 1 mg/l which is a risk factor for death from cardiovascular and kidney diseases. In the study by Anochie et al. (76), children with HIV-associated nephropathy (HIVAN) presented with nephritic syndrome or acute renal failure and responded to HAART and ACEI with guarded outcomes while microalbuminuria was observed as an early manifestation of HIVAN in 12% of children. Asymptomatic bacteriuria was reported in 10.3% of HIV-infected children in Benin (77) and was found to be higher in females with E. coli, Klebsiella and Staphylococcus aureus as predominant isolates. However, compared to HIV-uninfected children, there is no difference in the prevalence of UTI in HIV-infected children.

Neurologic complications

The neurologic manifestations of HIV in HIV-infected children are diverse with HIV encephalopathy, central nervous system opportunistic infections, neuropsychiatric manifestations and ART neurotoxicity as the more common presentations (78). Other features include peripheral neuropathy, central nervous system lymphoma, and seizure disorders. It has been estimated that without ART, 50-90% of all HIV-infected children develop a form of nervous system pathology. CDC-defining features of HIV encephalopathy include failure to attain or regression of developmental milestones, microcephaly and symmetric motor deficits (79). Opportunistic infections by organisms such as cytomegalovirus, varicella zoster virus, Cryptococcus neoformans, toxoplasma and tuberculosis have been responsible for encephalitis, meningitis, and meningoencephalitis with neurologic sequelae in HIV-infected children (80). Neuropsychiatric manifestations have been found in as many as 35% of HIV-infected children and include attention deficit hyperactivity disorder, depression, anxiety disorder and suicidal ideation (81). ART neurotoxicity includes neuropathy following mitochondrial toxicity from stavudine administration, hallucinations, and confusion following efavirenz as well as immune reconstitution inflammatory syndrome as central nervous microorganisms are being unmasked with HAART (82, 83). The cognitive ability of HIV-infected children is receiving attention due to their longer life span with increased access to HAART. This has raised interest in other health issues beyond mere survival. A comparative cross-sectional study in Lagos observed an increased prevalence of cognitive deficits among children living with HIV compared to HIV-negative children (84). Neurocognitive assessment is therefore advocated as part of their clinical evaluation to enable early identification of deficits and intervention. Younger age, poor socioeconomic status, and a low level of maternal education were associated factors apart from HIV infection (85).

Deaths in HIV

While the number of new infections among children globally has fallen by 58% since its peak in 2002, mortality from HIV among children has declined by only 40% due to persistently low coverage of ART in children compared with adults (86). HIV and other infectious diseases either singly or in combination were responsible for over 70% of the 860,000 under-five deaths in Nigeria in 2013 (87). Onankpa et al. reported that septicaemia and acute respiratory tract infections were the major admitting

diagnoses and major causes of deaths among HIV-infected Nigerian children while deaths from HIV infection accounted for 22.4% of the total deaths for the study period (18). Studies in the pre-HAART era in Ile-Ife (23) found that 46.3% of the children died within four months of diagnosis mainly from pneumonia and septicaemia while in Abuja (88) the mortality rate was 32.6% which accounted for 28.57% of total deaths in the paediatric unit during the period. In the Abuja study as well, pneumonia and septicaemia were the greatest contributors to mortality. In the study by Ojikutu et al. across 10 states in Nigeria (55), the mortality rate was 4.2% across a mean follow up period of 27 months. Predictors of mortality in the study were a low weight-for-age z-score as well as poor quality of care offered by the ART facility. In Port Harcourt, HIV was the major cause of mortality among children less than 5 years seen in the facility (89). In the 7-year report from a large cohort in Lagos that compared outcomes in both the pre-HAART and HAART eras (55), mortality in the HAART era was less and the rate was similar to other reports from diverse settings: 2.67 per 100 child years in the study as compared with 2.31 per 100 child years in China and 10% in the study compared with 7.7% in South Africa. Ojeniran et al. (55) also reported that predictors of mortality were a low CD4 count at ART initiation, an age of more than 2 years and the WHO clinical stages 3 and 4. Mortality rates reported in Nigeria parallel the trend in sub-Saharan Africa but are a far cry from the low mortality rates that have long been achieved in Western countries, for instance, Great Britain (90). Better access to ART, earlier diagnosis, and initiation of treatment as well as the better social support system in these Western countries are hugely responsible for the disparity in outcome.

Paediatric ART

The earlier guidelines for ART initiation in children were determined by CD4 count, CD4 percentage and clinical stage (43, 91). The Children with HIV Early Antiretroviral Therapy (CHER) trial in South Africa (92), which compared the early initiation of treatment of PCR diagnosed infants with treatment initiated on the basis of clinical stage or CD4 count, was the watershed event in paediatric ART guidelines. It demonstrated the survival benefit of early initiation of antiretroviral therapy, as mortality was reduced by 76%. The latest guidelines released in September 2015 which are an update to the 2013 Guidelines (93), are a departure from the previous guidelines in which ART initiation was based on clinical stage and CD4 counts. It recommends that paediatric ART treatment programs should treat every child who tests positive regardless of the clinical stage

or CD4 count in line with the test-and-treat strategy of treatment as prevention. Based on the new recommendations, the number of people eligible for antiretroviral treatment increased from 28 million to all of the 37 million people who currently live with HIV globally. According to UNAIDS estimates, expanding ART to all people living with HIV and expanding prevention choices can help avert 21 million AIDS-related deaths and 28 million new infections by 2030 (15).

Prophylaxis for Opportunistic Infections (OI)

A systematic review of the incidence of infections in HIV-infected children globally (94) identified bacterial pneumonia, tuberculosis, sepsis, pneumocystis jiroveci pneumonia, cerebral toxoplasmosis and cryptosporidium diarrhoea to be significant contributors with their incidence among ART naive children to be 25.09%, 12.36%, 3.95%, 3.48%, 3.06% and 2.92% respectively. The two most important drugs for prophylaxis are co-trimoxazole and isoniazid preventive therapies. Co-trimoxazole preventive therapy (CPT) is the use of co-trimoxazole for the prevention of several secondary bacterial and parasitic infections such as salmonella sepsis, Streptococcus pneumonia, toxoplasmosis, Pneumocystis jirovecii and malaria in HIV-infected individuals to reduce morbidity, improve quality of life and reduce mortality among HIV-infected children. Though the previous (2014) Nigerian treatment guideline stipulates indications based on age, clinical stage and immunological criteria for its initiation and discontinuation, the WHO in a recent update (95) recommended that in malaria-endemic countries, it should be used for life in all HIV-infected children regardless of age, clinical stage or CD4 count. This has been adopted by the 2016 Nigerian Paediatric HIV treatment guideline and thus all children who are HIV-infected are placed on cotrimoxazole prophylaxis till adulthood. HIV-exposed children are also placed on co-trimoxazole from the age of six weeks till their HIV status has been confirmed and they have stopped breastfeeding. If they are confirmed to be HIV negative, co-trimoxazole is discontinued. Isoniazid preventive therapy prevents the development of active tuberculosis; hence, the drug is indicated in all HIV-infected children above 12 months while those aged less than 12 months only receive it if they are close contacts of adults with tuberculosis.

Prevention

EMTCT: The global commitment to the elimination of mother-to-child transmission of HIV (EMTCT) provided the impetus to achieve the MDG target of mother-to-child transmission of HIV. Elimination, in the case of mother-to-child transmission of HIV, means the reduction of the rate of transmission to a level so low that it no longer constitutes a public health problem. EMTCT is a level ahead of the program of prevention of mother-to-child transmission (PMTCT) and is planned to build on its success. The minimum EMTCT impact targets include <50 new paediatric infections per 100,000 live births and a transmission rate of either <5% in breastfeeding populations or <2% in non-breastfeeding populations.

Specific levels of service delivery also need to be met to accomplish the EMTCT of HIV. These are the process targets and include antenatal care coverage (at least one visit) >95%, coverage of HIV testing of pregnant women >95% and antiretroviral treatment coverage of HIV-positive pregnant women >90%.

Infant feeding in HIV: The observations and reports decades ago of the diverse unique health benefits of exclusive breastfeeding (96, 97) led to its widespread promotion by the World Health Organization as a child survival strategy. Key factors among these benefits over other infant feeding methods include protection from major childhood killer diseases (pneumonia, diarrhoea) and better nutritional outcomes. The discovery of the transmission of HIV through breastfeeding in 1985 (98) and the subsequent recommendation for HIV-infected mothers not to breastfeed their infants introduced a clog in the wheel of promotion of exclusive breastfeeding. Research over the years has shown that in the absence of interventions, 15% to 25% of HIV-positive mothers who do not breastfeed will infect their infants during pregnancy or delivery. With breastfeeding, there is an absolute increase in transmission of about 5% to 20%. The alternative option to breast milk known variously as breast milk substitutes, infant formula or replacement feeds is associated with increased infant morbidity and mortality as reported in several sub-Saharan African countries (99, 100). The aim of infant feeding practices in the context of HIV should be not just the prevention of HIV transmission but also the ensuring of the health and survival of infants – referred to as HIV-free survival. This implies that young children are both alive and HIV-uninfected at a given point in time, usually measured at 18 months. Thus, the intention of interventions is to prevent HIV transmission through breastfeeding, while at the same time ensuring that mortality among these

children does not increase because of avoidance of, or modifications to, breastfeeding practices. Improved HIV-free survival has been reported in HIV-exposed infants when breastfed and when exclusively breastfed, compared with mixed feeding or replacement feeding (101). If an HIV-positive mother breastfeeds her infant while taking ARVs herself or giving ARVs to her infant each day, the risk of transmission over 6 months of breastfeeding is reduced to about 2%. If she breastfeeds for 12 months while taking ARV or giving them to the infant, then the risk is about 4% (102). Without these ARV interventions, about 14% to 17% of breastfed infants of HIV-positive mothers would become HIV infected by 18 months of age (103). The 2010 infant feeding guidelines by the WHO (104) recommend that women who breastfeed and receive ARVs (or whose infants are receiving ARVs) should exclusively breastfeed their infants for six months and continue breastfeeding until 12 months of age and then consider stopping gradually over a month only if appropriate replacement foods are available. The guideline also encourages national health authorities to recommend one infant feeding practice for HIV-positive mothers to be promoted and supported by maternal, newborn and child health services. The Federal Ministry of Health of Nigeria recommends and promotes exclusive breastfeeding for the first 6 months and complementary feeding for the second half of infancy, stopping all forms of breastfeeding by the end of the first year of life. Previous research conducted in Ile-Ife, Nigeria (105) revealed the general preference by mothers for breastfeeding. Another report (106) highlighted the various difficulties encountered by mothers as they struggle to surmount the AFASS criteria that must be satisfied before they can proceed with replacement feeding. However, other studies conducted in Nnewi (26) and Benin (107) showed a higher preference for breast milk substitute ranging from 83.5% to 100%. The higher social class of the clients in those cities, as well as a possible inclination of the health personnel to exclusive formula feeding, may be largely responsible for these observations.

The latest recommendation by the WHO (102) is that HIV-positive mothers can breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond (similar to the general population) while being fully supported for ART adherence. It also recommends that although exclusive breastfeeding is recommended, practising mixed feeding is not a reason to stop breastfeeding if the mother is on her ARV drugs.

School-based AIDS education and Sex education as interventions in secondary schools have been found to be effective in improving the knowledge, attitude, and practice of adolescents regarding HIV. A pre-intervention baseline survey in Ibadan (108) revealed that 35.3% of the students in the senior secondary schools surveyed have had sex out of which 28.3% had multiple sexual partners whereas 19.8% of the males used a condom consistently. This becomes more imperative since a study conducted as early as 2007 (109) in Southwestern Nigeria showed that the average age of exposure to internet pornography was 10 years with most parents who were surveyed lacking basic knowledge about the menace and its impact on children. The trend in this era of freely accessible mobile phones and tablets is likely to be worse.

Drug Optimization

Improvements have been made in optimizing available paediatric formulations of ARVs to make them more children friendly. The production of fixed-dose dispersible combinations of paediatric ARVs was arguably the most important step that improved treatment adherence. The recent development of Lopinavir and Ritonavir (LPV/r) as oral pellets which can be mixed with food (110) removed the obstacles of heat lability, unpleasant taste and difficult dosing associated with this protease inhibitor which is a key factor in paediatric ART therapy. The need for the development and expanded use of more simplified, less toxic and more robust drug regimens led to the Paediatric ARV Drug Optimization (PADO) meeting convened by the WHO in late 2013 to establish a roadmap for streamlining access to and uptake of paediatric ARVs. The development of dosing wheels for drug prescription has eased the tedious process of calculation of ART doses and has helped to reduce errors in under- and over-dosing.

Post-Exposure Prophylaxis for HIV/AIDS in Children

Post-exposure prophylaxis (PEP) is an important intervention to prevent HIV infection in infants and children, who may be accidentally exposed to HIV through community-acquired needle-stick injuries, scarification, and pre-mastication, or following sexual assault. The contributions of the various horizontal routes of HIV transmission to the burden of HIV in Nigeria have already been highlighted. Following the findings from a systematic review (111), the WHO recommended (112) that a combination of zidovudine (AZT) and lamivudine (3TC) be prescribed as the preferred

backbone regimen for HIV post-exposure prophylaxis among children of 10 years and younger while abacavir (ABC) and lamivudine (3TC) or tenofovir (TDF) and lamivudine (3TC) (or emtricitabine [FTC]) can be considered as alternative backbone regimens. It went on to add that ritonavir-boosted lopinavir (LPV/r) should be the preferred third drug for HIV post-exposure prophylaxis in this age group. Thus, this will cater for horizontal routes of paediatric HIV transmission which may become more relevant as progress on eMTCT continues.

Adolescents with HIV

Due to years of failure to prevent MTCT, as well as to the success of ART programs in keeping children alive, the burden of paediatric HIV will shift from toddlers and young children not on ART, to older children and adolescents, a growing proportion of whom will have initiated ART. Of an estimated 2.6 million children <15 years living with HIV worldwide currently, 2.1 million of them are HIV-infected adolescents aged 10-19 (113). One-sixth of all new HIV infections in both children and adults occur in adolescents aged 15-19 (114). Adolescents are the only age group in which AIDS-related deaths are increasing, with HIV being the leading cause of adolescent deaths in Africa and the second leading cause of death among adolescents globally (115). The principal reason is that for decades that age group has received the least attention in terms of programming and funding. They have been on the fringes of both the paediatric age group and adults.

Adolescents living with HIV have to contend with challenges such as stigma and discrimination following disclosure to schoolmates, orphanhood and consequent headship of their households, and school absenteeism (116, 117). These can impose an enormous psychological burden on them such that there have been reports of a higher prevalence of psychiatric hospitalizations among HIV-infected adolescents than their HIV-uninfected peers (118, 119). HIV-infected adolescents have a worse adherence to ART rates and higher viral non-suppression rates than adults and children (120, 121). Orphanhood, being out-of-school, lack of status disclosure and lack of caregiver support has been identified as predictors of poor adherence (122, 123). Sexual and reproductive health issues in adolescents living with HIV have been observed in studies from sub-Saharan Africa as there is low awareness of contraceptive methods (124) with oral/anal sexual intercourse being engaged in to avoid pregnancy (125). In their desire to have a family, few sexually active adolescents

were reported to have told their partners (126). The mental, psychosocial, sexual and reproductive health needs of adolescents deserve core attention in comprehensive adolescent HIV treatment centers above and beyond their ART needs as they exert a huge impact on their quality of life as well as on the outcome of the overall HIV program.

Challenges and Future Strategies

Despite the huge strides made globally and nationally in the control of HIV in children, a lot still needs to be done to achieve the eMTCT goals, the 90-90-90 target of 2021, and the SDG goal of ending HIV as a public health problem by 2030.

Mother-to-child transmission of HIV – the reduction of the burden of paediatric HIV rests squarely on improving access to PMTCT. The persistently low ANC attendance among pregnant women is an impediment against HIV counselling and testing for pregnant women as only 61% of pregnant women in Nigeria attended ANC at least once during their pregnancy among the cohort of women who delivered between 2008 and 2013 (127). With the geographic disparity in Nigeria regarding the prevalence of HIV, the focus is being placed on the 12+1 high HIV burden states which are responsible for over 75% of HIV infections among Nigerian women. The promotion of home-based testing and counselling as well as self-testing for HIV (HIVST) are current strategies that would increase access.

Paediatric HIV diagnosis, treatment, and care: the primary route of entry into care for HIV-infected children is through testing and counselling. Access to provider-initiated testing and counselling (PITC) is still very low in many facilities due to cost, the availability of test kits or the ignorance of health care providers. The Presidential Response Plan to HIV/AIDS by the Jonathan administration (128) aims to test 80 million Nigerians within two years. However, at the end of 2015, only 4,077,663 were tested and counselled. The integration of PMTCT and maternal, child health and family planning (MNCH/FP) interventions is still weak with missed opportunities for HIV testing and care for mothers and children. Parallel planning by various organizations and other tiers of government, the lack of funding for supervision and structural healthcare system limitations such as the irregular supply of essential commodities, the inadequate number of health care providers, irregular technical support and inadequate basic working conditions are factors that militate against

effective integration. Task shifting and task sharing are modalities that are being adopted to address the challenge of human resources regarding paediatric ART services which confront efforts at the scale-up of early infant diagnosis and treatment for HIV-infected children.

Orphans and vulnerable children: Of the 7.3 million orphans in Nigeria, 2.23 million were orphaned by HIV/AIDS (129). As HIV is a major contributor to OVCs in Nigeria, social support for the estimated 2 million orphans infected or affected by HIV would also ensure that this population will not constitute a time bomb (130). The 2003 Child Rights Act (CRA), in combination with the National Plan of Action for OVCs and the National Child Policy, provides a legal framework for the implementation of services for orphans and vulnerable children in Nigeria. The Ministry of Women's Affairs and Social Development at both the Federal and state levels coordinates the OVC response.

Early Infant diagnosis: Challenges with the EID program in Nigeria include an inadequate number of health facilities providing services, the erratic supply of EID commodities, and a long turnaround time for EID result retrieval, the inadequate capacity of health care providers, poor dried blood spot (DBS) sample logistic systems, and weak coordination of EID activities at the national and state levels. The SMART program implemented by the Clinton Health Access Initiative (CHAI) is being rolled out to reduce the turnaround time in receipt of results. It is an innovation based on the use of SMS printers to deliver results instantly from laboratories to health facilities.

The Workforce Shortage: As the number of HIV exposed and infected children is expected to rise progressively due to increasing access to HIV diagnostic testing as well as the implementation of the Test and Treat strategy, the issue of the workforce shortage comes to the fore. This is the result of the prevailing high patient-to-physician workforce ratio. The impact of this includes long waiting times in clinics and the burdening of physicians leading to prescription errors and burn out. Decentralisation of ART facilities, task shifting, task sharing and differentiated care are programs that have been incorporated and are being rolled out in line with the National HIV/AIDS Strategic Framework (131) and the 2016 National HIV Treatment Guideline (9). Decentralisation is the devolution of part of the responsibility for the offering of HIV treatment and care from the tertiary and secondary level ART centres to the primary level health facilities. It increases the number of facilities that can offer ART refills and basic clinical examinations and collect samples like dried blood spots.

This reduces the burden on the central/ tertiary ART facilities (the hub facility) while the peripheral hospitals (spoke facilities) take on basic roles and refer to the tertiary facility as soon as the need arises. Task shifting and task sharing are the processes of devolving either wholly (task shifting) or partly (task sharing) some of the tasks that were exclusively being handled by physicians to non-physician health care providers who have been trained and mentored to safely handle them. These tasks include HIV screening, ART initiation, ART refill, screening for opportunistic infections and referral for adverse drug events. Differentiated care is the delivery of a minimum package of HIV/AIDS treatment care and support services according to the diversity of the care needs of people living with HIV. In the differentiated care model four categories of patients are identified and for each category, a minimum care package of services is offered. These categories are the newly presenting patients who are well, the newly presenting who are unwell, the unstable patients and lastly, the stable patients. In the differentiated care model, the intervals between clinic appointments and the time spent at each clinic visit vary between the categories. Thus, the clinician can allot more time to focus intensively on the unstable and ill patients so as to offer them a better quality of care.

Funding gaps: The funding of HIV in Nigeria is essentially donor-driven. Out of the total expenditure on HIV/AIDS in 2010, international funds account for 74.65% while government accounts for 25%. The total funding is grossly insufficient and was reduced by 28.5% between 2008 and 2010. The participation of states and local governments in funding is still very low. As at 2010, state governments contributed less than 0.3% of the total government funding for HIV in Nigeria, with the Federal government accounting for 99.7% of public sector funding. The inadequate ownership of the HIV/AIDS response at the sub-National levels can explain the limited commitments and resourcing observed to date. In this regard the Presidential Comprehensive Plan of the Goodluck Jonathan Administration in 2015, advocated for up to 50% state financing of the State HIV/AIDS strategic plans through a mix of state-specific innovative funding sources (128). President Buhari in 2017 (132) has committed to using domestic resources to put an additional 50,000 clients (adults and children) on ARVs annually. The proportion of these that would be children and adolescents, however, remains to be determined. In the same vein, he promised to establish a private sector funded AIDS Trust Fund which will increase private sector contributions from 2.1% in 2014 to 10% by the end of 2018. He also announced plans to ensure that states contribute up to 1% of their monthly allocations to HIV financing (133).

Functional Cure for HIV infected newborns: "The Mississippi baby"

The possibility of a functional cure for HIV in newborns has generated a lot of interest following the report of the baby who was commenced on HAART at 30 hours of age, achieved viral suppression and then defaulted from the clinic, stopping HAART at the age of 18 months. The girl reappeared at 30 months of age and tested negative to all forms of viral testing (the proviral DNA, the plasma viral RNA, and HIV-1 antibodies) (134). However, at age 4, plasma viral RNA and HIV-1 antibodies were detected in her blood (135). A "functional" cure for HIV-1 is defined as a long-term host-mediated control of viral replication and remission of the symptoms of HIV-1 infection in the absence of antiretroviral therapy, even if replication-competent viruses remain in the body (136). Various immunomodulatory and genetic engineering modalities are being proposed and investigated to either "shock and kill" "the latent viral reservoir or permanently silence them" (137). It is widely believed that this discovery is a prelude to a further understanding of ways to achieve a virologic cure for the HIV infection in children.

Conclusion

New HIV infections among children continue to decline, and the gradual expansion of treatment coverage is allowing more children to survive on long-term ART. Achieving the 2020 target of "90-90-90" could end the AIDS epidemic by 2030. The Millennium Development Goal of reversing the HIV epidemic was reached ahead of the 2015 deadline – an incredible achievement that testifies to the power of national action and international solidarity. The progress achieved in the past 15 years should galvanize the global community to build on the momentum and end paediatric HIV infections by 2030.

References

1. Centers for Disease Control and Prevention (CDC) Current Trends Acquired Immunodeficiency Syndrome (AIDS) Update – United States. *MMWR Weekly* 1983; 24 June 32(24): 309-311.
2. The General Assembly. United Nations Millennium Declaration. United Nations (September 8, 2000) Accessed April 9, 2017.

3. United Nation: Sustainable Development Goals. Goal 3: Ensure healthy lives and promote well-being for all at all ages. Accessed from http://www.un.org/sustainabledevelopment/health/.
4. Garry RF, Witte MH, Gottlieb AA, et al. Documentation of an AIDS virus infection in the United States in 1968. *JAMA*. October 1988; 260(14): 2085–7.
5. Centers for Disease Control (CDC). Unexplained immunodeficiency and opportunistic infections infants – New York, New Jersey, California. *MMWR Morb Mortal Wkly Rep.* 1982 Dec 17; 31(49): 665–7.
6. Nasidi A, Harry TO, Ajose-Coker OO, et al. Evidence of LAV/HTLV III infection and AIDS-related complex in Lagos, Nigeria. *II International Conference on AIDS, Paris, France*, 1986 June 23–25.
7. Federal Ministry of Health. *National HIV Seroprevalence Sentinel Survey*. Abuja: Federal Ministry of Health, 1991.
8. Federal Ministry of Health. *National HIV Seroprevalence Sentinel Survey*. Abuja: Federal Ministry of Health, 2001.
9. Federal Ministry of Health/NASCP. *National Guidelines for HIV Prevention Treatment And Care*. December 2016.
10. National Agency for the Control of AIDS, Federal Republic of Nigeria. *Global AIDS Response – Country Progress Report Nigeria: GARPR* 2015 [accessed 2015 Nov 26]. Available from: <http://www.unaids.org/sites/default/files/en/dataanalysis/knowyourresponse/countryprogressreports/2014countries/NGA_narrative_report_2015.pdf.
11. Joint United Nations Program on HIV/AIDS (UNAIDS). *UNAIDS Data 2017* accessed at http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf.
12. UNICEF. *The State of The World's Children 2017*: CHILDREN IN A DIGITAL WORLD. eSocialSciences; 2017. Accessed from https://www.unicef.org/publications/files/SOWC_2017_ENG_WEB.pdf.
13. UNAIDS. 2014 Progress Report on the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, 2014.
14. United Nations. *The Millennium Development Goals Report. 2015*. Available at: http://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20rev%20(July%201).pdf. Accessed on Nov 28, 2015.

15. Joint United Nations Programme on HIV/AIDS (UNAIDS). *Fast-track: ending the AIDS epidemic by 2030*. Geneva: UNAIDS, 2015.
16. De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* 2000, 283: 1175–1182.
17. Ogunbosi BO, Oladokun RE, Brown BJ, Osinusi KI. Prevalence and clinical pattern of paediatric HIV infection at the University College Hospital, Ibadan, Nigeria: a prospective cross-sectional study. *Ital J Pediatr*. 2011, 37, 29.
18. Onankpa B, Airede L, Paul I, Dorcas I. Pattern of pediatric HIV/AIDS: a five-year experience in a tertiary hospital. *Journal of the National Medical Association*, 2008; 100(7): 821-825.
19. Oniyangi O, Awani B, Iregbu KC. The pattern of paediatric HIV/AIDS as seen at the National Hospital Abuja Nigeria. *Nigerian journal of clinical practice* 2007; 9(2): 153-158.
20. Ubesie AC, Iloh KK, Eze CU, et al. Clinical and Laboratory Profile of ARV Naive HIV Infected Children in the Era of Highly Active Anti-retroviral Therapy in Enugu, South-East Nigeria. *International Journal of Tropical Disease & Health,* 2014; 4(7): 753-759.
21. Angyo IA, Okpeh ES, Onah J. Paediatric AIDS in Jos, Nigeria. *West African Journal of medicine*, 1997; 17(4): 268-272.
22. Emodi IJ, Okafor GO. Clinical manifestations of HIV infection in children at Enugu, Nigeria. *Journal of tropical pediatrics* 1998; 44(2): 73-76.
23. Adejuyigbe EA, Oyelami O, Onayemi O, Durosinmi M A. Paediatric HIV/AIDS in Ile-Ife, Nigeria. *The Central African journal of medicine* 2002; 49(7-8): 74-78.
24. Ugochukwu EF. Clinical spectrum of paediatric HIV in Nnewi, Nigeria. *West African journal of medicine* 2006; 25(1): 10-16.
25. Ben O, Yusuf T. PCR pattern of HIV-exposed infants in a tertiary hospital. *The Pan African medical journal* 2014; 18: 23-26.
26. Kalu SO, Reynolds F, Petra GB, Ikechebelu JI, Dada MO, Oluboyo BO, & Igwegbe AO. Infant Feeding Choices Practiced among HIV Positive Mothers Attending a Prevention of Mother to Child Transmission (PMTCT) of HIV Program in Nnewi, Nigeria. *J AIDS Clin Res*. 2014; 5(300): 2.
27. Joint United Nations Programme on HIV/AIDS (UNAIDS) Geneva. *Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive*, 2011.
28. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus

type 1. Women and Infants Transmission Study Group. *N Engl J Med.* 1997; 336: 1337-42.
29. Mphatswe W, Blanckenberg N, Tudor-Williams G, et al. High frequency of rapid immunological progression in African infants infected in the era of perinatal HIV prophylaxis. *AIDS* 2007; 21: 1253–61.
30. Yogev R, Chadwick EG. Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus). In: Kliegman RM, Stanton B, Geme JS, Schor NF, Behrman RE. eds. *Nelson textbook of pediatrics*. 20th ed. Philadelphia. Elsevier Health Sciences, 2015.
31. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis* 2012; 206(11): 1695-705.
32. Filteau S. The HIV-exposed, uninfected African child. *Trop Med Int Health* 2009: 14: 276-87.
33. Manno D, Kowa PK, Bwalya HK, et al. Rich micronutrient fortification of locally produced infant food does not improve mental and motor development of Zambian infants: a randomized controlled trial. *Br J Nutr* 2012; 107(4): 556-66.
34. Le Roux SM, Abrams EJ, Nguyen K, Myer L. Clinical outcomes of HIV-exposed, HIV-uninfected children in sub-Saharan Africa. *Trop Med Int Health* 2016 July; 21(7): 829-45. Epub 2016 May 20.
35. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: a growing population with a vulnerable immune system? *Clin Exp Immunol* 2014; 176(1): 11-22.
36. Filteau S, Rowland-Jones S. Cytomegalovirus Infection May Contribute to the Reduced Immune Function, Growth, Development, and Health of HIV-Exposed, Uninfected African Children. *Frontiers in Immunology* 2016; 7: 257.
37. Anyabolu HC, Adejuyigbe EA, & Adeodu OO. Undernutrition and anaemia among HAART-naive HIV infected children in Ile-Ife, Nigeria: a case-controlled, hospital-based study. *The Pan African Medical Journal* 2014, vol. 18; e77-80.
38. Anyabolu HC, Adejuyigbe EA, Adeodu OO. Serum micronutrient status of Haart-naive, HIV infected children in South Western Nigeria: a case-controlled study. *AIDS research and treatment* 2014; Vol. 14: 1-8.
39. Eneh AU, Ugwu RO. Paediatric HIV at the University of Port Harcourt Teaching Hospital, Port Harcourt. *Nig J Paed*. 2007; 34: 24-30.

40. Temiye EO, Akinsulie AO, Ezeaka CV, Adetifa IM, Iroha EO, Grange AO. Pediatric HIV Working Group. Constraints and prospects in the management of pediatric HIV/AIDS. *Journal of the National Medical Association* 2006; 98(8): 1252.
41. Omoni AO, Christian PS, Sadoh WE, et al. Immunologic outcomes of antiretroviral therapy among HIV-infected Nigerian children and its association with early infant feeding and nutritional status at treatment initiation. *The Pediatric infectious disease journal* 2013; 32(7): e291-e297.
42. World Health Organization; Geneva. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/en (accessed 27 November 2017).
43. Federal Ministry of Health Nigeria. *National Guidelines for Paediatric HIV and AIDS Treatment, Care and Support*. 2007. Accessed on 25 November 2015 at: http://www.who.int/hiv/amds/Nigeria_paediatric_2007.pdf.
44. Federal Ministry of Health, Nigeria. *National Guidelines for Paediatric HIV and AIDS Treatment, Care and Support*. 2010.
45. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of internal medicine* 2000; 133(1): 21-30.
46. Iroha E, Esezobor CI, Ezeaka C, Temiye EO, Akinsulie A. Adherence to antiretroviral therapy among HIV-infected children attending a donor-funded clinic at a tertiary hospital in Nigeria. *African Journal of AIDS Research* 2010; 9(1): 25-30.
47. Mukhtar-Yola M, Adeleke S, Gwarzo D, Ladan ZF. Preliminary investigation of adherence to antiretroviral therapy among children in Aminu Kano Teaching Hospital, Nigeria. *African Journal of AIDS Research* 2006; 5(2): 141-144.
48. T Meloni S, Chaplin B, Chang C, Rawizza H, Okonkwo P, J Kanki P. Patterns of Adherence and Loss to Follow-up in Pediatric Patients on ART in Nigeria. *Current HIV research* 2015; 13(3): 210-218.
49. Lewis Kulzer J, Penner JA, Marima R, et al. Family model of HIV care and treatment: a retrospective study in Kenya. *Journal of the International AIDS Society* 2012; 15: 8.
50. Tollen MA. A package of primary health care services for comprehensive family-centered HIV/AIDS care and treatment programs in low-income settings. *Tropical Medicine & International Health*, 2009; 14: 663-672.

51. DeGennaro V, Zeitz P. Embracing a family-centered response to the HIV/AIDS epidemic for the elimination of pediatric AIDS. *Global Public Health* 2009; 4(4): 386-401.
52. Stricker SM, Fox KA, Baggaley R, Negussie E, de Pee S, Grede N, Bloem MW. Retention in care and adherence to ART are critical elements of HIV care interventions. *AIDS and Behavior* 2014 Oct 1; 18(5): 465-75.
53. Ojeniran MA, Emokpae A, Mabogunje C, Akintan P, Hoshen M, Weiss R. How are children with HIV faring in Nigeria? A 7-year retrospective study of children enrolled in HIV care. *BMC pediatrics* 2015; 15(1): 87-91.
54. Ugochukwu EE, Kalu SO. Early infant diagnosis of HIV infection in southeastern Nigeria: prevalence of HIV infection among HIV-exposed babies. *West African journal of medicine*. 2010; 29(1): 27-31.
55. Ojikutu B, Higgins-Biddle M, Greeson D. The association between quality of HIV care, loss to follow-up and mortality in pediatric and adolescent patients receiving antiretroviral therapy in Nigeria. *PLoS One* 2014 Jul 30; 9(7): e100039.
56. Mugglin C, Wandeler G, Estill J, et al. Retention in care of HIV-infected children from HIV test to start of antiretroviral therapy: a systematic review. *PLoS One* 2013 Feb 20; 8(2): e56446.
57. Wiener L, Mellins CA, Marhefka S, Battles HB. Disclosure of an HIV diagnosis to children: history, current research, and future directions. *J Dev Behav Pediatr*. 2007; 28(2): 15566.
58. Armistead L, Forehand R. For whom the bell tolls: parenting decisions and challenges faced by mothers who are HIV seropositive. *Clin Psychol: Sci Pract*. 1995; 2(3): 23950.
59. Sherman BF, Bonanno GA, Wiener LS, Battles HB. When children tell their friends they have AIDS: possible consequences for psychological well-being and disease progression. *Psychosom Med*. 2000; 62(2): 23847.
60. Bikaako-Kajura W, Luyirika E, Purcell DW, et al. Disclosure of HIV status and adherence to daily drug regimens among HIV-infected children in Uganda. *AIDS and Behavior* 2006 Jul 1; 10(1): 85.
61. World Health Organization. *Guideline on HIV disclosure counseling for children up to 12 years of age,* 2011.
62. Lesch AI, Swartz L, Kagee A, Moodley K, Kafaar Z, Myer L, Cotton M. Paediatric HIV/AIDS disclosure: towards a developmental and process-oriented approach. *AIDS care* 2007; 19(6): 811-6.

63. Brown BJ, Oladokun RE, Osinusi K, Ochigbo S, Adewole IF, Kanki P. Disclosure of HIV status to infected children in a Nigerian HIV Care Programme. *AIDS care* 2011; 23(9): 1053-1058.
64. Okechukwu AA, Okechukwu, OI. Clinical correlate of tuberculosis in HIV co-infected children at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria. *Nigerian journal of clinical practice*, 2011; 14(2): 206-211.
65. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *The Lancet* 2004; 364(9441): 1236-1243.
66. WHO. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. December 6, 2010. Available at: http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf.
67. Boehme CC, Nabeta P, Hillemann D, et al. A Rapid molecular detection of tuberculosis and rifampin resistance. *New England Journal of Medicine* 2010 Sep 9; 363(11): 1005-15.
68. Helb D, Jones M, Story E, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. *J Clin Microbiol*. 2010; 48: 229-237.
69. Chamla DD, Asadu C, Davies A, de Wagt A, Ilesanmi O, Adeyinka D, Adejuyigbe E. Patching the gaps towards the 90–90–90 targets: outcomes of Nigerian children receiving antiretroviral treatment who are co-infected with tuberculosis. *Journal of the International AIDS Society*. 2015 Dec 1; 18(7S6).
70. Ugochukwu EE. HIV/TB Co-infection in Nigerian children. *Nigerian Medical Journal* 2010; 51(3): 120.
71. Sadoh AE, Sadoh WE, Iduoriyekemwen NJ. HIV co-infection with hepatitis B and C viruses among Nigerian children in an antiretroviral treatment programme. *South African Journal of Child Health*, 2011; 5(1): 7-10.
72. Sadoh A.E, Sadoh WE., Idoriyekemwen N J. Some Laboratory Features of HIV Infected Nigerian Children Co-Infected with Hepatitis B and C. *Annals of Biomedical Sciences*, 2012; 11(1); 29-39.
73. Winston JA. HIV and CKD epidemiology. *Adv Chronic Kidney Dis*. 2010; 17(1): 1925.
74. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *American Journal of Kidney Diseases* 2002 Aug 1; 40(2): 221-6.
75. Esezobor CI, Iroha E, Oladipo O, et al. Kidney function of HIV-infected children in Lagos, Nigeria: using Filler's serum cystatin C-

based formula. *Journal of the International AIDS Society* 2010 Dec; 13(1): 17.
76. Anochie IC, Eke FU, Okpere AN. Human immunodeficiency virus-associated nephropathy (HIVAN) in Nigerian children. *Pediatric Nephrology* 2008; 23(1): 117-122.
77. Iduoriyekemwen NJ, Sadoh WE, Sadoh AE. Asymptomatic bacteriuria in HIV positive Nigerian children. *Journal of Medicine and Biomedical Research* 2012; 11(1): 88-94.
78. Crowell CS, Malee KM, Yogev R, Muller WJ. Neurologic disease in HIV-infected children and the impact of combination antiretroviral therapy. *Reviews in medical virology* 2014 Sep 1; 24(5):3 16-31.
79. Caldwell MB, Oxtoby MJ, Simonds RJ, Lou Lindegren M, Rogers MF. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and Mortality Weekly Report: Recommendations and Reports*. 1994 Sep. 30: 3-10.
80. Rotta NT, Silva C, Ohlweiler L, et al. AIDS neurologic manifestations in childhood. *Rev Neurol* 1999; 29: 319-322.
81. Govender R, Eley B, Walker K, et al. Neurologic and neurobehavioral sequelae in children with human immunodeficiency virus (HIV-1) infection. *J Child Neurol*. 2011; 26: 1355-1364.
82. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS* 2002; 16(9): 1201-1215.
83. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *Journal of Neurovirology* 2012; 18(5): 388-399.
84. Boyede GO, Lesi FE, Ezeaka CV, Umeh CS. The neurocognitive assessment of HIV-infected school-aged Nigerian children. *World Journal of AIDS* 2013 May 30; 3(02): 124.
85. Boyede GO, Lesi FE, Ezeaka VC, Umeh CS. Impact of sociodemographic factors on cognitive function in school-aged HIV-infected Nigerian children. *HIV/AIDS (Auckland, NZ*) 2013; 5: 145-152.
86. Joint United Nations Programme on HIV/AIDS (UNAIDS). *The Gap Report 2014: People Living with HIV*. Accessed November, 28, 2017.
87. UNICEF Nigeria. *Maternal and Child Health,* Garki, Abuja 2014 [accessed 2015 Nov 27]. Available from: http://www.unicef.org/nigeria/children_1926.html.
88. Okechukwu AA, Gambo D, Okechukwu OI. The clinical features of paediatric HIV/AIDS at a presentation at the University of Abuja Teaching Hospital, Gwagwalada. *Nigerian Journal of Medicine* 2008; 17(4): 433-438.

89. George IO, Alex-Hart BA, Frank-Briggs AI. Mortality pattern in children: A hospital-based study in Nigeria. *International journal of biomedical science* 2009; 5(4): 369.
90. Gibb DM, Duong T, Tookey PA, et al. National Study of HIV in Pregnancy and Childhood Collaborative HIV Paediatric Study. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ* 2003; 327(7422): 1019.
91. World Health Organization. *The WHO: Public-health approach to antiretroviral treatment against HIV in resource-limited settings.* World Health Organization, 2006.
92. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *New England Journal of Medicine* 2008; 359(21): 2233-2244.
93. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013*. Geneva: World Health Organization, 2014.
94. B-Lajoie MR, Drouin O, Bartlett G, et al. Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in low- and middle-income countries: a systematic review and meta-analysis. *Clinical infectious diseases* 2016 Mar 21; 62(12): 1586-94.
95. World Health Organization. *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach: December 2014: supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection,* 2014.
96. Jelliffe DB, Jelliffe EF. *Human milk in the modern world*. New York: Oxford University Press, 1978.
97. Feachem RG, Koblinsky MA. Interventions for the control of diarrhoeal diseases among young children: promotion of breast-feeding. *Bull WHO* 1984; 62: 271-291.
98. Centers for Disease Control and Prevention. Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus and acquired immunodeficiency syndrome. *MMWR* 1985; 34: 721-6–731-2.
99. Kagaayi J, Gray RH, Brahmbhatt H, et al. Survival of infants born to HIV-positive mothers, by feeding modality, in Rakai, Uganda. *PLoS One* 2008 Dec 9; 3(12): e3877.

100. Kafulafula G, Hoover DR, Taha TE, et al. Frequency of gastroenteritis and gastroenteritis-associated mortality with early weaning in HIV-1-uninfected children born to HIV-infected women in Malawi. *Journal of Acquired Immune Deficiency Syndromes* 2010 Jan 1; 53(1): 6-13.
101. Rollins NC, Becquet R, Bland RM, Coutsoudis A, Coovadia HM, Newell ML. Infant feeding, HIV transmission and mortality at 18 months: the need for appropriate choices by mothers and prioritization within programmes. *AIDS* 2008 Nov; 22(17): 2349.
102. World Health Organization. *Guideline: updates on HIV and infant feeding: the duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV*, 2016.
103. UNAIDS Reference Group on Estimates, Modelling, and Projections. *Working Paper on Mother-to-Child HIV Transmission Rates for use in Spectrum,* 6 June 2011, available at http://www. epidem.org/ Publications/MTCTratesworkingpaper.pdf, (accessed 2 Dec. 2015).
104. World Health Organization. *Guidelines on HIV and Infant Feeding 2010: Principles and Recommendations for Infant Feeding in the Context of HIV and a Summary of Evidence.*
105. Abiona TC, Onayade AA, Ijadunola KT, Obiajunwa PO, Aina OI, Thairu LN. Acceptability, feasibility and affordability of infant feeding options for HIV-infected women: a qualitative study in south-west Nigeria. *Maternal & child nutrition* 2006; 2(3): 135-144.
106. Adejuyigbe E, Orji E, Onayade A, Makinde N, Anyabolu H. Infant feeding intentions and practices of HIV-positive mothers in Southwestern Nigeria. *Journal of Human Lactation* 2008; 24(3): 303-310.
107. Sadoh WE, Sadoh AE, Adeniran KA, Abhulimhen-Iyoha BI. Infant-feeding Practices among HIV-infected Mothers in an HIV-treatment Programme. *Journal of health, population, and nutrition* 2008; 26(4): 463.
108. Fawole IO, Asuzu MC, Oduntan SO, Brieger WR. A school-based AIDS education programme for secondary school students in Nigeria: a review of effectiveness. *Health education research* 1999 Oct. 1; 14(5): 675-83.
109. Longe OB, Chiemeke SC, Onifade OF, Balogun FM, Longe FA, Otti VU. Exposure of children and teenagers to internet pornography in South Western Nigeria: Concerns, trends & implications. *Journal of information technology impact* 2007; 7(3): 195-212.

110. Kekitiinwa A, Musiime V, Thomason M, et al. Acceptability of lopinavir/r minitabs (pellets), tablets and syrups in HIV-infected children. *Group* 2015 Feb; 20: 40.
111. Penazzato M, Dominguez K, Cotton M, Barlow-Mosha L, Ford N. Choice of antiretroviral drugs for postexposure prophylaxis for children: a systematic review. *Clinical Infectious Diseases* 2015 May 11; 60 (suppl. 3): S177-81.
112. World Health Organization. *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents, and children: recommendations for a public health approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* World Health Organization, 2014.
113. UNAIDS. Global Report: *UNAIDS Report on the Global AIDS Epidemic 2013*. 2013 [cited 2017 June 15]. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Global_Report_2013_en_1.pdf.
114. United Nations Children's Fund. *Towards an AIDS-free Generation: Sixth Stocktaking Report.* 2013 [cited 2015 Sep 2]. Available from: http://www.childrenandaids.org/files/str6_full_report_29-11-2013.pdf.
115. Idele P, Gillespie A, Porth T, Suzuki C, Mahy M, Kasedde S, Luo C. Epidemiology of HIV and AIDS among adolescents: current status, inequities, and data gaps. *J Acquir Immune Defic Syndr.* 2014 July 1; 66 Suppl 2(): S144-53.
116. Cluver LD, Orkin M, Gardner F, Boyes ME. Persisting mental health problems among AIDS-orphaned children in South Africa. *J Child Psychol Psychiatry* 2012; 53: 363-70.
117. Cohen J, Reddington C, Jacobs D, et al. School-related issues among HIV-infected children. *Pediatrics* 1997; 100: E8.
118. Gaughan DM, Hughes MD, Oleske JM, Malee K, Gore CA, Nachman S. The Pediatric AIDS Clinical Trials Group 219C Team Psychiatric hospitalizations among children and youths with human immunodeficiency virus infection. *Pediatrics* 2004; 113: e544-51.
119. Mellins CA, Brackis-Cott E, Dolezal C, Abrams EJ. Psychiatric disorders in youth with perinatally acquired human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2006; 25: 432-37.
120. Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents

compared with adults in southern Africa. *J Acquir Immune Defic Syndr*. 2009; 51: 65-71.
121. Bygrave H, Mtangirwa J, Ncube K, Ford N, Kranzer K, Munyaradzi D. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. *PLoS One* 2012; 7: e52856.
122. Bakanda C, Birungi J, Mwesigwa R, et al. Survival of HIV-infected adolescents on antiretroviral therapy in Uganda: findings from a nationally representative cohort in Uganda. *PLoS One* 2011; 6: e19261.
123. Biadgilign S, Deribew A, Amberbir A, Deribe K. Barriers and facilitators to antiretroviral medication adherence among HIV-infected paediatric patients in Ethiopia: a qualitative study. *SAHARA J.* 2009; 6: 148-54.
124. Bakeera-Kitaka S, Nabukeera-Barungi N, Nöstlinger C, Addy K, Colebunders R. Sexual risk reduction needs of adolescents living with HIV in a clinical care setting. *AIDS Care* 2008; 20: 426-33.
125. Cherie A, Berhane Y. Oral and anal sex practices among high school youth in Addis Ababa, Ethiopia. *BMC Public Health*. 2012; 12: 5.
126. Birungi H, Mugisha J, Nyombi J, Obare F, Evelia H, Nyinkavu H. Sexual and reproductive health needs of adolescents perinatally infected with HIV in Uganda. 2008 July [accessed Feb 13, 2018 from; http://www.popcouncil.org/pdfs/frontiers/FR_FinalReports/Uganda_HIV.pdf].
127. Demographic N. Health Survey (NDHS) (2013). Household population and Housing characteristics. *National Population Commission (NPC*). Federal Republic of Nigeria, Abuja, Nigeria. 2017: 11-29.
128. FGN/NACA (2013). *President's Comprehensive Response Plan For HIV/AIDS in Nigeria*, 2013-2015.
129. Federal Ministry of Women Affairs and Social Development. *The Key findings of the 2008 Situation Assessment and Analysis on Orphans and Vulnerable Children (OVC) in Nigeria*. Abuja, Nigeria, 2008.
130. HIV and Social Protection UNAIDS 2015 http://childrenandaids.org/sites/default/files/2017-05/UNAIDS_Guidancenote_HIVandsocialprotection_en.pdf.
131. FGN/NACA. *National HIV and AIDS Strategic Framework 2017-2021*, 2017.
132. NACA, WHO and UNAIDS welcome President Buhari's new commitment to provide ARV for 50,000 additional people living

with HIV each year. Accessed from http://naca.gov.ng/naca-unaids-welcome-president-buharis-new-commitment-provide-arvs-50000-additional-people-living-hiv-year/ 7 Feb 2018.
133. Closing the HIV resource gap in Nigeria with more domestic funding. Accessed from http://www.unaids.org/en/resources/presscentre/featurestories/2017/december/20171214_nigeria Accessed 7 Feb 2018.
134. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med.* 2013; 369(19): 1828-35.
135. Siliciano JD, Siliciano RF. AIDS/HIV. Rekindled HIV infection. *Science* 2014; 345(6200): 1005-6.
136. Katlama C, Deeks SG, Autran B, et al. Barriers to a cure for HIV: new ways to target and eradicate HIV-1 reservoirs. *Lancet* 2013; 381(9883): 2109-17.
137. Liu C, Ma X, Liu, B, Chen C, Zhang H. HIV-1 functional cure: will the dream come true? *BMC Medicine* 2015; 13: 284.

Human Immunodeficiency Virus (HIV) and Pregnancy: The Current Concept in Management

Najemdeen A Adeleke
MBBS, FWACS,
and Moses O Abiodun
MBBS, FWACS, FMCOG

The treatment and care of HIV/AIDS patients have witnessed improvement in the last decades' widespread access to rapid diagnostic HIV testing in the antenatal care (ANC) setting, higher coverage of the prevention of mother-to-child transmission (PMTCT) now called elimination of mother-to-child transmission (EMTCT), antiretroviral therapy (ART) and ongoing transition towards initiating immediate lifelong ART (option B+) for infected individuals including pregnant women have contributed immensely to an improved prognosis in the management of HIV/AIDS. While the effects of HIV on pregnancy are dependent on factors which include gestational age, disease stage, viral load, CD4 count and access to the PMTCT service, pregnancy, on the other hand, has little effect on the natural course of HIV/AIDS. Some of the factors contributing to the less than optimal outcomes of management of HIV in pregnancy in the developing countries include stigmatization, low ANC attendance, constraints in access to PMTCT and poverty among others. Maternal and perinatal morbidity and mortality as well as the paediatrics HIV disease burden will be reduced with the implementation of comprehensive HIV treatment, care and support. This include the management of HIV-discordant couple, preconception care education and contraception, effective PMTCT and safe infant feeding, the elimination of mother-to-child transmission of HIV is achievable.

The origin and time of emergence of the HIV/AIDS virus have always been a topic of debate among scholars. However, the majority of opinions believe it originated in East Africa and that it crossed to man from our

closest animal relation in evolution that is the Chimpanzee/Gorilla. The earliest clinical diagnosis was in the late seventies to early eighties. Diagnosis of HIV/AIDS in a person was a hopeless case and seen as a death sentence in the early days of the disease. With much research and development that resulted in the isolation and characterization of the virus, especially HIV-1 and later HIV-2 and the modes of transmission plus the discovery of antiretroviral agents, the prognosis has changed favourably and HIV/AIDS became a manageable chronic communicable disease. Improved survival of the patients gave rise to the study of the disease and its management in pregnancy. Preponderantly, HIV/AIDS sufferers are people in the reproductive age group and more than half of them are women (1, 2). HIV/AIDS in pregnancy is a global public health issue of concern. Heterosexual modes of transmission and the high fertility rate in sub-Saharan Africa have continued to swell the population of HIV in pregnancy (2, 3).

Epidemiology

The global burden of HIV/AIDS in pregnancy is alarming and it mirrors the population level of the disease. Sub-Saharan Africa has the highest prevalence; other regions with a high prevalence include Asia and Eastern Europe. Western Europe and North America have low prevalence rates (4). In 2014 an estimated 50% of pregnant women in low- and middle-income countries had an HIV test and received their results, while an estimated 1,079,713, representing between 68 to79% of HIV positive pregnant women, receive ART for PMTCT (1).

In Nigeria, HIV surveillance is being carried out through the biennial HIV and Syphilis Sentinel sero-prevalence Survey among pregnant women attending antenatal clinics (ANC), the first survey was conducted in the year 1991. The National HIV prevalence therefore is a reflection of the disease presence among pregnant women. The highest prevalence of 5.8% was recorded in 2001, this has fallen to 3.0% in the 2014 survey (5). About 190,000 pregnant women and 400,000 children are living with HIV in Nigeria (3). There is differential prevalence across regions and states in the country, from 1.9% in the North West to 15.4% in the North Central. Benue, Cross-rivers, Rivers and Lagos state, all have prevalence above the national average. HIV is twice as common in urban compare to rural area (5, 6).

Immunity in Pregnancy

Pregnancy is a special physiological state which exerts some influence on the body's immune system. The foetoplacental unit is a sort of autograft, the maternal immune system has a special recognition so there is no rejection. The more genetically different the father of the baby is to the mother's HLA the more successful is the autograft.

The body diverts most of the proteins especially albumins to the growing foetus and placenta, thus there is little left for the synthesis of immunoglobulins in the immune system except there is an acute challenge by new infections. In pregnancy, there is an absolute reduction of the total CD4 count irrespective of HIV/AIDS status (7). This creates a state of relative immune suppression in pregnancy.

Effects of HIV on Pregnancy

The impact of HIV on pregnancy depends on a number of factors among which are the stage of the disease, gestational age and whether or not there is treatment with anti-retroviral medication especially highly active anti-retroviral drugs (HAART) and the presence co-morbidity. In the advanced stage of the disease and in the absence of treatment many pregnancy complications have been observed especially in developing countries. Many of these complications may be due to intervening infections that occurred. Among the complications are increased miscarriage, intrauterine growth restriction, preterm delivery, low birth weight and ultimately increased perinatal morbidity and mortality (7).

Effect of Pregnancy on HIV/AIDS

The natural course of HIV/AIDS has not been known to be affected significantly by pregnancy. There is no evidence that pregnancy accelerates the progression from HIV to AIDS (7).

Unique challenges of HIV in pregnancy in developing nations

Low up take of hiv counseling and testing.

A large proportion of women of reproductive age do not know their status. HIV is a chronic disease and it has no symptoms for a long-time after

infection. In the presence of low HCT in the general population and the absence of routine screening in the ANC, many pregnant women much like their non-pregnant counterparts who are seropositive are not aware of their infection.

Stigmatization: HIV/AIDS is still associated with a significant level of stigmatization and discrimination especially in developing nations including Nigeria (2). Studies have shown that pregnant women who are seropositive could experience domestic violence, sexual deprivation and neglect from husbands upon the disclosure of their status (8, 9). Discrimination at places of work is not uncommon. These scenarios discourage women from voluntary HCT. However, with ongoing publicity and enlightenment with health education by both governmental and non-governmental agencies (NGO) the situation is beginning to change.

Low ANC attendance and delivery in the health facility.

Many women do not access antenatal care from where they can access screening. The ANC attendance rate is about 61% and only about 36% are delivered at health facilities. Late booking is another peculiarity of the ANC attendee in many parts of the developing world. A sizable proportion of the mother- to- child transmissions could have occurred before booking, although the majority of MTCT occurred in the peripartum period.

Rudimentary pre-conception care.

Currently in Nigeria and many other Nations, pre-conception care is not well established. Where available it is confined to tertiary health facilities and is not comprehensive.

However, the health care providers managing HIV/AIDS in the population is expected to undertake the special care needs for their clients who desire to have babies just as it is being done for chronic non-communicable diseases such as hypertension and diabetes mellitus patients who wish to become pregnant. The specific actions required include ensure achievement of low viral load prio to conception, adjustment of the ARVs to avoid those that are contraindicated in pregnancy such as Efervirence. Maintenance of normal blood pressure and body mass index (BMI). The patient will benefit from prophylactic folic acid 5 mg/daily and nutrient supplements. The woman should be referred to the PMTCT service as soon as the pregnancy is confirmed. There is a compelling need for the

establishment of pre-conception care unit in the National reproductive health care programme.

Management of pregnant woman with HIV infection

Management of HIV in pregnancy is a collaborative service provided by many medical specialists, including the Obstetrician and gynaecologist who lead the team, the medical physician with experience in HIV/AIDS care, the laboratory physician, nurse/midwife, nutritionist and medical social workers with experience in the care of HIV patients.

Objectives of the management of HIV in pregnancy include the following:

i. Reduce the morbidity and mortality in the pregnant women by arresting further progression of the disease.
ii. Prevention or reduction of vertical transmission to the unborn baby through PMTCT services;
iii. Provide an entry point to the screening and treatment of the husband/partner and other members of the family who may be infected.

Antenatal care

The treatment of HIV in pregnancy is offered through the Prevention of Mother-to-Child Transmission (PMTCT).

Nigeria started PMTCT services in 2001 and the National Prevention of Mother-to-Child Transmission of HIV/AIDS has four components.

i. Primary prevention of HIV infection in women of the reproductive age group (15-49 years) and their partners.
ii. Prevention of unintended pregnancies among HIV-positive women.
iii. Prevention of transmission of HIV from infected mothers to their unborn babies and infants.
iv. Care and support for HIV-infected women, their infants and family members. The targets of the National PMTCT can be described as target percentages of 90%. Specifically, it targets the provision of quality HIV counselling and testing (HCT) to 90% of all pregnant women; the provision of efficacious ARV prophylaxis to 90% of HIV-positive pregnant women and exposed infants; the provision of quality infant feeding counselling to 90% of HIV-positive

pregnant women; and the provision of early infant diagnosis to 90% of exposed babies.

The risk of mother-to-child transmission (MTCT) is dependent on a number of factors, broadly classified into maternal, viral, foetal and obstetrics practice factors.

i. Maternal factors.
   Viral load.
   CD4+ lymphocyte count.
   Stage of HIV/AIDS.
ii. Viral factors.
   Pathogenicity of the virus. HIV-1 is (composed of different strains with varied aggressiveness) more pathogenic than HIV-2, and so has a greater tendency to vertical transmission.
   Presence of the p24 core antigen.
   Co-infection with both HIV-1 and HIV-2.
   Re-infection episodes.
iii. Foetal factors.
   Low birth weights.
   Intra uterine growth restriction (IUGR).
   Multiple pregnancies (transmission rate is inversely proportional to the order of delivery).
iv. Obstetrics factors.
   Chorionic villus sampling (CVS).
   Amniocentesis.
   Artificial rupture of membrane (ARM).
   Prolonged rupture of membrane >4 hours (either SPROM or ARM).
   Foetal scalp electrodes monitor.
   Foetal scalp blood sampling.
   Instrumental vaginal delivery.
   Chorioamnionitis.

Viral load is the most important factor as it is directly related to the rate of vertical transmission (10). Advanced maternal disease i.e. the WHO stages 3 and 4 and a low CD4 T-lymphocyte count are also important determinants of the transmission rate (11, 12).

HCT and routine screening

From different types of selective methods of testing for HIV in pregnancy in the past, screening for HIV during ANC has today become a routine procedure in both public and private health facilities. This has been brought about by sustained public enlightenment, championed by governmental and non-governmental organizations (NGOs) including development partners on the one hand and the availability of sensitive rapid test kits at affordable prices as well as the escalation of HCT screening and testing centres all over the country on the other hand (13). Routine HIV screening should be in place in sub-Saharan Africa.

The importance of screening for HIV in pregnancy for all pregnant women cannot be over emphasized, as it permits early detection of the infected pregnant women and babies at risk of MTCT. It enables the institution of the full measures of PMTCT for the benefit of the affected women and their unborn babies. ANC screening for HIV provides an entry point for the couples to access comprehensive care and support for the management of the disease. A negative screening test is a motivation for continued positive attitudes to remain HIV infection free.

The screening is in the context of adequate pre- and post-test counselling provided by either professional counsellors or health workers who have been trained for the purpose.

Screening tests: Anti-HIV antibodies detection tests are used for routine screening in the ANCs. There are three such tests namely Simple rapid tests, Enzyme-linked Immunosorbent Assay (ELISA) tests and Western Blot tests. As a result of improved sensitivity, and the acceptable specificity of simple rapid tests, they are used in the ANCs. The principle is that 2 tests must agree to accept the diagnosis but when there is discordance, the third test is used as a tiebreaker. In Nigerian PMTCT, Determine, Unigold and Statpak are used for screening, confirmatory and tiebreaker tests respectively. The HIV test-negative clients are counselled on how to stay negative and the test result is used as a positive reinforcement factor. Those that are seropositive will be enrolled into the PMTCT treatment services.

Treatment entry point counselling is needed. This is best done as couple counselling i.e. the pregnant woman and her partner, so as to provide information on the next phase of management. The need for the partner is to engender co-operation and support both morally and financially,

therefore there must be a status disclosure. This provides an opportunity to request the partner to have HCT. A partner's refusal to have HCT at this point does not preclude counselling and continuation of PMTCT.

Self HIV testing has become available (14) but its role and application in ANC are yet to be determined especially in the developing world.

Comprehensive baseline investigations are carried out. General and specific groups of tests are required. The general tests are FBC, LFT, E & U, creatinine clearance, FBS and Urine M.C.S. CXR with an abdominal shield is also included. Specific tests are CD4, CD8 and the CD4/CD8 ratio, viral load and the P24 antigen assay. Other specific tests that can be done especially in developed Nations include RNA and DNA PCR.

The tests are repeated either monthly or bi-monthly as the protocol in use at the centre demands.

Fig 1: Group Pmtct Counselling in an Antenatal Clinic.
Adapted from SIDCAIN (www.sidcain.org) GDM project © 2016

Initiation of anti-retroviral drugs (HAART) or Single agent ZidovudineAZT/Nevirapine NVP

ARVs are initiated for the therapeutic need of the woman, for prophylaxis and for the prevention of mother-to-child transmission (PMTCT). Evidence has shown that viral load reduction is the single most important step in reducing vertical transmission and HAART has been shown to be most effective in reducing HIV viral load. It is also tolerated in pregnancy (15, 16). The WHO criteria for the initiation of ARVs in the adult HIV patient including a CD4 count $<350/mm^3$ is applied. In addition, pregnancy alone is enough indication in others to prevent MTCT. The Nigerian PMTCT program was based on the WHO criteria.

However, in a resource constrained economy and with concern for toxicity, the older regime of single agent Zidovudine AZD/Nevirapine NVP, either short or long arm, can be used and it has been shown to be effective in reducing MTCT but not as much as HAART (17).

ARV (single agent or combination) can be commenced as early as 14 weeks gestation (where women book early and an early diagnosis is made) or later in pregnancy and even in labour (18, 19).

Whichever ARV regimen is employed, the drug is continued in labour and postpartum and the infant is given ARV prophylaxis for the first six weeks of life.

Untreated HIV in pregnancy carries MTCT transmission rates of between 15% to 25% in non-breastfeeding mothers in developed nations and about 25% to 45% in sub-Saharan Africa where breastfeeding is the culture (5, 20). However, with PMTCT implementation and exclusive replacement feeding (ERF), a transmission rate less than 2% has been achieved in advanced countries. Vertical transmission occurs during the prenatal period, labour and postpartum through breastfeeding. However, most of the transmission is in the peripartum period.

Groups of ARVs

There are many agents that are now available as anti-retroviral drugs. However, the main groups include 1. Reverse Transcriptase Inhibitor (RTI) which contains three sub-groups (i) Nucleoside Reverse Transcriptase Inhibitors NRTIs, such as Zidovudine (ZDV), Lamivudine (3TC), Abacavir (ABC) and Stavudine (d4T); (ii) Non-nucleoside Reverse

Transcriptase Inhibitors NNRTIs, Nevirapine (NVP) is a common example; and (iii) Nucleotide Reverse Transcriptase Inhibitor NtRTI, e.g., Tenofovir (TDR). 2. Protease inhibitors PIs, in this category are lopinavir and indinavir. Newer generations of ARV drugs are now available.

Monitoring

Patients on ARV especially HAART in pregnancy should be monitored for toxicity, hence the need for a repeat of the above investigations as contained in the protocol. However, toxicities observed in pregnant women are similar to those in the non-pregnant population. Some of the toxic effects observed in pregnant women on ARV are hepatic toxicity, leucopenia, thrombocytopenia and anaemia in both the mother and the infant. The majority of the drugs used in pregnant women have not been shown to have a teratogenic effect and are not associated with increased miscarriages. The patient should be placed on prophylaxis for opportunistic infections by the use of Sulfamethoxazole 800 mg and Trimethoprim 160 mg (co-trimoxazole) once daily. In tropical countries intermittent preventive therapy (IPT) for Malaria using Sulphadoxine pyrimethamine, a single dose of three tablets in the 2nd trimester and repeated in the 3rd trimester, before thirty-six weeks of pregnancy. Acute Malarial infection should be diagnosed promptly and adequately treated using the relevant national guidelines of ACT-based combination anti-malaria therapy.

Foetal surveillance

This is a high-risk pregnancy both for the mother and the foetus. The pregnancy should be dated with accuracy, there is a need for first-trimester ultrasonography especially where the pregnant woman is not sure of her LMP.

Anomaly ultrasonography is required between 16 and 20 weeks of gestation. ARVs including HAART have not been shown to increase the occurrence of congenital anomaly beyond the population background level. This should be a level 2 USS which should be available at General Hospitals and in many private health facilities. PHC providing prenatal and delivery for HIV clients are to work in collaboration with the nearest General Hospital for this investigation amongst other services.

Foetal well-being may be assessed by biophysical profile as from 32 weeks gestation, and can be repeated weekly or bi-weekly. However, this may not be indicated when foetal compromise is not observed.

ANC Appointments and Routine Care

In centres where focused ANC is being practised, the average number of visits is four. HIV clients usually need more than four visits being high risk pregnancies. There is a need for client-centred flexibility. All routine ANC services are observed in the case of HIV pregnancy as well. However greater emphasis is placed on adequate nutrition and appropriate supplements such as vitamin A and magnesium. Pregnancy complications such as pre-eclampsia PET and gestational diabetes mellitus GDM should actively be screened for especially in patients who are on ARV.

Pregnant women accessing PMTCT are monitored clinically and biochemically using CD4, CD8, the viral load where the facility exists, and complete blood count, liver function tests, and renal function tests carried out monthly. Toxicity to the specific ARV is monitored.

Delivery

In the absence of pregnancy complications, a reassuring foetal condition based on ANC clinical assessments and biophysical profile results. HIV pregnancy is allowed to go to term while anticipating spontaneous labour. The vaginal route is the main mode of delivery except there is an obstetric indication for caesarean section. This is made possible with the use of antenatal ARV. For women on HAART or long arm NVP and an undetectable viral load before labour, vaginal delivery is recommended. The pregnancy may be terminated before term if there is IUGR, PET or any other major complication especially as from 34-36 completed weeks of gestation.

Labour Management: As done in focused ANC management, delivery is planned and prepared for (especially the choice of place of delivery) right from the early ANC period. Labour in HIV woman should be managed at secondary and tertiary public health facilities and private hospitals with a requisite capacity especially in developing countries. Labour is monitored with Pathogram and prolonged labour is avoided. ARV is continued during labour. There should be no invasive procedure in foetal monitoring: hand held dopplar, cardiotocograph (CTG) or intra partum USS is

sufficient. In the poorest of conditions, the Pinnard foetoscope is good enough in experienced hands. ARM is avoided until delivery is imminent. If there is SPROM after 34 weeks gestation, delivery may be expedited by caesarean section as studies have shown that for patients not on HAART with the rupture of a membrane for more than 4 hours, the risk of MTCT is doubled (21). This may be particularly relevant in third world Nations where cost, availability and other logistics challenges may hinder the use of HAART. Delivery should be conducted by experienced labour ward staff and a paediatric team should be in attendance. The baby is bathed immediately after resuscitation.

All other routine labour management practices (analgesia and relevant investigation and treatment) are to be observed, using univasal precaution.

Caesarean Section in HIV Women

Routine Elective cesarean section is no longer practised. The vaginal route is used in women who are on ARV (HAART or Single agent), whose viral load is less than 1000 copies/mm^3. However, for those whose viral load is $\geq$1000 copies/mm^3 caesarean section may be used especially in advanced countries (22). In the third world, nations C/S rate may still be relatively higher in such patients compared to the general obstetric population because of the early recourse to abdominal delivery as a result of Chorioamnionitis, the pre-labour rupture of membranes when labour is remote, and PET. There is a low threshold for C/S intervention for prolonged labour in HIV-positive women. The ARV drug may be administered by parenteral routes especially for an emergency C/S. Prophylactic antibiotic is used for an elective C/S and a full therapeutic course is advocated for emergency cases especially in the third world setting.

Postpartum care

ARV is continued for both the mother and the baby at least for the first 4-6 weeks. The most important mean outcome measure of PMTCT is the infant HIV status. This is carried out by DNA, and PCR, testing of the newborn at 6 weeks. Rapid antibody testing is used at 6, 9, 12 and 18 months.

The woman can now be referred to a physician with expertise in HIV/AIDS care for the continuation of care. They are encouraged to join

the People Living With HIV/AIDS (PLWHA) group at the centre. The infant feeding option must have been decided during the antenatal period after adequate counselling. The choice lies between exclusive breastfeeding (EBF), exclusive replacement feeding (ERF), and rarely wet nursing (WN) by lactating women not infected with HIV. In a resource-poor setting, EBF practice is preferred. The HIV mother may breastfeed for 12 months or longer, up to 24 months once both the mother and baby/babies are on ARV and evaluations confirm non-detectable virus in the woman (24). The infant is referred to a paediatrician with expertise in HIV treatment for early HIV infant diagnosis and further management.

Contraception: Straightforward HIV alone does not preclude the use of any type of contraceptives for which the woman is eligible by the WHO eligibility criteria (23). An IUD that carries a risk for infection may not be the first choice but it is not contraindicated when the patient is carefully selected and properly counselled.

A hormonal injectable and slow releasing system IUD can be used as appropriate. However, some authorities have raised concerns that DMPA at the time of acquiring an infection may be associated with acceleration of the disease (24). The barrier method is the most appropriate after abstinence if acceptable by the couple and may well be the best choice, but this has the challenge of correct and consistent use. The importance of birth spacing and a limited family size (two children per woman) cannot be overemphasized in the life of an HIV-infected woman. This will permit her the opportunity to be able to take care of her lifelong HIV management as well as the proper care of the children. However, HIV infection is not a condition for limiting family size and has not been recommended either by the WHO or the Nigerian PMTCT program.

Management of a discordant couple

In Nigeria and possibly most developing countries the typical discordant scenario in the ANC is a seropositive wife and a seronegative husband (the practice in the ANC is to invite the partners of the women who are HIV positive for counselling and testing with the consent of the woman); if the pregnant woman had been negative the husband would not likely come to the ANC for screening especially in this environment and most third world Nations. In the sero discordant case, there is a need for rigorous and effective counselling especially for the husband/partner which should be followed with adherence by a home visit to prevent him from neglecting or

abandoning the wife. The need for adherence to ARV drugs by the pregnant woman and safe sex practices should be emphasized. In the case of a seronegative wife with a seropositive husband, the challenge here is for the woman to stay negative. HIV transmission per single act of unprotected sexual intercourse is 0.3 to 1.0% (4). A repeat screen in each trimester is recommended. Pre-exposure prophylaxis is an effective management option for the seronegative partner in this circumstance. Safe sex practices, especially the use of barrier methods, are recommended for the couple. The positive man is referred to the physician for management.

With appropriate and sustainable national government attention including funding and collaboration with international development partners, it is possible to achieve sero-MTCH transmission of HIV as demonstrated by countries like Armenia, Thailand, Cuba and Belarus (25).

References

1. Global update on the health sector response to HIV, 2014. Geneva, World Health Organization 2014 (http://www.who.Int/hiv/pub/progressreports/update2014/en/. Accessed 19 June 2015).
2. David Tigawalana 2010. Why African women are more vulnerable to HIV/AIDS. *Rwanda News Agency*. RNARI; Sunday 19 September 2010.
3. Averting HIV and AIDS AVERT: 2015. Global information and advice on HIV & AIDS. www. Avert. org.
4. Hawkins D.A. and Barton S.E. Maternal Medicine, Medical problems in Pregnancy. In Ian A Greer, Catherine Nelson-Piercy and Barry Walters (eds.) *HIV and pregnancy,* 2007.
5. Federal Ministry of Health Fact sheet 2015. HIV/Syphilis sentinel seroprevalence survey Among pregnant women attending Ante Natal Clinic Nigeria 2014. Department of Public Health National AIDS/STD Control Programme. Federal Ministry of Health. Abuja.
6. Adebobolo Bashorun, Patrick Nguku, Issa Kawu, Evelyn Ngige, Adeniyi Ogundiran Kabir Sabitu Abdul-salam Nasidi and Peter Nsubuga. A description of HIV prevalence trends in Nigeria from 2001 to 2010: What is the progress, where is the problem? *Pan. Afr Med J* 2014, 8 (suppl.1): 3.
7. RevaTripathi, Shakun Tyagi and Chanchi. Infections in Obstetrics and Gyn aecology. In Gauri Gandhi, Sumita Mehta and Swaraj Batra (eds) *HIV in Obstetrics and Gynaecology*. 2006.

8. Olowookere Samuel A, Fawole Olufunmilayo I, Adekanle Daniel A, Adeleke Najemdeen A, Abioye-Kuteyi Emmanuel A. Patterns and Correlates of Intimate Partner Violence to Women Living With HIV/AIDS in Osogbo, South West Nigeria, *Violence against Women* 2013; 1-11.
9. Adekanle DA, Olowookere AS, Adewole DA, Adeleke NA, Abioye-Kuteyi EE and Ijadunola MY. Sexual experiences of married HIV positive women in Osogbo, south-west Nigeria: Role of inappropriate status disclosure. *BMC Women's Health* 2015; 15(6): 4-7.
10. Ioannidis JP, Abrams EJ, Ammann A, Bulterys M, Goedert JJ, Gray L, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J. Infect Dis.* 2001; 183: 539-45.
11. WHO 2005. Interim WHO Clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. African region. WHO/ HIV/2005.02.
12. Gracia PM, Kalish LA, Pitt, J, Minkoff H, Quinn TC, Burchett SK, et al. Maternal levels of plasma human immunodeficiency type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission study group. *N Engl J Med* 1999; 341: 394-402.
13. Federal Ministry of Health. 2013. National HIV AIDS and Reproductive Health Survey 2012 (NARHS-Plus).
14 World Health Organization 2016. Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV testing services. WHO December 2016.
15. WHO 2004. Antiretroviral drugs for treating pregnant women and prevention of HIV-1 infection in the infants: guidelines on care, treatment, and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva: WHO, 2004.
16. Siegfried N, Van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Assessed up to date: 17 January 2011.
17. Thorne C, Newell ML. Are girls more at risk of intra-uterine acquired HIV infection than boys? *AIDS* 2004; 18(2): 344-47.
18. Petra study team. Efficacy of three short-course regimens of Zidovudine and Lamivudine in preventing early and late transmission of HIV-1 from mother-to-child in Tanzania, South Africa and Uganda (Petra study): a randomized, double-blind, placebo-controlled trial. *Lancet* 2002; 359(9313): 1178-86.

19. Jackson JB, et al. Intrapartum and Neonatal single dose Nevirapine compared with Zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow up of the HIVNET 012 randomized trial. *Lancet* 2003; 362(9387): 859-68.
20. Working group on Mother-To-Child Transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; 8: 506-10.
21. Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C, et al. Combination anti-retroviral strategies for the treatment of pregnant HIV 1 infected women and prevention of perinatal HIV 1 transmission. *J Acquir Immune Defic Syndr.* 2002; 29: 484-94.
22. Limpongsanurak, S. Efficacy and safety of caesarean delivery for prevention of mother-to-child transmission of HIV-1. RHL commentary (last revised: 15 December 2006) The WHO reproductive health library; Geneva: World Health Organization, 2006.
23. World Health Organization WHO. Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use. Second Edition. Geneva, Switzerland: WHO, 2000.
24. Lavreys L, Baeten JM, Kreiss JK, et al. Injectable contraceptive use and genital ulcer disease during the early phase of HIV-1 infection increase plasma virus load in women. *J Infect Dis*. 2004; 189: 303-11.
25. WHO. World Health Organization fact sheet on HIV/AIDS, updated November 2017.

NEUROLOGICAL MANIFESTATIONS OF HIV/AIDS

ADEKUNLE FATAI MUSTAPHA, FMCP
AND OLUYEMI MARY ADEBANJO
MBCHB, MWACP

Neurological disease is the first manifestation of HIV infection in about 20% of patients (1, 2, 3). In advanced disease, about 60% of patients will have a clinically evident neurologic disorder (1, 2, 3). Up to 90% of patients with advanced disease have pathologic abnormalities of the nervous system at autopsy (2, 4, 5). Neurological diseases seen in HIV-positive patients can be grouped into four (a) those that result from the direct or indirect effect of HIV itself e.g., HIV-associated neurocognitive disorder, HIV-myelopathy and HIV meningitis; (b) those that result from immune dysregulation and immunodeficiency e.g., opportunistic infections, malignancies, immune-mediated neuropathies; (c) those that are secondary to the use of antiretroviral therapy e.g., neuro-immune reconstitution inflammatory syndrome, ART-related distal sensory neuropathy, nucleoside-induced myopathy; and (d) other neurological diseases that are encountered among HIV seronegative patients.

HIV affects all levels of the neuroaxis; the brain, spinal cord, meninges, peripheral nerves and the muscles. Neurologic dysfunction can also manifest at any stage of the infection e.g. aseptic meningitis and acute inflammatory demyelinating polyneuropathy at seroconversion. In advanced disease, depletion of CD4 cells and accompanying severe immunosuppression increase susceptibility to opportunistic infections and malignancies e.g., cryptococcal meningitis, CNS toxoplasmosis, progressive multifocal leukoencephalopathy, primary CNS lymphoma, Kaposi's sarcoma.

Following the commencement of antiretroviral therapy and recovery of the immune system, the patient may mount an inflammatory response to preexisting latent infection in the nervous system leading to the

paradoxical worsening of symptoms [Neuro-immune Reconstitution Syndrome] (6). Muscular disorders may accompany the use of nucleoside reverse transcriptase inhibitors e.g., Zidovudine-myopathy and HIV-associated neuromuscular weakness syndrome (7, 8). Metabolic disorders secondary to the use of protease inhibitors (9, 10) are risk factors for vascular events like stroke. In countries where there is an availability of antiretroviral drugs, peripheral neuropathy and HIV-associated neurocognitive disorders predominate whereas opportunistic infections are commoner in developing countries.

Central Nervous System Disorders in HIV Infection

HIV Associated Neurocognitive Disorders (HAND)

HIV enters the central nervous system during the early phase of infection (11). Proposed mechanisms of entry include the "trojan horse" mechanism whereby the infected circulating CD4 T-lymphocytes and monocytes convey the virus through the blood-brain barrier (12); and migration of free viruses in between the endothelial cells of or via transcytosis through endothelial cells (13, 14). Monocyte-derived macrophages and microglia cells are the main sources of productive infection in that they support active replication and transmission of HIV within the central nervous system (15). While astrocytes are nonproductively infected, the infection of oligodendrocytes and neurons is questionable (15). Neuronal injury and neuronal loss as seen in HIV-associated neurocognitive disorders result from either the direct effect of viral proteins such as gp120, Tat and Vpr produced by infected cells or the indirect effect of inflammatory mediators such as TNF-α, nitric oxide and reactive oxygen produced by activated macrophages, microglia, lymphocytes and astrocytes (15). HAND encompasses cognitive disorders of varying severity seen in HIV-positive patients. Components of HAND include; Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV-associated Dementia [HAD, previously known as HIV encephalopathy, AIDS Dementia Complex] (16).

Before the advent of HAART, HAD used to be the commonest form of HAND and was associated with high fatality (17, 18). Although the present prevalence of HAND is similar to the pre-HAART era, milder forms of the disease are commoner with ANI accounting for 70% of all cases (19, 20). Low CD4 count, older age, cardiovascular risk factors, hepatitis C co-infection, substance abuse particularly methamphetamine,

and low educational status are identifiable risk factors for HAND (19, 21-26).

HAND is diagnosed using neuropsychological testing and functional status assessment (16). Abnormalities are observed in the following cognitive domains; psychomotor speed, attention, frontal lobe function, and verbal and non-verbal memory. Symptoms are mild in ANI and MND with an unremarkable neurologic examination. HAD is characterized by severe cognitive impairment, behavioural changes and motor abnormalities. Psychomotor retardation in the form of poor mentation, poor concentration, and bradykinesia is common. Other features include executive dysfunction, apathy, and depression. Hypertonia, hyperreflexia, decreased saccadic eye movement and frontal release signs are present on examination. The presence of focal neurologic deficits suggests another diagnosis. HIV myelopathy may co-exist.

Brain MRI in HAD (see Fig. 1) shows cerebral atrophy, symmetric periventricular and deep white matter hyperintensity on T2 imaging with the relative sparing of the subcortical white matter and posterior fossa structures (27). There is no enhancement or mass effect.

In the pre-HAART era, a high CSF viral load correlated with lower neuropsychological scores in the advanced disease but this is now a less reliable marker as patients on HAART have an undetectable level of viral load in CSF (28). Other indices of CSF analysis are essential in excluding confounding aetiologies.

The mainstay of treatment is the initiation of ART in ART-naive or optimizing therapy in patients on ART to suppress HIV RNA to undetectable levels in the plasma and CSF.

Although the use of ART with high CNS penetration-effectiveness has led to a reduced proportion of patients with a detectable CSF viral load (29), there is evidence that their use does not improve neurocognitive performance (30) and may, in fact, increase the risk of HAD (31, 32).

Progressive Multifocal Leukoencephalopathy (PML)

HIV infection accounts for 85% of cases of PML with a prevalence of 4-5% among HIV+ patients (33, 34, 35). It is a late complication, typically occurring when the CD4 count is below 200 cells/uL, although there are a few reports of PML in patients with a CD4 count >500 cells/uL (36, 37).

PML occurs following infection of the oligodendrocytes by John Cunningham (JC) virus, a polyomavirus leading to multifocal demyelination within the central nervous system (38, 39). The disease often results from the reactivation of a latent infection, as 39-69% of the adult population are seropositive for JC virus (40, 41). With the advent of HAART, both the incidence and mortality associated with the disease have declined.

The clinical presentation is subacute progressive focal neurologic deficits. Depending on the area of the brain involved, symptoms may include hemiparesis (frontal lobe), sensory loss, aphasia, apraxia (parietal lobe), visual field defect (occipital lobe), and ataxia (cerebellar peduncles). Seizures are uncommon; seen in 20% of patients when lesions are near the cortex (42, 43). The spinal cord is rarely involved (44) while the peripheral nervous system and optic nerve are spared (45).

The definitive diagnosis is made either histopathologically or by the combination of typical clinical and radiologic features in the presence of virologic evidence of JC virus (46). The polymerase chain reaction test for JC DNA in a CSF sample is highly specific (47).

Brain MRI, the preferred neuroimaging, demonstrates single or multiple multifocal white matter lesions commonly affecting the parieto-occipital and frontal lobes. The lesions are hyperintense on T_2-weighted images (see Fig. 2) while they are hypointense on T_1-weighted images (39). Unlike CNS toxoplasmosis and PCNSL, mass effect is absent. In advanced disease, there is involvement of U-fibres due to the coalescence of lesions.

Brain biopsy findings include demyelination, enlarged oligodendrocyte nuclei with JC virus inclusion, and bizarre-looking astrocytes.

The mainstay of therapy is the initiation of antiretroviral therapy in ART-naive HIV positive patients or the optimizing of therapy in patients already on ART to achieve adequate viral suppression. A number of drugs with anti-JCV activity are currently under study with controversial reports (48-51).

CNS Toxoplasmosis

Worldwide, about 13 million HIV+ people have co-infection with Toxoplasma gondii; 87.1% occurring in sub-Saharan Africa (52).

T. gondii, an intracellular protozoan parasite, is acquired through the ingestion of raw or undercooked meat, contaminated water and cat faeces (53). CNS toxoplasmosis is an encephalitis, almost always resulting from the reactivation of an old infection by T. gondii (54).

It is a late complication of HIV infection common when the CD4 count is less than 200 cells/uL; the risk is greatest at a CD4 count <50 cells/uL (55). It is, in fact, the commonest cause of mass lesions in HIV+ patients (56). The widespread prophylactic use of sulfamethoxazole-trimethoprim for Pneumocystis jiroveci pneumonia in HIV+ patients has led to a decline in the incidence of CNS toxoplasmosis. Fever, headache, altered sensorium and focal neurologic deficit(s) are common symptoms (57). Movement disorders like hemiballismus or hemichorea may occur when contralateral basal ganglia are involved (58). Extracerebral manifestations like chorioretinitis and pneumonitis may occur though they are rare in AIDS patients (59).

Definitive diagnosis requires typical clinical findings, the presence of mass lesion(s) on neuroimaging and the detection of Toxoplasma gondii in a clinical sample (59).

When lumbar puncture is not contraindicated, cerebrospinal fluid (CSF) analysis demonstrates nonspecific abnormalities which include elevated protein with variable glucose and pleocytosis. Detection of T. gondii DNA in the CSF sample, in the presence of typical clinical and radiologic findings confirms the diagnosis of CNS toxoplasmosis.

A positive serum IgG antibody indicates previous exposure to T. gondii. A negative result does not rule out toxoplasmosis as the antibody response may not be adequate in severe immunosuppression.

Brain CT scan or MRI typically shows multiple (rarely single) ring-enhancing mass lesions (see Fig. 3) with vasogenic oedema. Common sites include the basal ganglia and the grey-white matter junction. Thallium single-photon emission computed tomography (SPECT) shows a decreased uptake in the toxoplasmosis abscess, in contrast to primary CNS lymphoma (60).

Brain biopsy is indicated when there is no response to 14 days of empirical treatment.

The recommended treatment consists of an induction phase where a combination of oral pyrimethamine (loading dose 200 mg orally, then 50 mg {<60 kg} or 75 mg {>60 mg}, daily), sulfadiazine (1000 mg {<60 kg} or 1500 mg {>60 kg} orally 6 hourly and leucovorin (10-25 mg orally daily)) is given (59). Leucovorin is given to prevent pyrimethamine-induced haematologic toxicity. Sulfadiazine can be substituted with clindamycin (600 mg IV or orally 6 hourly) in patients who are allergic to sulfa. Atovaquone (1.5 mg orally 12 hourly) is another alternative. The induction phase should be continued for 6 weeks before a maintenance phase is commenced. Here, oral pyrimethamine (25-50 mg/day), oral leucovorin (10-25 mg/day), and oral sulfadiazine (500-1000 mg 6 hourly) or clindamycin (800 mg t.d.s) are continued until the CD4 count is greater than 200 cell/uL. Thereafter, prophylaxis with double-strength sulfamethoxazole-trimethoprim daily or three weekly is commenced. Glucocorticoids should only be administered when clinically indicated to treat mass lesion.

Primary CNS Lymphoma (PCNSL)

PCNSL is a late complication of HIV infection typically occurring when the CD4 count is ≤50 cells/uL. It is secondary to toxoplasmosis as a cause of mass lesion in HIV-positive patients (61). PCNSL is commonly a high-grade B-cell non-Hodgkin's lymphoma associated with Epstein- Barr virus (EBV) infection (62).

The symptoms develop insidiously. Clinical presentations include headaches, seizures, change in personality, and focal neurologic deficits. Fever is uncommon in contrast to CNS toxoplasmosis.

The detection of EBV DNA in the CSF and characteristic findings on neuroimaging supports the diagnosis (63). CSF analysis, if lumbar puncture is not contraindicated, reveals lymphocytic pleocytosis, normal glucose concentration, and normal to mildly elevated protein concentration.

Brain CT or MRI typically demonstrates a single enhancing lesion (rarely multiple) commonly located in the periventricular region and frontal lobes (see Fig. 4). There is increased blood flow on a perfusion-weighted scan as against the low blood flow in CNS toxoplasmosis. In addition, a thallium SPECT scan shows an increased uptake in contrast to the low uptake in toxoplasmosis.

When in doubt, biopsy gives the definitive diagnosis.

Suppression of HIV load with Highly Active Antiretroviral Therapy (HAART) is pivotal in management. The treatment options include radiotherapy, chemotherapy using high dose methotrexate, and the use of antiviral agents (e.g., ganciclovir). There is no consensus on the best mode of treat ment but improved survival has been reported in studies where the aforementioned modes of treatment were used (64-67). Glucocorticoids are employed in the management of cerebral oedema.

HIV and Stroke

HIV confers a risk of developing stroke, particularly ischaemic stroke (68, 69). Possible mechanisms of ischaemic stroke in HIV+ patients as reviewed by Benjamin et al. (70) include increased antiphospholipid antibodies; protein S deficiency; viral vasculitis; accelerated atherosclerosis; cardioembolism secondary to HIV-associated dilated cardiomyopathy and infective endocarditis; opportunistic infections and cancer; HIV-associated vasculopathy; and the use of HAART. The possible mechanisms of haemorrhagic stroke identified in the same review include; HIV-associated thrombocytopenia; aneurysm resulting from HIV-associated vasculopathy; and mycotic aneurysm from bacterial endocarditis.

Cryptococcal Meningitis

It is the infection of the meninges by Cryptococcus neoformans, an encapsulated fungus found in the soil and avian droppings. Inhalation of the fungus causes an asymptomatic pulmonary infection followed by haematogenous spread to the meninges. Cryptococcal meningitis is an opportunistic infection occurring at the late stage of HIV infection typically when the CD4 count is less than 100 cell/uL. It is therefore common among HIV-positive patients who are not on antiretroviral therapy. Worldwide, an estimated 223,000 new cases of cryptococcal meningitis occur yearly; 73% of which are from sub-Saharan Africa (71). An annual death rate of 181,100 results from the disease (71).

In HIV+ patients, symptoms of cryptococcal meningitis develop insidiously, commonly presenting as subacute meningitis or meningoencephalitis. Features of meningism, e.g., neck pain, neck stiffness, and Kernig and Brudzinski signs, are often absent owing to a

depressed immunity and an inability to mount an adequate inflammatory response. A nonspecific headache and fever are the common symptoms (72).

As the infection progresses, the patient may develop raised intracranial pressure, altered sensorium, cranial nerve palsy (particularly cranial VI), and papilloedema. Focal neurological deficits may be present in meningoencephalitis.

The cerebrospinal fluid analysis demonstrates nonspecific abnormalities; mildly elevated protein, low-to-normal glucose concentration, and lymphocytic pleocytosis. The CSF opening pressure may be elevated with a pressure of >25 cm H_2O in 60 to 80% patients (73, 74).

Diagnosis can be made through CSF microscopy, culture, and cryptococcal antigen testing. Indian ink staining, a rapid and commonly available diagnostic tool, has a sensitivity of 86% (75). Its sensitivity decreases to 42% when the fungal burden is less than 1,000 colony-forming units (CFU)/mL on a quantitative CSF culture (75).

Serum culture and cryptococcal antigen testing are sensitive for cryptococcaemia and can be done when lumbar puncture is contraindicated. Serum antigen testing has also been found to be a useful initial screening tool in diagnosing cryptococcosis in HIV+ patients (76).

Cranial MRI may reveal the enhancement of meninges, enlarged Virchow-Robin spaces or a cryptococcoma.

Treatment is in three phases: induction, consolidation and maintenance. The recommended drug treatment for induction is a combination of intravenous amphotericin B, 0.7-1 mg/kg/day and oral flucytosine 25 mg/kg six hourly for two weeks or until the CSF is sterile (59).

Side effects of amphotericin B include thrombophlebitis, rigor, nephrotoxicity and electrolyte disturbance notably hypokalaemia and hypomagnesaemia. The induction phase is followed by the consolidation phase which consists of oral fluconazole 400 mg daily for at least eight weeks. Thereafter, 200 mg of oral fluconazole is continued daily in the maintenance phase. Fluconazole is discontinued after one year of the maintenance phase, in the absence of symptoms of a cryptococcal disease, and when the CD4 count is ≥100 cells/uL with suppressed HIV RNA in response to effective antiretroviral therapy. Raised intracranial pressure

can be managed by the daily drainage of CSF via lumbar puncture; the initial volume drained should be one that reduces the CSF opening pressure by at least half (77). In severe cases, CSF shunting is considered. Mannitol and corticosteroids are not recommended for the management of raised intracranial pressure (78).

Complications include raised intracranial pressure, treatment failure, relapse and Immune Reconstitution Syndrome (IRIS). The risk of IRIS is higher when antiretroviral therapy is initiated before the end of the induction phase of treatment (79, 80).

HIV Meningitis

It is a self-limiting illness; aseptic meningitis typically occurring at the time of seroconversion (81). HIV directly causes meningitis. Treatment is supportive.

HIV Myelopathy (or Vacuolar Myelopathy)

HIV myelopathy is a late complication of HIV infection. It commonly co-exists with HAD and peripheral neuropathy. It is clinically and histopathologically similar to the subacute degeneration of the cord seen in vitamin B12 deficiency (82). Both disease conditions affect the dorsal column and lateral tracts. A metabolic disorder of the vitamin B12-dependent transmethylation pathway has been implicated in HIV myelopathy (83).

Symptoms begin in the lower limbs because the thoracic segments of the cord are the first to be affected. The usual presentation is progressive leg weakness associated with stiffness, sensory loss and sphincteric dysfunction (84). Affectation of the dorsal column presents as loss of vibratory and proprioception sensation in the lower limbs, sensory ataxia and a positive Romberg sign. Involvement of lateral corticospinal tracts presents as spastic paraparesis, extensor plantar response. Sphincteric and erectile dysfunctions result from the affectation of autonomic fibres within the spinal cord. Prominent back pain and a definite sensory level suggest another diagnosis.

Histology reveals asymmetric vacuolation and myelin pallor involving dorsal and lateral tracts commonly in the thoracic cord segment. The serum level of vitamin B12 is usually normal.

HIV myelopathy has no definitive treatment. Symptomatic management is the mainstay of treatment. Physiotherapy and muscle relaxants (e.g., baclofen, tizanidine) improve spasticity. Sildenafil, if not contraindicated, can be used for erectile dysfunction. Imipramine and Oxybutynin are used in treating urinary incontinence and frequency respectively.

Peripheral Nervous System Disorders in HIV

Peripheral Neuropathy

Distal Sensory Polyneuropathy (DSP)

DSP is the commonest form of peripheral neuropathy seen in HIV+ patients (85-87). There are two forms; HIV-mediated DSP and ART-related DSP. These two are indistinguishable clinically or by laboratory investigations. While HIV-mediated DSP is typically seen in advanced immunosuppression when the CD4 count is <200 cells/uL, ART-related DSP can develop at any stage of the disease in patients on ART particularly the dideoxynucleoside reverse transcriptase inhibitors e.g., stavudine (d4T), didanosine (ddl), and zalcitabine (ddc). DSP in this case, is probably due to mitochondrial toxicity that is associated with these drugs.

HIV-mediated DSP may result directly from the infection of the dorsal root ganglia by HIV or indirectly from the neurotoxicity caused by the inflammatory cytokines and free radicals released by infected macrophages (88). The risk factors include male sex and older age >50 years, a low CD4 count and a high viral load, diabetes, height, d4T exposure, and substance abuse (89-94). Statin use may be protective (92).

The clinical presentation usually is a symmetrical painful, burning sensation in the lower limbs following a stocking distribution, though in the advanced stage of the disease the glove distribution may be observed. There is a loss of sensation to temperature and pinprick but preservation of joint position sense. Allodynia and hyperalgesia are common. Ankle and knee reflexes are depressed or absent. Distal weakness may be present in advanced disease. Autonomic dysfunction commonly co-exists (95).

Investigations are done to exclude other aetiologies of peripheral neuropathy such as diabetes mellitus or vitamin B12 deficiency. Nerve conduction studies reveal features in keeping with axonal neuropathy.

Drugs used for the general management of neuropathic pain are employed. Mild analgesics may control the mild form of the disease. Other classes of drug include; anticonvulsants (gabapentin, pregabalin, lamotrigine); antidepressants (amitriptyline, duloxetine); and topical agents (capsaicin, lidocaine). Aside from gabapentin and a high concentration capsaicin patch (96-98), many of these agents were not found to be significantly more effective than a placebo in controlled trials (99-101). In ART-related DSP, the dideoxynucleosides are either replaced or the dose reduced without compromising virologic control.

HIV-Associated Multiple Mononeuropathy

It can occur at any stage of HIV infection. Early multiple mononeuropathy, a self-limiting disease may present at the time of seroconversion, in which case, immune-mediated mechanisms are implicated (102). Late multiple mononeuropathy is typically seen when the CD4 count is ≤50 cells/uL and is associated with infectious agents, particularly cytomegalovirus (103-105).

It manifests as multiple asymmetric sensory and motor deficits involving cranial nerves, nerve roots and peripheral nerves. The facial nerve is the most commonly affected cranial nerve (106).

Peripheral nerves such as the median nerve (carpal tunnel syndrome), the common peroneal nerve (foot drop), the lateral femoral cutaneous nerve (meralgia paresthetica), and the phrenic nerve (diaphragmatic paralysis) can be affected (72).

A polymerase reaction of a blood sample for CMV should be considered in severe cases. Investigations for hepatitis B, hepatitis C, lymphoma, diabetes mellitus, and cryoglobulinaemia should be considered. Nerve conduction studies show features of axonal degeneration.

Corticosteroids, intravenous immunoglobulin, and plasmapheresis are available options of treatment (107, 108). Disease secondary to CMV infection is treated with ganciclovir or foscarnet.

Inflammatory Demyelinating Polyneuropathy

HIV infection can present with either acute or chronic inflammatory demyelinating polyneuropathy (AIDP or CIDP). AIDP (also known as

Guillain-Barre Syndrome) is common during seroconversion while CIDP can occur at any stage of HIV infection (109-111).

Typical presentations include ascending weakness, hyporeflexia/areflexia, autonomic dysfunction, cranial nerve palsies, and minor sensory deficits.

There are elevated protein concentration and lymphocytic pleocytosis on CSF analysis. This is in contrast to AIDP seen in HIV-negative patients where the CSF is acellular despite an elevated protein concentration. Features of electrophysiology are consistent with primary demyelination, often with secondary axonal degeneration. Treatment is the same as in HIV-negative patients; intravenous immunoglobulin or plasmapheresis. The use of a steroid is the third option in the case of CIDP.

Progressive Polyradiculopathy

Progressive polyradiculopathy, a late complication of HIV infection, typically results from CMV infection. It is common at a CD4 count of fewer than 50 cells/uL (112). Other causes of polyradiculopathy in HIV patients include herpes simplex virus type 2, tuberculosis meningitis, syphilis, varicella-zoster virus and spinal lymphoma (113-115). It presents as cauda equina syndrome; severe pain, paraesthesia, asymmetric weakness of the legs; occasionally the arms in advanced cases, “saddle” anaesthesia, and bowel and bladder dysfunction (116).

CSF findings in CMV-polyradiculopathy are pleocytosis (predominantly polymorphonuclear neutrophils), decreased glucose level, a markedly elevated protein level and a positive polymerase chain reaction for CMV (72). MRI with contrast may show non-specific enhancement of the nerve root. Investigations to exclude other aetiologies; herpes simplex virus, varicella-zoster virus, and lymphoma should be considered in patients in whom CMV has been excluded.

CMV polyradiculopathy is treated with intravenous ganciclovir (5 mg/kg 12 hourly) or foscarnet (90 mg/kg 12 hourly) for 3-6 weeks followed by lifelong use of valganciclovir and foscarnet (72). Cidofovir in combination with HAART is also effective (117). Agents such as gabapentin, pregabalin, amitriptyline, lamotrigine, and duloxetine are used for the symptomatic relief of neuropathic pain.

Autonomic Neuropathy

Autonomic neuropathy commonly coexists with HIV DSP; more than half of HIV DSP patients are affected (118). The clinical presentations include orthostatic hypotension, xerostomia, xerophthalmia, urinary incontinence, sexual dysfunction, gastroparesis, diarrhoea, constipation, sluggish pupillary reaction and sweating abnormalities (119).

Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

It is a multisystemic disease characterized by CD8 T-cell lymphocytosis and the infiltration of organs by CD8 T-lymphocytes. It is similar to Sjogren syndrome, though in contrast to DILS, the infiltrates in Sjogren syndrome are predominantly CD4 T-cells (120). DILS is common among middle-aged African-American men (121), though the disease is becoming less prevalent with the widespread use of HAART (122). The most commonly infiltrated organ in DILS is the salivary gland (121). Other extraglandular sites include the lungs, muscle, liver, the peripheral nerves and the kidneys. The presentation is similar to Sjogren syndrome; parotid gland enlargement, xerostomia, and xerophthalmia. Myositis, lymphocytic interstitial pneumonia, peripheral neuropathy, interstitial nephritis, and hepatitis may occur with the involvement of muscles, lungs, peripheral nerves, kidneys and the liver respectively (121, 123-125).

Diagnosis is made when an HIV-positive patient has bilateral salivary gland enlargement, or xerostomia for more than six months with histological evidence of lymphocytic infiltration of the salivary or lacrimal gland in the absence of neoplastic or granulomatous involvement (120). The mainstay of treatment is the initiation of HAART (126). Corticosteroids are considered in patients with significant symptoms (122).

HIV-Associated Neuromuscular Weakness Syndrome

It presents with ascending weakness similar to what is seen in AIDP but occurs in the setting of high serum lactate and lactic acidosis in patients on nucleoside antiretroviral therapy (127). Systemic symptoms such as fatigue, nausea, vomiting, weight loss, and abdominal distention are also present. A possible underlying pathophysiology is mitochondrial toxicity associated with nucleoside analogues. Treatment is supportive and

includes the discontinuation of the nucleoside ART and medical management of the lactic acidosis.

HIV-Associated Myopathy

HIV-associated myopathy though uncommon, can occur at any stage of HIV infection (128). Causes include Zidovudine therapy, polymyositis, opportunistic infections (pyomyositis), vasculitis, and HIV-wasting syndrome. Clinical features include myalgia, muscle weakness (focal or symmetric proximal weakness), and fever (in myositis secondary to bacterial or fungal infection). In HIV-wasting syndrome, there is involuntary weight loss and generalized muscle wasting in the setting of chronic diarrhoea and fever. Serum creatine kinase is elevated in most cases. It is normal for HIV-wasting syndrome. Ragged-red fibres on the muscle biopsy suggest mitochondrial toxicity due to nucleoside analogues. The mainstay of treatment is to address the underlying cause e.g., withdrawal of Zidovudine in the case of Zidovudine-induced myopathy, the use of corticosteroids in inflammatory myositis, the use of antimicrobials for infectious cases, and the use of anabolic steroid for HIV-wasting syndrome.

References

1. Snider WD, Simpson DM, Nielsen S, Gold JW, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. *Ann Neurol*. 1983; 14: 403–18.
2. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. *J Neurosurg*. 1985; 62: 475–95.
3. Koppel BS, Wormser GP, Tuchman AJ, Maayan S, Hewlett D, Jr, Daras M. Central nervous system involvement in patients with acquired immune deficiency syndrome (AIDS). *Acta Neurol Scand*. 1985; 71: 337–53.
4. Rosenblum ML, Bredesen DE, Levy RM. Algorithms for the treatment of AIDS patients with neurological diseases. In: Rosenblum ML, Levy RM, Bredesen DE, editors. *AIDS and the Nervous System*. New York: Raven Press, 1988, 389–96.
5. de la Monte SM, Ho DD, Schooley RT, Hirsch MS, Richardson EP Jr. Subacute encephalomyelitis of AIDS and its relation to HTLV-III infection. *Neurology*. 1987; 37: 562–9.

6. Venkataramana A, Pardo CA, McArthur JC, Kerr DA, Irani DN, Griffin JW. Immune reconstitution inflammatory syndrome in the CNS of HIV-infected patients. *Neurology* 2006 Aug 8; 67(3): 383–8.
7. Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. *Lancet* 1991; 337(8740): 508–510.
8. HIV Neuromuscular Syndrome Study Group. HIV-associated neuromuscular weakness syndrome. *AIDS* 2004; 18(10): 1403–1412.
9. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; 12: F51–F58.
10. Stein JH, Klein MA, Bellehumeur JL, et al. Use of Human Immunodeficiency Virus-1 Protease Inhibitors Is Associated With Atherogenic Lipoprotein Changes and Endothelial Dysfunction. *Circulation* 2001; 104: 257–262.
11. Kramer-Hammerle S, Rothenaigner I, Wolff H, Bell JE, Brack-Werner R. Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. *Virus Res.* 2005; 111(2): 194–213.
12. Peluso R, Haase A, Stowring L, Edwards M, Ventura P. A Trojan Horse mechanism for the spread of visna virus in monocytes. *Virology* 1985; 147(1): 231–236.
13. Bomsel M. Transcytosis of infectious human immunodeficiency virus across a tight human epithelial cell line barrier. *Nat Med.* 1997; 3(1): 42–47.
14. Banks WA, Freed EO, Wolf KM, Robinson SM, Franko M, Kumar VB. Transport of human immunodeficiency virus type 1 pseudoviruses across the blood-brain barrier: role of envelope proteins and adsorptive endocytosis. *J Virol*. 2001; 75(10): 4681–4691.
15. Ghafouri M, Amini S, Khalili K, Sawaya BE. HIV-1 associated dementia: symptoms and causes. *Retrovirology*. 2006; 3: 28.
16. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; 69: 1789–1799.
17. Grant I, Atkinson JH, Hesselink JR, Kennedy CJ, Richman DD, Spector SA, McCutchan JA, et al. Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections: studies with neuropsychologic testing and magnetic resonance imaging. *Ann Intern Med*. 1987; 107: 828–836.

18. Ellis RJ, Deutsch R, Heaton RK, Marcotte TD, McCutchan JA, Nelson JA, et al. Neurocognitive impairment is an independent risk factor for death in HIV infection. *Arch Neurol*. 1997; 54: 416–424.
19. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders (HAND) persist in the era of potent antiretroviral therapy: The CHARTER Study. *Neurology* 2010; 75: 2087–2096.
20. McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, et al. Dementia in AIDS patients: incidence and risk factors. *Neurology* 1993; 43: 2245–2252.
21. Fazeli PL, Crowe M, Ross LA, Wadley V, Ball K, Vance DE , et al. Cognitive functioning in adults aging with HIV: a cross-sectional analysis of cognitive subtypes and influential factors. *J Clin Res HIV AIDS Prev*. 2015; 1: 155–169.
22. Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes O, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. *Neurology* 2004; 63: 822–827.
23. McCutchan JA, Marquie-Beck JA, FitzSimons CA, Letendre SL, Ellis RJ, Heaton RK, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology* 2012; 78: 485–492.
24. Vivithanaporn P, Nelles K, DeBlock L, Newman SC, Gill MJ, Power C, et al. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *J Neurol Sci*. 2012; 312: 45–51.
25. Weber E, Morgan EE, Iudicello JE, Blackstone K, Grant I, Ellis RJ, et al. Substance use is a risk factor for neurocognitive deficits and neuropsychiatric distress in acute and early HIV infection. *J Neurovirol*. 2013; 19: 65–74.
26. Becker JT, Kingsley LA, Molsberry S, Reynolds S, Aronow A, Levine AJ, et al. Cohort profile: recruitment cohorts in the neuropsychological sub-study of the Multicenter AIDS Cohort Study. *Int J Epidemiol*. 2015; 44: 1506–1516.
27. Sharma R, Ho M-L . HIV associated dementia. Available from: https://radiopaedia.org/articles/hiv-associated-dementia [Accessed on 25th Feb, 2018].
28. Cysique LA, Brew BJ, Halman M, Catalan J, Sacktor N, Price RW, et al. Undetectable cerebrospinal fluid HIV RNA and beta-2 microglobulin do not indicate inactive AIDS dementia complex in

highly active antiretroviral therapy-treated patients. *J Acquir Immune Defic Syndr*. 2005; 39: 426-429.

29. Letendre SL, Mills AM, Tashima KT, Thomas DA, Min SS, Chen S, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. *Clin Infect Dis*. 2014; 59: 1032–1037.
30. Ellis RJ, Letendre S, Vaida F, Haubrich R, Heaton RK, Sacktor N, et al. Randomized trial of central nervous system-targeted antiretrovirals for HIV-associated neurocognitive disorder. *Clin Infect Dis*. 2014; 58: 1015–1022.
31. Etherton MR, Lyons JL, Ard KL. HIV-associated neurocognitive disorders and antiretroviral therapy: current concepts and controversies. *Curr Infect Dis Rep.* 2015; 17: 485.
32. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *J Neurovirol*. 2012; 18: 388–399.
33. Focosi D, Marco T, Kast RE, Maggi F, Ceccherini-Nelli L, Petrini M. Progressive multifocal leukoencephalopathy: what's new? *Neuroscientist* 2010 June; 16(3): 308–23.
34. Zheng HC, Yan L, Cui L, Guan YF, Takano Y. Mapping the history and current situation of research on John Cunningham virus – a bibliometric analysis. *BMC Infect Dis*. 2009; 9: 28.
35. Taoufik Y, Gasnault J, Karaterki A, Pierre Ferey M, Marchadier E, Goujard C. Prognostic value of JC virus load in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *J Infect Dis*. 1998 Dec; 178(6): 1816–20.
36. Delobel P, Brassat D, Delisle MB, Scaravilli F, Clanet M. Progressive multifocal leukoencephalopathy in an HIV patient with normal CD4 T-cell count and magnetic resonance imaging. *AIDS* 2004 Mar 5; 18(4): 702–4.
37. Mascarello M, Lanzafame M, Lattuada E, Concia E, Ferrari S. Progressive multifocal leukoencephalopathy in an HIV patient receiving successful long-term HAART. *J Neurovirol*. 2011 Apr; 17(2): 196–9.
38. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: Has the disease outgrown its name?" *Ann Neurol*. 2006; 60(2): 162–73.
39. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. Oct 2009; 9(10): 625–636.

40. Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. *J Infect Dis*. Mar 15 2009; 199(6): 837–846.
41. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*. Sep 2010; 68(3): 295–303.
42. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology* Jan 24 2006; 66(2): 262–264.
43. Khoury MN, Alsop DC, Agnihotri SP, et al. Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive multifocal leukoencephalopathy. *Ann Neurol*. May 2014; 75(5): 659–669.
44. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *J Neurovirol.* Oct 2007; 13(5): 474–476.
45. Sudhakar P, Bachman DM, Mark AS, Berger JR, Kedar S. Progressive Multifocal Leukoencephalopathy: Recent Advances and a Neuro-Ophthalmological Review. *J Neuroophthalmol*. 2015 Sep; 35(3): 296–305.
46. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology* 2013 Apr 9; 80(15): 1430–8.
47. Bossolasco S, Calori G, Moretti F, Boschini A, Bertelli D, Mena M, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2005 Mar 1; 40(5): 738–44.
48. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M. Progressive Multifocal Leukeoncephalopathy Consortium. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord*. 2015 Nov; 8(6): 255–73.
49. De Luca A, Fantoni M, Tartaglione T, Antinori A. Response to cidofovir after failure of antiretroviral therapy alone in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology* 1999 Mar 10; 52(4): 891–2.
50. Huang SS, Skolasky RL, Dal Pan GJ, Royal W 3rd, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol*. 1998 Jun; 4(3): 324–32.

51. Aksamit AJ. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. *J Neurovirol*. 2001 Aug; 7(4): 386–90.
52. Wang Z-D, Wang S-C, Liu H-H, Ma H-Y, Li Z-Y, Wei F, et al. Prevalence and burden of Toxoplasma gondii infection in HIV-infected people: a systematic review and meta-analysis. *The Lancet HIV* 2017; 4(4): e177–e188.
53. Baril L, Ancelle T, Goulet V, Thulliez P, Tirard-Fleury V, Carme B. Risk factors for Toxoplasma infection in pregnancy: a case-control study in France. *Scand J Infect Dis*. 1999; 31(3): 305–9.
54. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med*. 1992 Dec 3; 327(23): 1643–8.
55. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA* 1984 Aug 17; 252(7): 913–7.
56. Bhigjee AI, Naidoo K, Patel VB, Govender D. Intracranial mass lesions in HIV-positive patients – the KwaZulu/Natal experience. Neuroscience AIDS Research Group. *S Afr Med J.* 1999 Dec; 89(12): 1284–8.
57. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA* Aug 17 1984; 252(7): 913–917.
58. Rabhi S, Amrani K, Maaroufi M, et al. Hemichorea-hemiballismus as an initial manifestation in a Moroccan patient with acquired immunodeficiency syndrome and toxoplasma infection: a case report and review of the literature. *The Pan African Medical Journal* 2011; 10: 9.
59. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. [Accessed on 20/02/2018].
60. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients. *AJNR Am J Neuroradiol.* Nov 1994; 5(10): 1885–1894.

61. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Evaluation and management of intracranial mass lesions in AIDS. *Neurology* 1998; 50: 21–26.
62. Camilleri-Broet S, Davi F, Feuillard J, et al. AIDS-related primary brain lymphomas: histopathologic and immunohistochemical study of 51 cases. *Hum Pathol*. 1997; 28: 367–74.
63. Thomas F. Central Nervous System Lymphoma in HIV. Available from: https://emedicine.medscape.com/article/1167482-workup [Accessed on 24th Feb, 2018].
64. Moulignier A, Lamirel C, Picard H, Lebrette MG, Amiel C, Hamidi M, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. *Neurology*. 2017 Aug 22; 89 (8):796-804.
65. Nagai H, Odawara T, Ajisawa A, Tanuma J, Hagiwara S, Watanabe T, et al. Whole brain radiation alone produces favourable outcomes for AIDS-related primary central nervous system lymphoma in the HAART era. *Eur J Haematol*. 2010 Jun; 84(6): 499–505.
66. Bossolasco S, Falk KI, Ponzoni M. Ganciclovir is associated with low or undetectable Epstein-Barr virus DNA load in cerebrospinal fluid of patients with HIV-related primary central nervous system lymphoma. *Clin Infect Dis*. 2006 Feb 15; 42(4): e21–5.
67. Aboulafia DM, Ratner L, Miles SA. Antiviral and immunomodulatory treatment for AIDS-related primary central nervous system lymphoma: AIDS Malignancies Consortium pilot study 019. *Clin Lymphoma Myeloma*. 2006 Mar; 6(5): 399–402.
68. Qureshi A, Janssen R, Karon J, Weissman J, Akbar M, Safdar K, et al. Human immunodeficiency virus infection and stroke in young patients. *Arch Neurol* 1997; 54: 1150–1153.
69. Cole J, Pinto A, Hebel J, Buchholz D, Earley C, Johnson C, et al. Acquired immunodeficiency syndrome and the risk of stroke. *Stroke* 2004; 35: 51–56.
70. Benjamin LA, Bryer A, Emsley H et al. *Lancet Neurol*. 2012 Oct; 11(10): 878–890.
71. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis.* 2017 Aug; 17(8): 873–881.
72. Sacktor N, Rumbaugh J, Sevigny J, Estanislao LB. HIV neurology. In: Brust JCM. *CURRENT Diagnosis & Treatment Neurology*. 2nd ED. New York, United States: Mc Gray-Hill Education Europe, 2011, 461-474.

73. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis*. Jan 2000; 30(1): 47–54.
74. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS* Mar 27 2009; 23(6): 701–706.
75. Boulware DR, Rolfes MA, Rajasingham R, von Hohenberg M, Qin Z, Taseera K, et al. Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. *Emerging infectious diseases* 2014; 20(1): 45–53.
76. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. *Clin Infect Dis*. May 1994; 18(5): 789–792.
77. Fessler RD, Sobel J, Guyot L, et al. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology: Official Publication of the International Retrovirology Association*. Feb 1 1998; 17(2): 137–142.
78. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. *N Engl J Med*. Feb 11 2016; 374(6): 542–554.
79. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. *Clin Infect Dis*. Jun 1 2010; 50(11): 1532–1538.
80. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. Jun 26 2014; 370(26): 2487–2498.
81. Serrano P, Hernández N, Arroyo JA, de Llobet JM, Domingo P. Bilateral Bell palsy and acute HIV type 1 infection: Report of 2 cases and review. *Clin Infect Dis*. 2007; 44: e57–e61.
82. Petito CK, Navia BA, Cho ES, Jordan BD, George DC, Price RW. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1985; 312: 874–879.

83. Keibutz KD, Giang DW, Schiffer RB, Vakil N. Abnormal vitamin B12 metabolism in human immunodeficiency virus infection. *Arch Neurol*. 1991; 48: 312–314.
84. Rani P, Thomas FP. HIV-Associated Vacuolar Myelopathy. Available from: https://emedicine.medscape.com/article/1167064-overview#showall [Accessed on 25th Feb, 2018].
85. Cornblath DR, McArthur JC. Predominantly sensory neuropathy in patients with AIDS and AIDS-related complex. *Neurology* 1988 May; 38(5): 794–6.
86. de Gans J, Portegies P. Neurological complications of infection with human immunodeficiency virus type 1. A review of literature and 241 cases. *Clin Neurol Neurosurg*. 1989; 91(3): 199–219.
87. Ferrari S, Vento S, Monaco S, et al. Human immunodeficiency virus-associated peripheral neuropathies. *Mayo Clin Proc*. 2006 Feb; 81(2): 213–9.
88. Hao S. The Molecular and Pharmacological Mechanisms of HIV-Related Neuropathic Pain. *Curr Neuropharmacol*. 2013 Sep; 11(5): 499–512.
89. Watters MR, Poff PW, Shiramizu BT, et al. Symptomatic distal sensory polyneuropathy in HIV after age 50. *Neurology*. 2004 Apr 27; 62(8): 1378–83.
90. Evans SR, Ellis RJ, Chen H, Yeh TM, Lee AJ, Schifitto G, et al. Peripheral neuropathy in HIV: prevalence and risk factors. *AIDS* 2011 Apr 24; 25(7): 919–28.
91. Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology* 1999 Feb; 52(3): 607–13.
92. Chen H, Clifford DB, Deng L, Wu K, Lee AJ, Bosch RJ, et al. Peripheral neuropathy in ART-experienced patients: prevalence and risk factors. *J Neurovirol*. 2013 Dec; 19(6): 557–64.
93. Cherry CL, Skolasky RL, Lal L, Creighton J, Hauer P, Raman SP, et al. Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. *Neurology* 2006 Mar 28; 66(6): 867–73.
94. Robinson-Papp J, Gelman BB, Grant I, Singer E, Gensler G, Morgello S, et al. Substance abuse increases the risk of neuropathy in an HIV-infected cohort. *Muscle Nerve* 2012 Apr; 45(4): 471–6.
95. Centner CM, Bateman KJ, Heckmann JM. Manifestations of HIV infection in the peripheral nervous system. *Lancet Neurol*. 2013 Mar; 12(3): 295–309.

96. Hahn K, Arendt G, Braun JS, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol*. 2004 Oct; 251(10): 1260–6.
97. Simpson DM, McArthur JC, Olney R, et al. Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003 May 13; 60(9): 1508–14.
98. Simpson DM, Brown S, Tobias J. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology* 2008 Jun 10; 70(24): 2305–13.
99. Simpson DM, Schifitto G, Clifford DB, et al. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. *Neurology* 2010 Feb 2; 74(5): 413–20.
100. Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *JAMA* 1998 Nov 11; 280(18): 1590–5.
101. Estanislao L, Carter K, McArthur J, et al. A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. *J Acquir Immune Defic Syndr*. 2004 Dec 15; 37(5): 1584–6.
102. Sugimoto H, Konno S, Takamiya K, Nemoto H, Wakata N, Kurihara T. A case of primary HIV infection presenting as mononeuritis multiplex. *Rinsho Shinkeigaku* 2006 Aug; 46(8): 561–3.
103. Harada H, Tamaoka A, Yoshida H, Ohkoshi N, Mochizuki A, Hayashi A, et al. Horner's syndrome associated with mononeuritis multiplex due to cytomegalovirus as the initial manifestation in a patient with AIDS. *J Neurol Sci*. 1998 Jan 21; 154(1): 91–3.
104. Kaku M, Simpson DM. HIV neuropathy. *Curr Opin HIV AIDS* 2014 Nov; 9(6): 521–6.
105. Gabbai AA, Castelo A, Oliveira AS. HIV peripheral neuropathy. *Handb Clin Neurol*. 2013; 115: 515–29.
106. Thomas FP. HIV-Associated Multiple Mononeuropathies. Available from: https://emedicine.medscape.com/article/1167942-overview#showall [Accessed on 26th Feb, 2018].
107. Luciano CA, Pardo CA, McArthur JC. Recent developments in the HIV neuropathies. *Curr Opin Neurol*. 2003 Jun; 16(3): 403–9.
108. Whitley RJ, Jacobson MA, Friedberg DN, et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. International AIDS Society-USA. *Arch Intern Med*. 1998 May 11; 158(9): 957–69.

109. Kumar S, Alexander M, Markandeyulu V. Guillain-Barre syndrome presenting in the anti-HIV seroconversion period. *Neurol India* 2003 Dec; 51(4): 559.
110. Brannagan TH, Zhou Y. HIV-associated Guillain-Barre syndrome. *J Neurol Sci*. 2003 Apr 15; 208(1–2): 39–42.
111. Verma A. Epidemiology and clinical features of HIV-1 associated neuropathies. *J Peripher Nerv Syst*. 2001 Mar; 6(1): 8–13.
112. Wulff EA, Wang AK, Simpson DM. HIV-associated peripheral neuropathy: epidemiology, pathophysiology and treatment. *Drugs* 2000 Jun; 59(6): 1251–60.
113. Chen-Plotkin AS, Christopoulos KA, Venna N. Demyelinating polyneuropathy and herpes simplex lumbosacral radiculitis in a patient with chronic HIV infection. *AIDS* 2007; 21 (12): 1663–1664.
114. Masjuan J, Corral I, Fernandez-Ruiz LC. Mycobacterial acute lumbosacral polyradiculopathy as the initial manifestation of AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997; 15: 175.
115. Lanska MJ, Lanska DJ, Schmidley JW. Syphilitic polyradiculopathy in an HIV-positive man. *Neurology*. 1988; 38: 1297–301.
116. Anders HJ, Goebel FD. Cytomegalovirus, polyradiculopathy in patients with AIDS. *Clin Infect Dis*. 1998 Aug; 27(2): 345–52.
117. Douthwaite ST, Taegtmeyer M, Stow R. Cidofovir treatment of HIV-associated cytomegalovirus polyradiculopathy. *AIDS* 2006; 20(4): 632-4.
118. Robinson-Papp J, Sharma S, Simpson DM, Morgello S. Autonomic dysfunction is common in HIV and associated with distal symmetric polyneuropathy. *J Neurovirol*. 2013; 19(2): 172–180.
119. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The autonomic symptom profile: a new instrument to assess autonomic symptoms. *Neurology* 1999; 52(3): 523–528.
120. Itescu S, Winchester R. Diffuse infiltrative lymphocytosis syndrome: a disorder occurring in human immunodeficiency virus-1 infection that may present as a sicca syndrome. *Rheum Dis Clin North Am*. 1992; 18: 683–697.
121. Kazi S, Cohen PR, Williams F, et al. The diffuse infiltrative lymphocytosis syndrome: clinical and immunogenetic features in 35 patients. AIDS 1996; 10: 385–391.
122. Reveille JD. The changing spectrum of rheumatic disease in human immunodeficiency virus infection. *Semin Arthritis Rheum*. 2000; 30: 147–166.

123. Lesprit P, Fornairon S, Michaut P, et al. Renal involvement in the diffuse infiltrative CD8 lymphocytosis syndrome. *AIDS* 1997; 11: 262–263.
124. Sancho JM, Ribera JM, Vaquero M, et al. Diffuse infiltrative CD8 lymphocytosis syndrome in a patient with HIV-1 infection. *Med Clin (Barc)*. 2000; 115: 399.
125. McArthur C, Subtil-DeOliveira A, Palmer D, et al. Characteristics of salivary diffuse infiltrative lymphocytosis syndrome in West Africa. *Arch Pathol Lab Med*. 2000; 124: 1773–1779.
126. Bachmeyer C, Dhote R, Blanche P, et al. Diffuse infiltrative CD8 lymphocytosis syndrome with predominant neurologic manifestations in two HIV-infected patients responding to zidovudine. *AIDS* 1995; 9: 1101–1102.
127. HIV Neuromuscular Syndrome Study Group. HIV-associated neuromuscular weakness syndrome. *AIDS* 2004; 18: 1403–1412.
128. Verma S, Misca E, Estanislao L, Simpson D. Neuromuscular complications in HIV. *Curr Neurol Neurosci Rep.* 2004; 4: 62–67.

T2 MRI showing cerebral atrophy as evidenced by prominent gyri and sulci, dilatation of the ventricles with periventricular flaring

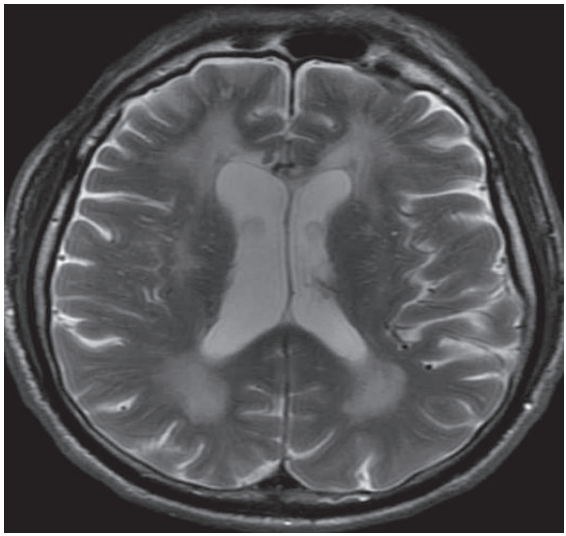


Figure 1: HIV-Associated Dementia
Available from: https://radiopaedia.org/articles/hiv-associated-dementia [Accessed on March 7, 2018]

T2 MRI showing hyperintense multiple white mater lesions and evidence of cerebral atrophy

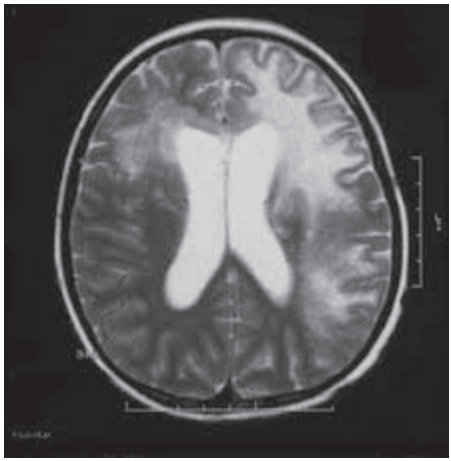


Figure 2: Progressive multifocal leukoencephalopathy
Available from:
https://radiopaedia.org/articles/progressive-multifocal-leukoencephalopathy
[Accessed on March 7, 2018]

MRI T1 post-contrast axial view of the brain showing multiple ring-enhancing lesions in the right cerebral hemisphere with minimal shift of midline to the contralateral side. There are another two regions of patchy enhancement at the grey-white matter junction of the left cerebral hemisphere

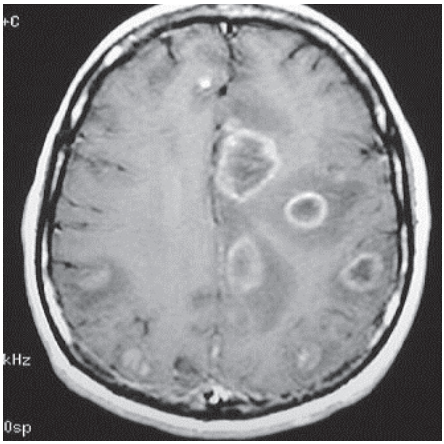


Figure 3; CNS toxoplasmosis
Available from:
http://neuroradiologyteachingfiles.com/bfa.html [Accessed on March 7, 2018]

T1 MRI post-contrast axial view of the brain showing a homogenously hyperintense periventricular lesion with mass effect evidenced by compression of the posterior horn of the right lateral horn

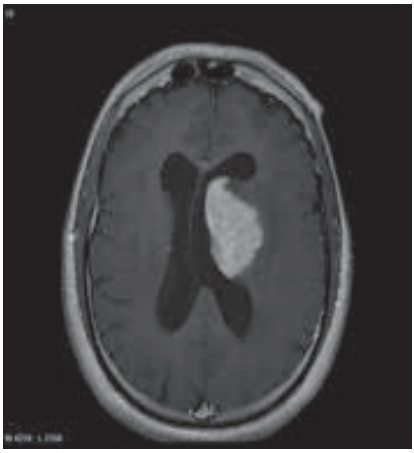


Figure 4; Primary CNS lymphoma
Available from:
https://radiopaedia.org/articles/toxoplasmosis-vs-lymphoma [Accessed on March 7, 2018]

HIV/AIDS AND MENTAL HEALTH

JULIANAH TEMILOLA MOSANYA
MBBS, FWACP

HIV and mental health have a longstanding history but the recent advancement in the diagnosis and treatment of HIV/AIDS has transformed the infection from an invariably fatal disease to a manageable chronic illness. This has implications for the mental health of people living with the infection. This review highlights the complex relationship that exists between HIV/AIDS and mental health and the different mental health issues that could complicate HIV infection. It explores the implications of recent advances made in the treatment of HIV/AIDS for the mental health of those affected. In addition, the diagnosis and treatment of mental disorders in people living with HIV and AIDS are examined. The availability of mental health care and barriers to the care of the mental health of people living with HIV/AIDS, especially in the low- and middle-income countries are also highlighted.

Psychosocial issues have been intimately related to Human Immunodeficiency Virus (HIV) infection since it was discovered in 1981. In the early phase of the discovery of HIV/Acquired Immune Deficiency Syndrome (AIDS), a psychiatric consultation was sought for difficult to treat patients or those with obvious mental health issues like; depression, withdrawal, confusion and refusal of treatment despite illness progression. Staff and family members ostracized those affected because of their severe fear of contracting an illness which had an unclear aetiology and a mystic perception. The negative reactions from staff and family members increased the distress of those affected resulting in a significant psychological impact. These patients frequently became withdrawn and unresponsive which necessitated the invitation of mental health specialists (1). The recent advancement in the management of HIV/AIDS has transformed it from an invariably fatal disease to a manageable chronic medical condition allowing sufferers to live longer.

Mental health issues significantly influence the presentation, treatment and outcome of many chronic medical conditions including HIV/AIDS (2). The burden of a mental health problem in the presence of another chronic medical condition is enormous; it creates a barrier to care, impedes adherence to treatment and increases healthcare utilization (3). Mental health issues have consistently been reported as prevalent in HIV/AIDS since it was first recognized (4).

The relationship between HIV/AIDS and mental health is complex; with mental health issues occurring both as the consequences of and a predisposition to the infection. The psychological and behavioural issues associated with HIV/AIDS can be broadly categorized into two types. The first group may result from the direct effect of the virus on the brain, or the secondary effect of opportunistic infections related to AIDS or an adverse effect of antiretroviral drugs. These are usually referred to as Neuropsychiatric disorders; an example in this category is the AIDS-dementia complex. The second group usually results from the psychosocial consequences of the infection. The diagnosis of HIV infection results in significant psychological distress in many individuals (5). Many individuals experience some form of emotional distress from the time they consider going for HIV testing (6, 7) because of the implication of having a positive test result. The diagnosis of HIV or AIDS comes with serious implications like discrimination and stigmatization (8, 9) as well as a possibility of a fatal outcome. Psychological issues may arise from the burden of having a chronic disease, experiencing HIV-related bereavement, a deteriorating health condition and social difficulties.

People with mental disorders have a higher risk of contracting HIV infection than the general population (10, 11). Conversely, some HIV vulnerable groups like injection drug users (IDU), homosexuals and sex workers are known to have higher rates of psychiatric disorder than the general population. The seroprevalence of HIV among patients with mental disorders is significantly higher than that reported in the general population (12-14). Possible reasons adduced to this include engagement in high-risk sexual behaviours like; unprotected sex, having multiple sexual partners, sexual abuse, sex trading, inconsistent condom use and needle sharing in those with substance use disorders (15, 16).

Different studies across the world have reported a high rate of psychiatric morbidity among patients with HIV (3, 17-20). In a study by Bing et al. (2001) in the United States (US), about half of the respondents screened

positive for a psychiatric disorder (21). In India, 49% screened positive compared with only 9% among healthy controls using the General Health Questionnaire (GHQ) (18). Adewuya et al. (2007) in Nigeria reported a prevalence of 59.1% of psychiatric disorders among HIV-positive individuals compared with 19.5% among the HIV-negative control (20). Commonly reported disorders among the population with HIV were mood disorders especially depression, anxiety disorders and alcohol and substance use disorders (22).

The advent of antiretroviral therapy (ART) revolutionized the management of HIV/AIDS with a significant reduction in morbidity and mortality (23). There has been a significant reduction in the incidence of some neuropsychiatric disorders associated with HIV like AIDS dementia complex since ART was introduced (24, 25). The improvement in HIV care following the introduction of ART has however not been associated with a reduction in a certain aspect of psychiatric morbidity especially those resulting from the indirect effect of the infection viz-a-viz the psychosocial sequel of HIV infection (24, 26, 27).

Despite the high prevalence and burden of mental health issues in HIV infection, recognition and treatment are still largely suboptimal especially in sub-Saharan Africa where the burden of HIV is concentrated.

Mental Disorders associated with HIV/AIDS

Depressive disorders

Depressive illness has been consistently reported as the most common mental disorder in people living with HIV/AIDS (PLWHA) in the high- and low-income countries of the world (20, 21, 28). It is characterized by undue sadness, reduced energy, loss of interest, sleep abnormalities, suicidal ideation, poor concentration, appetite changes, ideas of guilt, ideas of self-harm, and reduced self-esteem. Depression is associated with poor treatment adherence (29-31), faster disease progression, poorer quality of life and increased morbidity and mortality in PLWHA (32, 33).

Despite the burden associated with depression in HIV and the availability of effective treatment, diagnosing depression in PLWHA could be difficult. This is because the somatic symptoms of depression which include appetite changes, reduced energy, etc., sometimes overlap symptoms of HIV/AIDS. Moreover, patients hardly disclose affective,

cognitive and behavioural symptoms because they were unaware they could be due to a treatable psychiatric disorder (5).

Alcohol and Substance use disorders

Psychoactive substance use problems are highly associated with HIV/AIDS, either as a risk factor for the infection or an aftermath of it. Substance use problems are a major risk for the spread of HIV (34). Hazardous drinking and substance use disorders are common among PLWHA (21, 35). Any form of substance use disorder predisposes an individual to a greater risk of contracting or transmitting HIV infection (36). Individuals with HIV/AIDS who have substance use disorders are more likely to engage in HIV risky behaviours thereby increasing the risk of infecting others with HIV. The likelihood of an HIV-positive person abusing a psychoactive substance is substantially high; as such individuals find solace in drugs to combat the negative emotions experienced following the diagnosis (37).

In a large representative sample of PLWHA in the United States, nearly half of the sample reported using an illicit drug in the preceding 12 months. Twenty-five per cent reported the use of an illicit drug other than marijuana while 12% had drug dependence. Factors independently associated with drug dependence in this study were younger age group and not living with a spouse (21). HIV persons who are heavy alcohol drinkers are more likely to have other psychiatric disorders than those who do not use alcohol (21). Alcohol use is an important predictor for non-adherence to HAART (38). Rosenberg et al. (2001) identified substance use as one of the major correlates of HIV/AIDS risk behaviour in individuals with severe mental illness (39).

Anxiety disorders

Anxiety disorders have been found to be a common co-morbidity of HIV/AIDS. Different types of anxiety disorders that have been reported among PLWHA include generalized anxiety disorder, panic attack, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder and post-traumatic stress disorder. Els et al. (1999) in South Africa found panic disorder to be the commonest anxiety disorder among a sample of 100 clinic patients, followed by generalized anxiety disorder while the least was obsessive-compulsive disorder (40). Contrary to predominant panic disorder in the South African study, generalized

anxiety disorder was more prevalent in a study by Bing et al. (2001) in the United States (21).

Psychotic disorders

Symptoms of psychosis are delusions, hallucinations and disorganized behaviour. Psychotic disorders are severe but uncommon. Prevalence of new onset psychosis in patients with HIV varies depending on the stage of the disease (41). Psychotic symptoms could also arise from organic causes like delirium, a side effect of antiretroviral medications, opportunistic infections and cerebral neoplasm (41, 42). Lower doses of antipsychotic medication are recommended in HIV infection because PLWHA are often sensitive to the side effects of these drugs (41, 43).

Suicidality in the patient with HIV

A significant suicidal risk is associated with HIV/AIDS (44). Schlebusch and Govender (2015) reported an elevated suicidal risk in HIV seropositive patients 6 weeks after Voluntary Counselling and Testing (VCT) compared with their risk 72 hours after diagnosis (45). The level of risk according to different reports depends on the sociodemographic, psychological and illness factors. Sociodemographic variables with a significant association with greater suicidal ideation were; female gender, unemployment and low educational level (46-48). Psychological correlates of suicidality include hopelessness and depression (47).

Adjustment disorder

Adjustment disorder is also a common diagnosis in individuals with the diagnosis of HIV/AIDS (4). Adjustment disorder is a diagnosis of exclusion. The diagnosis is made when an individual develops significant psychological and behavioural symptoms, following stressful life events that do not meet the diagnostic criteria for another psychiatric diagnosis.

HIV risk in patients with mental disorders

Studies have shown that patients with mental illness are more prone to high-risk behaviour that could lead to them acquiring or transmitting HIV. Evidence available is more in support of severe mental illness like schizophrenia (49). In a study conducted on outpatients with severe mental disorders in southwestern Nigeria, the prevalence of HIV high-risk

behaviour was 48%. (50). About 90.2% of the respondents had schizophrenia and related psychotic disorders while the rest had affective disorders (50). There are more conflicting reports for anxiety and depression which are more prevalent mental disorders among those infected with HIV. A meta-analysis conducted by Crepaz and Marks 2001 to examine the impact of depression and anxiety on high-risk sexual behaviour found little evidence to support the assertion (51).

Consequences of untreated mental disorders in HIV

Untreated mental disorder in individuals with HIV/AIDS is a barrier to the initiation of antiretroviral medications in those that are eligible (52). Poor adherence to antiretroviral drugs is common in PLWHA who have co-morbid mental health and substance-use problems (30, 53). Sub-optimal adherence is a public health problem as it is associated with increased viral load and the development of resistant strains of the virus. Furthermore, the presence of mental health problems is associated with poorer quality of life (54, 55).

Prompt recognition and treatment of mental disorders in patients with HIV/AIDS improve the outcome. However, mental health issues are poorly recognized in patients with HIV (28, 56). Reasons for poor detection may sometimes be related to the symptomatology of HIV which is sometimes similar to that of mental health disorders like depression; others may be related to the stigmatization of mental illness or the poor availability of mental health resources in low- and middle-income countries.

Management of mental health issues in HIV

One of the reasons that pre- and post-test counselling is recommended for HIV testing was the serious emotional and psychological consequences following the diagnosis (7). The World Health Organization (WHO) recommends that mental health care is integrated into the management of people living with AIDS (57). It is essential to screen patients with PLWHA for common mental health disorders because they hardly volunteer information concerning their mental state (27).

Mental health care has been integrated into HIV treatment in high-income countries because of the established association between mental health and HIV. Integration of mental health into HIV care in low- and middle-

income countries is hampered by several factors including poor health resources, stigmatization, poor funding, low prioritization of mental health, etc. (58, 59).

The outcome of proper management of mental health problems in HIV

Studies have established that treatment of mental health problems in patients with HIV improves the outcome. Yun et al. (2005) reported improvements in adherence to antiretroviral therapy among depressed HIV-infected patients who were treated with antidepressant medications compared to those who were not treated (60). Effective treatment for substance use and dependence resulted in decreased HIV risk behaviour, improved adherence to antiretroviral medication and a better outcome (61, 62).

References

1. Cohen MA, Gorman JM. *Comprehensive Textbook of AIDS Psychiatry*. Oxford University Press, 2008.
2. Blank MB, Himelhoch S, Walkup J, Eisenberg MM. Treatment Considerations for HIV-Infected Individuals with Severe Mental Illness. *Current HIV/AIDS Reports*. 2013; 10(4): 10.
3. Mijch A, Burgess P, Judd F, Grech P, Komiti A, Hoy J, et al. Increased health care utilization and increased antiretroviral use in HIV-infected individuals with mental health disorders. *HIV Medicine.* 2006; 7(4): 201-74.
4. Jacob KS, Eapen V, John JK, Jacob JT. Psychiatric Morbidity in HIV infected individuals. *Indian Journal of Medical Research*. 1991; 93: 62-6.
5. Andersen L, Kagee A, O'Cleirigh C, Safren S, Joska J. Understanding the experience and manifestation of depression in people living with HIV/AIDS in South Africa. *AIDS Care*. 2015; 27(1): 59-62.
6. Freeman M, Patel V, Collins PV, Bertolote J. Integrating mental health in global initiation for HIV/AIDS. *British Journal of Psychiatry.* 2005; 187(1): 1-3.
7. Carter DB. Societal Implications of AIDS and HIV Infection. *Marriage and Family Review*. 1989; 13: 1-2, 129-86.
8. Owolabi RS, Araoye MO, Osagbemi GK, Odeigah L, Ogundiran A, Hussain NA. Assessment of stigma and discrimination experienced by people living with HIV and AIDS receiving care/treatment in

University of Ilorin Teaching Hospital (UITH), Ilorin, Nigeria. *Journal of the International Association of Physicians in AIDS Care (Chic).* 2012; 11(2): 121-7.

9. Dahlui M, Azahar N, Bulgiba A, Zaki R, Oche OM, Adekunjo FO, et al. HIV/AIDS-Related Stigma and Discrimination against PLWHA in Nigerian Populations. *PLoS One.* 2015; 10(12): e0143749.
10. Cournos F, McKinnon K. HIV seroprevalence among people with severe mental illness in the United States: a critical review. *Clinical Psychology Review*. 1997; 17(3): 259-69.
11. Blank MB, Mandell DS, Aiken L, Hadley TR. Co-occurrence of HIV and serious mental illness among Medicaid recipients. *Psychiatric Services*. 2002; 53(7): 868-73.
12. Carey MP, Weinhardt LS, Carey KB. Prevalence of infection with HIV among the seriously mentally ill: Review of research and implications for practices. *Professional Psychology: Research and Practice.* 1995; 26: 262-8.
13. Steele FR. A moving target: CDC still trying to estimate HIV-1 prevalence. *Journal of HIV Research.* 1994; 6: 25-6.
14. Silberstein C, Galanter M, Marmor M, Lifshultz H, Krasinski K, Franco H. HIV-1 among inner city dually diagnosed inpatients. *American Journal of Drug and Alcohol Abuse*. 1994; 20: 101-13.
15. McKinnon K, Cournos F, Herman R. HIV among people with chronic mental illness. *Psychiatry Quarterly*. 2002; 73: 17-31.
16. Meade CS, Sikkema KJ. HIV risk behaviour among adults with severe mental illness: a systematic review. *Clinical Psychology Review*. 2005; 25: 433-57.
17. Brian W, William CM, Kathryn W, Bradley G. Prevalence of DSM-IV defined Mood, Anxiety and Substance use disorder in an HIV clinic in the Southeastern United State. *Journal of Acquired Immune Deficiency Syndromes*. 2006; 42: 298-306.
18. Chauhan VS, Chaudhury S, Sudarsanan S, Srivastava K. Psychiatric morbidity in asymptomatic human immunodeficiency virus patients. *Industrial Psychiatry Journal*. 2013; 22(2): 125-30.
19. Lyketsos CG, Hutton H, Fishman M, Schwartz J, Treisman GJ. Psychiatric morbidity on entry to an HIV primary care clinic. *AIDS.* 1996; 10: 1033-9. *AIDS Care*. 1996; 10: 1033-9.
20. Adewuya AO, Afolabi MO, Ola BA, Ogundele OA, Ajibare AO, Oladipo BF. Psychiatric disorders among the HIV-positive population in Nigeria: a control study. *Journal of Psychosomatic Research*. 2007; 63(2): 203-6.

21. Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*. 2001; 58(8): 721-8.
22. Das S, Leibowitz GS. Mental health needs of people living with HV/AIDS in India: a literature review. *AIDS Care*. 2011; 23(4): 417-25.
23. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced Human Immunodeficiency Virus infections. *New England Journal of Medicine*. 1998; 338: 853-60.
24. Zirulnik JL, Perez HM. HIV psychiatry in the era of combined antiretroviral therapy: top five issues. *Journal of the International AIDS Society*. 2015; 18: 20725.
25. Maschke M, Kastrup O, Esser S, Hengge U, Hufnagel A. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART)s. *Journal of Neurology, Neurosurgery and Psychiatry*. 2000; 69(3): 376-80.
26. Siegel K, Daniel Karus D, Dean L. Psychosocial Characteristics of New York City HIV-Infected Women Before and After the Advent of HAART. *American Journal of Public Health.* 2004; 94(7): 1127-32.
27. Jonsson G, Davies N, Freeman C, Joska J, Pahad S, Thom R, et al. Guideline Management of mental health disorders in HIV-positive patients by the Southern African HIV Clinicians Society. *South African Medical Journal of HIV Medicine*. 2013; 14(4): 155-65.
28. Sulyman D, Abiodun OA, Yussuf AD. Detection of Psychiatric disorders by physicians attending to people living with HIV/AIDS (PLWHA) in a Nigerian University Teaching Hospital. *Journal of Biology, Agriculture and Healthcare*. 2013; 3(15): 92-6.
29. Gonzalez JS BA, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. *Journal of Acquired Immune Deficiency Syndromes*. 2011; 58(2): 181-7.
30. Ammassari A, Antinori A, Aloisi MS, Trotta MP, Murri R, Bartoli L, et al. Depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy among HIV-infected persons. *Psychosomatics*. 2004; 5: 394-402.
31. Starace F, Ammassari A, Trotta MP, Murri R, DeLongis P, Izzo C, et al. Depression is a risk factor for suboptimal adherence to highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*. 2002; 31(3): 136-9.

32. Ickovics JR, Hamburger ME, Vlahov D, Schoenbaum EE, Schuman P, Boland RJ, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women. *Journal of American Medical Association*. 2001; 285: 1466-74.
33. Leserman J. Role of depression, stress, and trauma in HIV disease progression. *Psychosomatic Medicine*. 2008; 70(5): 539-45.
34. Zhao M, Ling W. HIV/AIDS and drug use in China – Interactions, impacts, and issues. *Substance Use and Misuse.* 2012; 47: 1015-25.
35. Conigliaro J, Justice AC, Gordon AJ, Bryant K. Role of alcohol in determining human immuno-deficiency virus (HIV)-relevant outcomes: A conceptual model to guide the implementation of evidence-based interventions into practice. *Medical Care.* 2006; 44(8): 1-6.
36. Klinkenberg WD, Sacks S. HIV/AIDS Treatment Adherence, Health Outcomes and Cost Study Group. Mental disorders and drug abuse in persons living with HIV/AIDS. *AIDS Care*. 2004; 16(1): 22-42.
37. Garey L, Bakhshaie J, Sharp C, Neighbors C, Zvolensky MJ, Gonzalez A. Anxiety, depression, and HIV symptoms among persons living with HIV/AIDS: the role of hazardous drinking. *AIDS Care*. 2015; 27(1): 80-5.
38. Venkatesh KK, Srikrishnan AK, Mayer KH, Kumarasamy N, Raminani, Thamburaj E, et al. Predictors of Nonadherence to Highly Active Antiretroviral Therapy Among HIV-Infected South Indians in Clinical Care: Implications for Developing Adherence Interventions in Resource-Limited Settings. *AIDS Patient Care and STDs*. 2010; 24(2): 795-803.
39. Rosenberg SD, Trumbetta SL, Mueser KT, Goodman LA, Osher FC, Vidaver RM, et al. Determinants of risk behavior for human immunodeficiency virus/acquired immunodeficiency syndrome in people with severe mental illness. *Comprehensive Psychiatry*. 2001; 42: 263-71.
40. Eis C, Boshoff W, Scott C, Strydom W, Joubert G, Elna van der Ryst. Psychiatric Co-morbidity in South African HIV/AIDS patients. *South African Medical Journal*. 1999; 89: 992-5.
41. Sewell DD. Schizophrenia and HIV. *Schizophrenia Bulletin*. 1996; 22(3): 465-73.
42. Foster R, Olajide D, Everall P. Antiretroviral therapy-induced psychosis: case report and brief review of the literatures. *HIV Medicine.* 2003; 4(2): 139-44.

43. Sewell DD, Jeste DV, McAdams LA, Bailey A, Harris MJ, Atkinson JH, et al. Neuroleptic Treatment of HIV-Associated Psychosis. *Neuropsychopharmacology*. 1994; 10(4): 223-9.
44. Sherr L, Lampe F, Fisher M, Arthur G, Anderson J, Zetler S, et al. Suicidal ideation in UK HIV clinic attenders. *AIDS* 2008; 22(13): 1651-8.
45. Schlebusch L, Govender RD. Elevated Risk of Suicidal Ideation in HIV-Positive Persons. *Depression Research and Treatment*. 2015; 2015: 1-6.
46. Kinyanda E, Hoskins S, Nakku J, Nawaz S, Patel V. The prevalence and characteristics of suicidality in HIV/AIDS as seen in an African population in Entebbe district, Uganda. *BioMed Central Psychiatry*. 2012; 12: 63.
47. Schlebusch L, Govender RD. Age, gender and suicidal ideation following voluntary HIV counseling and testing. *International Journal of Environmental Research and Public Health*. 2012; 9(2): 521-30.
48. Schlebusch L, Vawda N. HIV-infection as a self-reported risk factor for attempted suicide in South Africa. *African Journal of Psychiatry*. 2010; 13(4): 280-3.
49. Carey MP, Carey KB, Maisto SA, Gordon CM, Vanable PA. Prevalence and correlates of sexual activity and HIV-related risk behavior among psychiatric outpatients. *Journal of Consulting and Clinical Psychology*. 2001; 69(5): 846-50.
50. Abayomi O, Adelufosi A, Adebayo P, Ighoroje M, Ajogbon D, Ogunwale A. HIV risk behavior in persons with severe mental disorders in a psychiatric hospital in Ogun, Nigeria. *Annals of Medical and Health Sciences Research*. 2013; 3(3): 380-4.
51. Crepaz N, Marks G. Are negative affective states associated with HIV sexual risk behaviors? A meta-analytic review. *Health Psychology*. 2001; 20: 291-9.
52. Tegger MK, Crane HM, Tapia KA, Uldall KK, Holte SE, Kitahata MM. The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals. *AIDS Patient Care and STDs*. 2008; 22(3): 233-43.
53. Ingersoll K. The impact of psychiatric symptoms drug use and medication regimen on non-adherence to HIV treatment. *AIDS Care*. 2004; 16(2): 199-211.
54. Yang MH, Chen YM, Kuo BIT, Wang KY. Quality of life and related factors for people living with HIV/AIDS in Northern Taiwan. *Journal of Research in Nursing*. 2003; 11: 217-26.

55. Tostes MA, Chalub M, Botega NJ. The quality of life of HIV-infected women is associated with psychiatric morbidity. *AIDS Care*. 2004; 16: 177-86.
56. Gallego L, Barreiro P, López-Ibor JJ. Diagnosis and clinical features of major neuropsychiatric disorders in HIV infection. *AIDS Review*. 2011; 13: 171-9.
57. World Health Organization Psychosocial Support [database on the Internet] 2005 [cited 25th March, 2015]. Available from: http://www.who.int/hiv/topics/psychosocial/support/en/print.html.
58. Marais DL, Petersen I. Health system governance to support integrated mental health care in South Africa: Challenges and opportunities. *International Journal of Mental Health Systems*. 2015; 9: 14.
59. Collins PY, Holman AR, Freeman MC, Patel V. What is the relevance of mental health to HIV/AIDS care and treatment programs in developing countries? A systematic review *AIDS*. 2006; 20(12): 1571-82.
60. Yun LWH, Maravi M, Kobayashi JS, Barton PL, Davidson AJ. Antidepressant treatment improves adherence to antiretroviral therapy among depressed HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 38: 432-8.
61. Berg KM, Mouriz J, Li X, Duggan E, Goldberg U, Arnsten JH. Rationale, design, and sample characteristics of a randomized controlled trial of directly observed antiretroviral therapy delivered in methadone clinics. *Contemporary Clinical Trials*. 2009; 30(5): 481-9.
62. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine*. 2000; 343: 1290-7.

COUNSELLING IN HIV/AIDS

SUNDAY O OLAREWAJU
AND OLUWAPELUMI D ADEYERA

Good counselling assists people to make informed decisions and cope better with their health conditions, helps clients to identify potential solutions to problems which can cause emotional turmoil, strengthens self-esteem, promotes behavioural change and optimal mental health, and helps them to lead more positive lives as well as prevent further transmission of HIV. In order to achieve this objective, health care workers involved in the provision of HIV/AIDS counselling to clients within or outside health facilities must be equipped with information on the 3Cs Principles of Counselling and Testing – Counselling, Confidentiality and Consent – to be observed, the procedures to be followed during pre-test and post-test counselling to prepare the patient or client for any type of result, whether negative or positive, the different models through which HIV counselling and testing are delivered as well as the challenges encountered in the delivery of an effective counselling and testing session. The facts are outlined in different sub-sections of this chapter (Counselling in HIV Settings, 3Cs Principles of Counselling and Testing, and Ethical Principles and Barriers to Effective Counselling and Testing), hoping that such information will be useful in reducing the transmission of the infection through standard HIV counselling and testing practice.

Counselling is a confusing term with a different meaning for different people. According to the *Concise Oxford Dictionary*, it is the process of assisting and guiding clients especially by a trained person on a professional basis to resolve personal, social or psychological problems or difficulties (1).

Counselling can only be viewed as a confidential dialogue between a counsellor and a client(s) aimed at helping the client cope with a difficult situation through informed decision-making. It helps clients identify potential solutions to problems which cause emotional turmoil, improve communication and coping skills, strengthen self-esteem and promote

behavioural change and optimal mental health. Counselling is not about giving advice or having a conversation. It is not information giving or a search for diagnosis.

The following steps are involved in counselling processes:

1. Identification and an appropriate response to feelings, thoughts and actions or behaviours and relationships;
2. Acceptance of the client's perceptions and feelings;
3. Confidentiality and privacy;
4. Being voluntary;
5. Avoidance of self-disclosure;
6. Communication.

It is different from advice because it focuses on the client's feelings and helps the client figure out what to do while the counsellor spends more time with the client. In addition, it is different from health education because it is a two-way interaction between a client/counsellee and a counsellor while health education is usually a one-way process. However, in health education, accurate information about a subject matter is provided to a person or a group of people to make them more knowledgeable about the subject, so that they can make informed choices while in counselling, the counsellor works together with the counsellee to find solutions that are appropriate to their situation. This is thus helping clients to gain confidence in their ability to make decisions and to find solutions to their problems. Counselling is guided by the principles of confidentiality, acceptance and individualism, as well as non-judgment, self-determination**,** controlled emotional involvement, and purposeful expression of feelings.

Counselling in HIV/AIDS Settings

HIV counselling and testing are an integral part of HIV/AIDS. Without HIV counselling and testing, diagnosing HIV may not be possible except when an individual comes down with some of the known symptoms of the disease. Notwithstanding, counselling helps a patient cope with the possible outcome of the HIV test and make informed decisions as well as evaluate their behaviour and its consequences. For instance, a negative test result offers an opportunity to reinforce the importance of safe and risk-reducing behaviour while those with a positive result are referred to other

centres where they can access treatment and other supportive services necessary for survival and development.

The goals of counselling and testing in an HIV setting are as follows:

- Prevention of HIV transmission
  - From a +ve tested person to a -ve or untested partner/s;
  - From a +ve tested pregnant woman to a child;
  - From a +ve or untested partner/s to -ve tested persons.
- Early uptake of services
  - Counselling for positive living;
  - Social support;
  - Legal advice;
  - Future planning;
  - Medical care;
  - Family planning;
  - Emotional care.
- Societal benefits
  - Reduction of stigma;
  - Promote awareness;
  - Support human rights.
- Increase adherence to
  - ARV therapy;
  - Preventive services;
  - ARV regimens for PMTCT;
  - Infant feeding options.

3CSPrinciples, HIV Counselling and Testing Procedures

The 3Cs principles to be observed in all types of counselling and testing entail Counselling, Confidentiality and Consent. The counselling and testing procedure entails three distinct components namely pre-test counselling, testing and post-test counselling.

Pre-test counselling, done before blood is taken for the HIV test, is meant to prepare the individual for the test and assess the risk level to HIV virus that the person possesses. It also helps one to anticipate the result, whether it turns out to be HIV positive or negative (2).

The following steps are involved while carrying out pre-test counselling.

Step 1: The first step entails introducing the clients to the process of HIV counselling and testing by a trained counsellor, with special emphasis on the confidentiality of the test result to make the client feel comfortable with the procedure.

Step 2: In the second step, the counsellor obtains information on the client's personal characteristics, personal habits/risk such as smoking or drug use and other relevant medical and testing history (past and present) which is entered into the HIV client intake Register.

Step 3: Here, an individual risk assessment and risk reduction and the client's knowledge**,** misconceptions and misunderstandings on issues related to HIV/AIDS are addressed. In addition, risky behaviour such as sexual history (issues related to a steady partner, a husband/wife, a boyfriend/girlfriend, other partners, condom use, etc.), as well as the history of past illnesses, previous blood transfusion, sexually transmitted infections, etc., are explored and strategies for reducing the risk are discussed.

Also, clients are assessed on their understanding concerning the test, whether positive or negative, its personal implications and its meaning.

Education is provided by the counsellor on safer sex practices (including a condom demonstration when appropriate) and healthy lifestyle practices.

Step 4: The benefits of HIV testing, the duration of the test, the meaning of positive and negative results, and the concept of the window period are explained by the counsellor to clients at this stage.

Step 5: At stage 5, the counsellor helps the client to consider his/her options in terms of acceptance of the decision to carry out the HIV test. The counsellor also encourages his/her clients to discuss HIV testing with their partner and to encourage the partner to come for counselling and testing with him/her.

Step 6: Here, informed consent is explained and obtained and other supportive measures are identified. An arrangement is made between the counsellor and the client on when to come in for post-counselling sessions.

The second component is the taking of the blood sample and the test by using rapid test kits. According to the HIV testing algorithm, reagents are

used and the testing is done in series, i.e., one test before another. The reagents used according to the national guideline are Determine for screening, Unigold for confirmation and Stat Pack as the tiebreaker. Individuals who are non-reactive to the Determine reagent are said to have a negative result and are asked to come back in 3 months' time to exclude the window period. On the other hand, individuals who are reactive to Determine are further tested with Unigold to confirm their positivity. Candidates with a discordant result, i.e., reactive to Determine and non-reactive to Unigold, are subjected to further testing with the tiebreaker reagent i.e., Stat Pack which gives the final accurate result. The last component is post-test counselling which involves disclosure of the result, counselling and referrals, depending on the outcome. It has two major components depending on whether the result is positive or negative.

Ethical Principles in Counselling and Testing

Counselling in HIV requires that the ethical requirements are followed and adhered to (3). The ethical principles in HIV counselling follow the ethical principles in counselling:

- Autonomy: This follows the respect for a person's freedom to make his or her own decisions. Individuals are free to choose their own way and their self-determination must be respected. In HIV counselling, the choice of the client must be respected by all means as clients are believed to have the ability to make their own decisions after they are given enough information (4, 5).
- Informed consent: Informed consent in HIV counselling follows the principle of respect for autonomy. Obtaining informed consent from the client cannot be over-emphasized. It forms the basis for "voluntary counselling and testing" bearing the "voluntary" component of the service. Beyond ethics, informed consent is a legal concept making it a vital component. The client must be capable of understanding risks and benefits, must be competent, able to make decisions on their own and be free of coercion or force. The provider must also provide all the necessary information for the client to make an informed decision and he or she is free to persuade, however, the client must not be pressurized (5-7).
- Confidentiality: This is a legal obligation as much as it is a legal concept. The information between the provider and the client should be kept confidential by all means. The client should be informed that confidentiality will be kept in order to build trust. It

enables the client to open up and also to access the service knowing that their information will be kept confidential. Furthermore, unless stated otherwise by the client, it is not apt for the provider to disclose the results of HIV testing to a third party (8-10).

- Beneficence and non-maleficence: Beneficence means to do good, be equal, proactive and in general do things that will benefit the client. Non-maleficence means to "do no harm", that is not to intentionally inflict harm or do things that could put the patient at risk. This is important in HIV counselling as the client should not be at risk or in harm's way for accessing the service (5,11).
- Justice: This implies fairness and equity and not equality. This is not treating all individuals in the same way, rather, it is treating each according to their peculiarities (5, 11).

While the above are the underlying principles for HIV counselling, there are exceptions to these principles. Furthermore, in some instances, an ethical dilemma occurs where there are two or more contending courses of action for the provider. When the provider chooses the course of action in an ethical dilemma, the ethical principles supporting the contending courses of action are thereby compromised (12).

The principle of confidentiality has been found to contend with the principle of beneficence and non-maleficence in HIV counselling (13). This is such an instance where providers have to choose between keeping their patient's confidentiality thereby causing harm to the partner who is at risk or "doing no harm" to the partner, therefore, breaching the confidentiality of the patient (13). There is no clear-cut solution in solving an ethical dilemma (13). Some professionals use rational justification to evaluate the pros and cons of choosing one ethical principle over another while some make decisions based on their personal characteristics and moral beliefs. An integrated model to address an ethical dilemma was later proposed by making use of the morals, beliefs, experiences, and characteristics of the professional including the rational evaluation of each principle (12). A provider/counsellor has to take reasonable precautions, conduct a critical evaluation, and seek consultation in choosing a course of action as each situation has its own peculiarities (13).

Barriers to effective HIV Counselling and Testing

HIV counselling and testing are a way of effectively controlling HIV infection. They involve pre-counselling in order to help clients assess their

risk and determine whether or not to take the test; testing which involves the analysis of blood and body fluids for antigens to the infection; and post-counselling which helps and supports clients when they receive their results (12). Despite the ability of HCT services to control the infection, their uptake is still low in Nigeria (14, 15).

Some of these barriers hindering people from accessing HCT include:

- Personal factors like perceived invulnerability, lack of time, lower educational status, partner disapproval, denial, lack of the perceived benefit of testing, and fear (16-22).
- System factors: limited access to HCT, cost, proximity, an inconvenient operating period, and poor staff attitude (16, 17, 23, 24).
- Societal factors: gender inequality, stigmatization, myths and misconception, and the cultural norm of silence (16, 17, 25).

While accessing the HCT service, there are factors that can also impinge on the counselling process, some of which are:

- Personnel factors:
  - There is a lack of trained staff (17).
  - Counsellors also have other roles in the health facility, therefore, they are swamped with work leaving little time for counselling duties. Counselling sessions are therefore not conducted or conducted hurriedly leaving the clients with inadequate information (17).
  - Emotional exhaustion or burnout for counsellors following a heavy workload (17).
  - The inability of providers to openly discuss all sexual and reproductive health issues (25)
  - Staff behaviour: some providers stigmatize, embarrass, isolate, judge and ignore clients (25).
  - Difficulty in following up (26).
- Facility setting: There can be a lack of privacy in the discussion setting, distractions during sessions (17), a lack of infrastructure and laboratory materials, a lack of funding, and a lack of policies prioritizing counselling (17).
- Individual factor: An inability for the client to relax and open up during the discussion, and not showing up for regular sessions (26).

Cultural beliefs and HIV

People's beliefs and culture cannot be separated from their health. The social patterns, norms and beliefs affect the way people experience illnesses and how they manage them. Culture impacts so much on health and health systems and HIV/AIDS is not an exception. In Nigeria for instance, there are some cultural practices and beliefs which influence HIV/AIDS. Some cultural beliefs could enhance the spread of the virus while others may inhibit its spread. Polygamy, female genital mutilation, widowhood inheritance, circumcision, and early marriage are some cultural beliefs which enhance the spread of HIV/AIDS. However, a high premium placed on virginity in Nigerian culture helps to inhibit the spread of HIV/AIDS through sexual transmission. Gender inequality as a cultural influence has been argued to either inhibit or fuel the spread of the virus. The restrictions that come with gender inequality limit the exposure of women and limit promiscuity while the lack of power and autonomy associated with gender inequality leads to women being exploited (27, 28).

References

1. Counseling. https://www.skillsyouneed.com/learn/counselling.html.
2. NACA. HIV counseling and testing. http://naca.gov.ng/hct-hiv-counseling-and-testing/.
3. Elsabe K. HIV legal and ethical issues. *South African J HIV Med*. 2003; 2: 25-28.
4. Laar AK, DeBruin DA, Craddock S. Partner notification in the context of HIV: An interest-analysis. *AIDS Res Ther*. 2015; 12(1): 1-8. doi:10.1186/s12981-015-0057-8.
5. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics.* New York, USA: Oxford University Press, 1994.
6. Atwell BL. The modern age of informed consent. *U Rich L Rev*. 2006; 40: 591.
7. Hanssens C. Legal and Ethical Implications of Opt-out HIV Testing. *Clin Infect Dis*. 2007; 45(Supplement 4): S232-S239. doi:10.1086/522543.
8. Canadian HIV/AIDS Legal Network. Counselling in the context of the criminalization of HIV:1-2. www.aidslaw.ca/community-kit.
9. Hong Kong Advisory Council on AIDS. *Principles of Consent , Discussion and Confidentiality Required of the Diagnostic HIV Test,* 2011.
10. Ministry of Health and Social Welfare TUR of T. *HIV and AIDS*

Voluntary Counselling and Testing Module8: Counselling Skills, Ethical Codes and Supervision of Counselling Practice, 2008.
11. Davis T, Forester-Miller H. *Practitioner's Guide to Ethical Decision Making*, 2016.
12. Garcia JG, Forrester LE, Jacob AV. Ethical dilemma resolution in HIV/AIDS counseling: Why an integrative model? *Int J Rehabil Heal*. 1998; 4(3): 167-181. doi:http://dx.doi.org/10.1023/A:1022906713575.
13. Secker MJ, Wood N. HIV/AIDS-related Ethical Dilemma of Confidentiality. *Grad Student J Psychol*. 2009; 11: 52-58.
14. Federal Ministry of Health. National human immunodeficiency virus and acquired immunodeficiency syndrome and Reproductive Health Survey 2012 (plus II): Human immunodeficiency virus Testing. *J HIV Hum Reprod*. 2014; 2(1): 15. doi:10.4103/2321-9157.135744.
15. Ijadunola KT, Abiona TC, Odu OO, Ijadunola MY. College students in Nigeria underestimate their risk of contracting HIV/AIDS infection. *Eur J Contracept Reprod Heal Care*. 2007; 12: 131-137.
16. Amu EO, Ijadunola KT, Bamidele JO, Odu OO. Barriers to and determinants of HIV counselling and testing among adults in Ayedaade Local Government Area, Osun State, Nigeria. *J Med Sci*. 2013; 13(8): 803-808. doi:10.3923/jms.2013.803.808.
17. UNAIDS. *Voluntary Counselling and Testing (VCT). UNAIDS Technical Update*, 2000.
18. Peralta L, Deeds BG, Hipszer S, Ghalib K. Barriers and Facilitators to Adolescent HIV Testing. *AIDS Patient Care STDS*. 2007; 21(6): 400-408. doi:10.1089/apc.2006.0112.
19. Musheke M, Ntalasha H, Gari S, et al. A systematic review of qualitative findings on factors enabling and deterring uptake of HIV testing in sub-Saharan Africa. *BMC Public Health*. 2013; 13(1): 220-226. doi:10.1186/1471-2458-13-220.
20. Daftary A, Padayatchi N, Padilla M. HIV testing and disclosure: a qualitative analysis of TB patients in South Africa. *AIDS Care*. 2007; 19(4): 572-577. doi:10.1080/09540120701203931.
21. Deblonde J, De Koker P, Hamers FF, Fontaine J, Luchters S, Temmerman M. Barriers to HIV testing in Europe: A systematic review. *Eur J Public Health*. 2010; 20(4): 422-432. doi:10.1093/eurpub/ckp231.
22. Choi K-H, Lui H, Guo Y, Han L, Mandel JS. Lack of HIV testing and awareness of HIV infection among men who have sex with men, Beijing, China. *AIDS Educ Prev*. 2006; 18(1): 33-43. doi:10.1521/aeap.2006.18.1.33.
23. Larsson EC, Thorson A, Nsabagasani X, Namusoko S, Popenoe R,

Ekström AM. Mistrust in marriage – Reasons why men do not accept couple HIV testing during antenatal care – A qualitative study in eastern Uganda. *BMC Public Health*. 2010; 10. doi:10.1186/1471-2458-10-769.

24. Morin SF, Khumalo-Sakutukwa G, Charlebois ED, et al. Removing barriers to knowing HIV status: Same-day mobile HIV testing in Zimbabwe. *J Acquir Immune Defic Syndr*. 2006; 41(2): 218-224. doi:10.1097/01.qai.0000179455.01068.ab.
25. National AIDS Control Programme National Institute of Health Islamabad, Joint UN Programme on HIV/AIDS (UNAIDS). *Counseling for HIV/AIDS*, 1994.
26. Fonchingong CC, Mbuagbo TO, Abong JT. Barriers to counselling support for HIV/AIDS patients in south-western Cameroon. *African J AIDS Res*. 2004; 3(2): 157-165. doi:10.2989/16085900409490330.
27. Udeh S, Emelumadu FO, Nwabueze SA, Echendu A, Ogbonna BO. Socio-Cultural Factors Influencing HIV/AIDS Prevalence in Nigeria ; A Review. *Elixir Bio Sci*. March 2016; 92: 39097-39103.
28. Kadiri KK, Kharie M, Prof A, Su C. HIV/AIDS and Cultural Practices in Nigeria : An Implication for HIV/AIDS Preventive Communication Campaign. *Issn*. 2014; 27: 3275. www.iiste.org.

PHARMACOLOGICAL TREATMENTS OF HIV/AIDS

WASIU OLALEKAN ADEBIMPE, FWACP, PHD
AND NAJEEMDEEN AJAO ADELEKE, FWACS

Pharmacological treatment had been the mainstay of managing People Living with HIV (PLHIV) in nearly four decades of the disease, which has defied any cure. The World Health Organization (WHO) from time to time releases the "Rapid Advice" documents to member countries for them to follow, adapt, or adopt in managing HIV as a disease and to inform policy decisions. Thus, antiretroviral drug (ARVs) treatment modalities have changed over time.

The goals of ARV are to reduce morbidity and prolong the life of PLHIV, to achieve a rapid and sustained suppression of the viral load, as well as to facilitate their ability to live positively and enjoy an improved quality of life. Since ARVs are not without side effects and toxicities are common, health care workers should become familiar with in-country guidelines on HIV management. This chapter provides an up-to-date modality for HIV treatment in developing countries as it affects different groups including adults, children, and pregnant women.

As the world commenced the "HIV Test and Start" approach in 2017, all HIV-positive clients commenced antiretroviral therapy (ART) immediately once they were diagnosed as HIV positive. This approach has numerous advantages including early viral suppression. At the same time, there are implications for ARV availability most especially in developing countries where ARV accessibility is largely donor dependent. This also applies to the 2016 recommendations that Antiretroviral Therapy (ART) should be given to all People Living with HIV, with the objectives of reducing the risk of disease progression and achieving appreciable viral suppression.

Nearly four decades since the first case of HIV was reported, the disease has defied a definitive cure. Pharmacological treatment had been the mainstay of managing PLHIV. In the year 2010 alone, about 700,000 lives were saved due to ART (1). HIV is a chronic illness and drug resistance is not desired, it is necessary to ensure that PLHIV adhere to the recommended treatments, and health care workers follow the in-country guidelines in client management. Drugs employed in the treatment of HIV infection are generally referred to as Anti Retro-Viral drugs (ARVs), and the process of treatment is called Antiretroviral Therapy (ART).

ARVs are usually used in drug combinations (multi-therapy) to cover the various mechanisms and points in HIV transmission. Antiretroviral combination therapy delivers better suppression of HIV replication; and significantly prevents the potentials of the resistance mutation genes and variants of the virus from developing (2).

Goals of ART

1. To reduce morbidity and prolong the lives of PLHIV: ARVs inhibit viral replication and lead to a significant boost in immunity, thereby preventing the occurrence of various morbidities associated with HIV infection as well as mortality from the disease.
2. To improve the coping ability of PLHIV, their ability to live positively and improve their quality of life: HIV-positive clients on ARVs may have the opportunity of improved immunity provided by the drug to live a normal life and cope with social functions and societal responsibilities.
3. To achieve rapid and sustained suppression of the viral load, and enhance immunity by increasing the CD4+ cell count: ARVs increase the CD4 cell count of clients, and the T-helper cell component of the white blood cells of clients leading to a boost in immunity.
4. To prevent the development of opportunistic and other susceptible infections: ARVs prevent the occurrence of infections which otherwise would not have occurred in the presence of a functional immune system. Tuberculosis remains the most common opportunistic infection (OI) associated with HIV (3).
5. Prevention of mother-to-child transmission (PMTCT) of HIV: ARVs prevent MTCT during any of the trimesters of pregnancy, childbirth, and the postnatal period when used either as treatments or as prophylaxis.

Mechanisms of action of ARVs

ARVs work by interrupting the mechanism of HIV replication and transmission at one stage or another. Full details of HIV replication are available in the earlier chapter of this book. The summary of the mechanisms related here is as follows:

1. At the binding site between the human CD4 cell and the virus: ARVs could prevent the fusion of these 2 entities. This prevents the subsequent release of the viral core into the cytoplasm of the host and inhibits viral replication at this stage. ARVs in this category operate under the mechanism of "Fusion inhibition"; and are called "Fusion Inhibitors."
2. At the point of synthesizing the reverse transcriptase enzyme: ARVs can inhibit the conversion or transcription of viral RNA into DNA. ARVs in this category operate under the mechanism of Reverse Transcriptase Inhibition, and are generally referred to as "Reverse Transcriptase Inhibitors."
3. Some ARVs inhibit viral replication by preventing viral attachment to the chemokine receptors (mainly CCR5 or CXCR4) on the T-cell surface. ARVs in this category operate under the mechanism of "Chemokine receptors antagonism."
4. At the point of producing the protease enzyme: ARVs have the ability of preventing HIV from being assembled and released from the infected CD4+ cells, thereby inhibiting the virus from further replication. ARVs in this category operate under the mechanism of "Protease inhibition"; and are referred to as "Protease Inhibitors."
5. At the point of transporting the double-stranded DNA into the nucleus of the host: ARVs can prevent the release of the "Integrase" enzyme and prevent subsequent viral integration into the chromosome of the host. ARVs in this category operate under the mechanism of "Integrase inhibition"; and are generally called "Integrase inhibitors."

Classes of ARVs

Based on the various mechanisms of action discussed earlier, ARVs can be classified into 5 broad categories:

1. Reverse Transcriptase Inhibitors (RTIs): there are 3 subgroups of this class of ARV depending on their glycoprotein molecule background. These include
   a. Nucleoside Reverse Transcriptase Inhibitors (NRTIs): common examples include Zidovudine (ZDV or AZT), Lamivudine (3TC), Emtricitabine (FTC), Abacavir (ABC) and Stavudine (d4T).
   b. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): common examples include Efavirenz (EFV) and Nevirapine (NVP).
   c. Nucleotide Reverse Transcriptase Inhibitors (NtRTIs): Tenofovir (TDF) is the most common example in this category.
2. Protease Inhibitors (PIs): examples include Lopinavir, Indinavir, Nelfinavir, Lopinavir+ ritonavir (LPV/r), and Ritonavir (RTV).
3. Fusion inhibitors: an example is Enfuvirtide (T-20).
4. Integrase inhibitors: common examples include Raltegravir, Elvitegravir and Dolutegravir.
5. CCR5 inhibitors: an example is Maraviroc.

Some ARVs were formulated by the pharmaceutical companies into "Fixed Dose Combinations" for ease of drug administration and oral consumption by clients. Such combinations reduce pill burden and increase adherence and effectiveness over the long-term (4). Common ARV combinations include:

a) 3TC/d4T/NVP ZDV/ABC/3TC
b) 3TC/NVP/ZDV
c) ZDV/3TC
d) 3TC/d4T

Historically, the Nucleoside Reverse Transcriptase Inhibitor called Zidovudine (ZDV or AZT) was the first effective drug against HIV, and it was approved by the US FDA in 1987. The use of a single drug therapy may not achieve steady viral suppression and patients may still inevitably die from the inability of these mono-therapies to effectively boost immunity (5).

When 3 or more ARV drugs from at least 2 different groups or classes of ARVs are combined, such a combination is called Highly Active Antiretroviral Therapy (HAART). Such combinations have been documented to cause a 60% to 80% decline in rates of deaths and hospitalizations related to AIDS (6). HAART is the standard drug

combination in the treatment of HIV towards effective viral suppression. In order for such combinations to halt disease progression, 2 NRTIs acting as a "backbone" and 1 NNRTI, or a PI acting as a "base" are desired (7).

Recommendations for HAART = 2NRTI+1NNRTI

Example is AZT+3TC+NVP

Table 1: Properties and side effects of common ARVs (NRTIs)

ARVs	PREPARATIONS	DOSING	PHARMACO-KINETICS	TOXICITY
ZDV AZT Retrovir*	10 mg/ml oral solution, 100 mg capsule, 300 mg tablet	Children: 180-240 mg/m2/dose bd to a max of 300 mg/dose Adult: 250-300 mg bd	Oral bioavailability 60%, no food effect	Bone marrow suppression Anaemia, lactic acidosis. Do not use with HB <7 g/dl. Cross reacts with d4T and should not be used together. Blue black discoloration of nails.
3TC Epivir*	10 mg/ml oral solution, 100 mg, 150 mg tablets	Children: 4 mg/kg/dose to a max of 150 mg/dose Adult: 150 mg bd or 300 mg od	Oral bioavailability 86%, no food effect. Renal excretion unchanged	Pancreatitis, liver toxicity, mild peripheral neuropathy. Discontinue with high serum amylase level
FTC Emtriva*	200 mg tablet	Adult: 200 mg od	Oral bioavailability 90%, no food effect. Renal excretion	Minimal toxicity and no drug interactions
d4T Zerit*	1 mg/ml oral powder 30 mg tablet	Children: 1 mg/kg/dose bd to a max of 430 mg/dose Adult: 30 mg bd	Oral bioavailability 86%, no food effect. Renal excretion 50%	Generally, no longer in use due to major toxicity. Peripheral neuropathy, lipodystrophy, metabolic

				syndrome, lactic acidosis, hepatitis, pancreatitis
ABC Ziagen*	20 mg/ml suspension 300 mg tablet	Children: 8 mg/kg/dose bd to a max of 200 mg/dose Adult: 300 mg bd or 600 mg od	Oral bioavailability 83%, no food effect but alcohol increases its level by 41%. Renal excretion of metabolites 82%	Hypersensitivity reactions

*Trade name

Table 2: Properties and side effects of common ARVs (NNRTIs, NtRTIs, PIs)

TDF Viread*	300 mg tablet	Adult: 300 mg od	Oral bioavailability 25-39%, levels increase 40% with fatty meal, renal excretion, minimal toxicity
EFV Sustiva*	30 mg/ml syrup 200 mg capsule 600 mg capsule	Children:19.5 mg/kg/day syrup Adult: 600 mg od (800 mg od) when combined with Rifampicin in clients >60 kg	Oral bioavailability 42%, avoid high fat meals. It is metabolized by Cytochrome P450, 14-34% excreted in the urine
NVP Viramune*	10 mg/ml solution 200 mg tablet	Children: 120 mg/m^2 od for 2 weeks, increased to a max of 120-200 mg/m^2 bd to a max of 200/mg/dose Adult: 200 mg od for 1st 2 weeks, then increase to bd dose	Oral bioavailability >90%, no food effect. It is metabolized by Cytochrome P450, 80% was excreted in the urine

LPV/r Kaletra*	200 mg LPV/50 mg r	Adult: 400 mg LPV/100 mg r bd	Bioavailability not determined, fat increases its AUC by 50-80%, take with food. It is metabolized by Cytochrome P450

*Trade name

Pre-ART evaluations

Before HIV-positive clients commence the use of ARVs, it is important that certain information is obtained from the client and his or her case notes, and that the health care worker ascertains the readiness of the client to adhere to the prescribed drugs. There are basically two categories of pre-evaluation exercises to be carried out before commencing ARVs: (a) an initial clinical and laboratory evaluation; and (b) an adherence evaluation.

Initial clinical and laboratory evaluation

1. Correct HIV diagnosis: It is essential for the health care worker to ensure that the client was truly diagnosed HIV positive using the country's guidelines.
2. The WHO clinical staging: to ensure eligibility for ART.
3. CD4 cell count: to also ensure eligibility for ART.
4. Viral load level: to assess the current level in the system of the client.
5. Clinical evaluation to exclude renal and cardiovascular diseases, pregnancy, anaemia, HBV, TB, Sexually Transmitted Infections, previous ARV use, tobacco and alcohol use, etc.
6. ART eligibility: according to the country's guidelines.
7. Initial laboratory evaluation: haematological, blood chemistry, renal function test, liver function test, etc., as may be applicable.
8. The presence of opportunistic infections most especially TB.
9. The presence of co-existing diseases.
10. The need for prompt referrals for other health services that may not be available within the health care setting.

ARV adherence

Adherence is a term used to describe the patient's behaviour in taking the right drugs at the right dose at the right time and at the right frequency, all based on a mutual agreement between the client and the health care provider. Adherence scores >95% are necessary in order to maximize the benefits of ART. Adherence is mandatory before the commencement of ART and throughout the treatment process. Based on the daily dose regimen, it is usually calculated as the number of doses of drugs taken as a percentage of the total number of doses prescribed, e.g., taking 9 out of 10 prescribed doses = 90% adherence. Thus it is important that the health care worker conducts adherence counselling sessions (about 3 times) for clients as indicated. Self-reported adherence is not always reliable, thus the health care worker may have to rely on other indices such as the calculated adherence percentage, the pill count as well as the pharmacy pick up records to ensure that the client comes on every clinic day and eventually takes his drugs holistically. It is mandatory to consider adherence counselling sessions in the following circumstances:

- During HIV education, counselling and testing services (HTS);
- When discussing the benefits and risks associated with ART;
- When assessing the readiness of patients before commencing ARVs;
- When discussing how to identify and ameliorate the factors that might interfere with successful treatment adherence;
- Referral services;
- Shared decision-making: during adherence counselling, a client should be allowed to open their mind and make the final decision to commence ART (8). Such a decision would encourage an adherence level that would delay or avoid drug resistance, even achieve an undetectable viral load level (9).

The inability of patients to adhere to ART may be due to some barriers such as communication difficulties between the client and the health care providers, language or literacy barriers, unstable living situations (including limited or absent social support), discomfort associated with the disclosure of HIV status, and inadequate knowledge about HIV. It is however important that the health care worker makes efforts to address the general concerns of the clients about ARVs. Some of these concerns include non-toleration of the drugs due to serious side effects, low blood levels of ARVs which could foster drug resistance (10), the development

of multi-drug resistant strains which can be passed onto others (11), and the high cost of ARVs (12). Even in developing countries where ARVs are donor dependent, the indirect cost could be high for clients with low socio-economic status.

ARV adherence counselling should be a continuous exercise for all clients on ARVs to ensure that the right numbers of the right drugs are taken at the right dose and at the right time.

ARV treatments

ART is perhaps the single most important accomplishment in the management of HIV infections since the illness has no cure. Claims of an HIV cure by some scientists and traditional health systems in some countries are not yet proven. There are numerous benefits of Antiretroviral Therapy, and these include:

- The restoration of the immune function;
- The preservation of the immune system;
- Overall improvement of the health of the PLHIV;
- The suppression of viral replication;
- A decrease in the risk of mother-to-child transmission.

Pharmacological treatments using ARVs must follow the country's national guidelines. From time to time, the WHO releases the "Rapid Advice" documents to member countries for them to follow, adapt, or adopt in managing HIV as a disease and to inform policy decisions. It is expected that the relevant Technical Working Groups (TWGs) at country level review these WHO documents and advise national governments on the best line of action that suits their country, based on available evidence, resources and prevailing circumstances. Countries are also expected to have their own Standard Operating Procedures (SOPs) to guide stakeholders in HIV management, care and support.

All persons who are eligible for ARVs should have access to baseline and periodic laboratory investigations, ongoing HIV adherence counselling and treatment monitoring and follow up for optimum care. For HIV treatments, it is important and beneficial to commence ART early. HIV treatments before 2015, as well as the September 2015+ new WHO recommendations which henceforth should be adopted by countries all over the world, would be discussed.

Rationale for early start of ARVs

Several studies have supported the best practice of early ARV initiation as a panacea for effective viral suppression. In the NA-ACCORD study (13), it was found that patients who started ART at lower CD4 counts had a 69% likelihood of having mortality. In 2015 the START (14) and TEMPRANO (15) studies also confirmed this benefit of longevity among those who commenced ART early.

The immune system recovers faster in those who commence ART early (16), and there is a low prevalence of HIV-related cancers according to the 2008 DAD study group (17). Though a minimal survival advantage was reported (18), those who commence ART at levels ≤500 cells/mm have several benefits (8, 19). In addition, accumulating evidence suggests a low prevalence of health complications, such as neuro-cognitive dysfunction (20) and cardiovascular disease (21). Generally, other benefits of early therapy include reduced morbidity and mortality (22, 23), a reduction in the occurrence of antiretroviral resistance (24), decreased risk of sexual transmission of HIV (25), and prevention of the development of a compromised immune system (26).

Adult and adolescent ART

(a) Recommendations for Adult and Adolescent ART up till 2015 September

General criteria for initiating ART among adults: the guidelines for the use of antiretroviral drugs in the treatment of HIV have changed over time. Since the introduction of antiretroviral medications several years ago, it has been agreed by most clinicians that HIV-positive patients with low CD4+ cell counts should be treated. No consensus was reached relating to whether or not patients with high CD4+ cell counts should be treated (27). However, it was unanimously agreed that patients with advanced immune-suppression (i.e., CD4+ cell counts less than 350/μL) should be treated (28). The WHO eligibility criteria for ART treatments could be summarized as follows:

1. All HIV-positive people with a CD4 count less than 350 cells/mm^3 (including pregnant women) irrespective of the WHO clinical staging;
2. The WHO clinical stages 3 and 4 irrespective of the CD4+ count;
3. Co-infection with TB or HBV requiring treatments.

It is important to classify eligible treatment regimens as first and second line regimens and salvage therapy.

1st line treatment regimen: Using HAART, the preferred regimens are

AZT + 3TC + EFV (or NVP)

TDF + 3TC (or FTC) + EFV (or NVP)

AZT + 3TC + NVP

The initial regimen preferred by the WHO for adults and adolescents with HIV as of June 30, 2013 (29) is TDF + 3TC (or FTC) + EFV.

The WHO advice of June 2013 had been adopted in most countries up till 2015. Because of an increased incidence of hepatotoxicity, Nevirapine should not be used in women with CD4 counts >250 cells/mm^3 or men with CD4 counts >400 cells/mm^3

2nd line treatment regimen: This is used when the 1st line regimen is no longer working effectively and the desired immunologic and virologic improvements are not achieved. It also depends on accessibility, and the availability of ARVs. A boosted PI + 2 NRTIs are always recommended.

TDF + 3TC (or FTC) + LPV/r – if d4T or ZDV was used in the 1st line therapy.

If TDF was used in the 1st line, then use AZT + 3TC + LPV/r in prescriptions.

Some of the reasons for switching from the first to the second line treatment regimen include: toxicity, co-morbidities requiring treatments, pregnancy state, drug interactions and treatment failure. This failure could be: virologic failure (a viral load increase), immunological failure (the CD4 cell count declining) or clinical failure (symptoms adding up or the WHO clinical staging increasing or progressing, or opportunistic infection or malignancies showing up). The client should be on a good adherence state for 9-12 months before switching is considered.

Salvage (or third line) therapy: This is used when the 2nd line drugs fail. Prescribing ARV combinations to implement this third line treatment category requires great pharmacological expertise and the use of newer

ARVs. Some of the drugs used here are still undergoing clinical trials and caution should be exercised when using them.

(b) Adult and adolescent ART: New 2015+ WHO recommendations

In September 2015, the World Health Organization (19) recommended that ALL patients with HIV irrespective of CD4 count should be offered antiretroviral treatment. Patient should be carried along in making therapy choices during adherence counselling in order to prevent viral resistance and promote adherence.

To corroborate this evidence-based recommendation, the current US DHHS guidelines (8) published in April 2015 state that:

- ALL HIV-infected individuals should be offered ART in order to reduce the risk of disease progression.
- HIV-infected individuals should also receive ART for the prevention of transmission of HIV.
- Patients should be offered the full benefits of adherence counselling during which the benefits and risks of therapy are discussed before starting ART. The importance of adherence should be continuously discussed.

The preferred initial regimens for adults and adolescents in the United States are

- TDF/FTC and raltegravir or dolutegravir (integrase inhibitors);
- ABC/3TC (two NRTIs) and dolutegravir for patients who have tested negative for the HLA-B*5701 gene allele;
- TDF/FTC, elvitegravir (an integrase inhibitor) and cobicistat (inhibiting the metabolism of the former) in patients with good kidney function (gfr >70);
- TDF/FTC, ritonavir, and darunavir.

Many countries (most especially the developing nations) have to switch to the new guidelines for the maximum benefits of their citizens. However, many countries may find it difficult to commence these new recommendations majorly because ARV supply is donor dependent, HIV funding is dwindling most especially from donor agencies and international partners, and there is a need for appreciable and adequate

logistic support to maintain the management of these newer generation ARVs.

Paediatric ART

Up until 2015, the general criteria for initiating ART among children were:

Commence for stages 3 and 4 irrespective of the CD4 percentage cell count.

Commence for stages 1 or 2 with the following:

CD4+ <25% (<7500 cells/ul) for children less than 12 months.
CD4+ <20% (1500 cells/ul) for children 12-35 months.
CD4+ <15% (350 cells/ul) for children 36-59 months.
CD4+ <15% (200 cells/ul) for children 5 years old.

Under this regimen that was adopted based on earlier WHO rapid advice, ARVs are being given as follows, ZDV + 3TC + EFV or a PI as may be indicated.

The new 2015+ WHO guidelines recommend treating all children less than 5 years old, and all children above 5 years with WHO clinical Staging 3 or 4 or CD4 cell counts less than 500. In children less than 3 years who had never been exposed to NNRTIs in the past, a PI-based regimen was found to be superior to an NNRTI-based regimen (30). The new United States DHHS guidelines (8) also support the above recommendation, but in addition include PI-based options for children who are more than 3 years old.

The WHO recommends for children less than 3 years:

- ABC (or ZDV) + 3TC + LPV/r

And for children from 3 years to less than 10 years and adolescents <35 kilograms:

- ABC + 3TC + EFV

ART in PMTCT

The importance of giving ART to mothers (and babies) during pregnancy and/or intra-partum is to substantially reduce the risk of HIV transmission (31, 32).

Pregnant women are advised to register for antenatal care (ANC) as early as possible. This would give potentially HIV-positive women the opportunity of early PMTCT care. It is mandatory for health care workers to give an "opt out of HIV counselling and testing" to all pregnant women enrolled into care, as well as to give comprehensive PMTCT services to those who tested positive. Pregnancy in an HIV-positive woman is an indication for taking ARVs irrespective of the CD4 count, viral load or WHO clinical stage. PMTCT management can be broadly divided into (a) practice up to the date in 2015; and (b) the new 2015 September 2015+ WHO rapid advice, guidelines and recommendations which all member nations are expected to key into.

(a) PMTCT treatments up till 2015

The general eligibility criteria for ART initiation also apply to PMTCT. ARV treatment should be given to

- All pregnant women in the WHO clinical stage III or IV irrespective of CD4 count;
- All pregnant women with a CD4 cell count less than 350 irrespective of the WHO clinical staging.

Pregnant women who do not fall into any of the above categories would take ARVs not as treatment for their own health but as prophylaxis (covering a period).

The fact that PMTCT is accessible in most health facilities in most countries has led to the categorization of PMTCT centres as facilities that could provide at least "maternal prophylaxis." Thus, the previous practice of giving a single dose regimen or prophylaxis (e.g., a single dose NVP) as PMTCT care is no longer popular even in developing countries where resources are limited to ensure optimal care.

Pregnant women may present to the clinician under any of the following different clinical scenarios or settings:

Clinical setting 1: A pregnant woman who is eligible for ART treatment, but not on ART

What to do: commence mother on ART.

Preferred regimen = AZT + 3TC + (NVP or EFV).

For pregnant women co-infected with HBV, an alternative regimen is TDF + (3TC or FTC) + (NVP or EFV).

Because of its potential teratogenicity, EFV is contraindicated in the 1st trimester of pregnancy. Reactions to NVP should be substituted for a PI.

For the baby: all infants irrespective of the type of infant feeding should receive daily NVP from within 72 hours of birth to 6 weeks of age. Babies <2.5 kg should receive 10 mg or 1 ml NVP once daily. Give 15 mg or 1.5 ml daily to babies >2.5 kg.

Clinical setting 2: Pregnant women not eligible for ART treatment

What to do: commence ARV prophylaxis.

Mother: commence maternal triple ARV prophylaxis as early as 14 weeks or as soon as the woman presents during pregnancy, and continue till one week after the cessation of the infant's exposure to breast milk. If the mother decides not to breastfeed, stop ARV prophylaxis one week after delivery. Options of ARV prophylaxis include:

AZT + 3TC + LPV/r
AZT + 3TC + EFV
AZT + 3TC (or FTC) + EFV
AZT + 3TC + ABC
TDF + 3TC (or FTC) + EFV

NB: NVP should be avoided at a high CD4 count (CD4 >350).

Baby: all infants irrespective of the type of infant feeding should receive NVP daily from within 72 hours of birth to 6 weeks of age.

Clinical setting III: a pregnant woman is already on ART

What to do: continue ART. Replace EFV with NVP or a PI in the first trimester of pregnancy.

Baby: all infants irrespective of the type of infant feeding should receive NVP daily from within 72 hours of birth to 6 weeks of age.

Clinical setting IV: a pregnant woman presenting or seen for the first time in labour or after delivery

What to do:

Mother: carry out HIV testing during labour and commence maternal ARV prophylaxis. For a mother presenting after delivery, her ART eligibility should be determined and she should be treated accordingly following in-country guidelines.

Baby: if the mother is breastfeeding but not yet commenced on ART, give daily NVP from birth and continue until the baby is no longer exposed to breast milk or breastfeeding.

If the mother is breastfeeding and eventually commenced on ART, the baby should receive daily NVP from birth, and this should continue until 6 weeks after the mother had commenced ART.

If the mother is not breastfeeding, give daily NVP from birth until the baby is 6 weeks of age.

Clinical setting V: a pregnant woman with co-existing TB

What to do: treat the TB first, and delay ART until the second trimester if possible, using the following ARVs in decreasing order of preference:

EFV + 2 NRTIs
AZT + 3TC+ ABC
Ritonavir boosted PI + 2 NRTIs (changing rifampicin to rifabutin)
AZT + 3TC + TDF

Baby: all infants irrespective of the type of infant feeding should receive daily NVP from within 72 hours of birth to 6 weeks of age.

Give prophylactic INH to the baby from birth (5 mg/kg once daily) until 6 months of age (1 tab = 200 mg) irrespective of feeding practice. Delay BCG until completion of this prophylaxis or repeat BCG after completion of the course of INH.

Indications for co-trimoxazole (CTX) prophylaxis among pregnant women include

- All HIV-positive pregnant women with CD4 counts less than 350.
- All HIV-positive pregnant women with WHO clinical stages 2, 3 or 4.
- All HIV-exposed infants (from 6 weeks of age) until HIV is excluded.

CTX adult dose: 960 mg OD

Baby: Commence co-trimoxazole syrup from 6 weeks until the diagnosis of HIV is confirmed.

CTX is contraindicated in patients with an allergy to sulphur-containing drugs.

(b) Recommended PMTCT treatments as from September 2015+

The WHO 2015+ guidelines (19) recommend that programs follow Option B+ for PMTCT. Option B+ recommends providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of the CD4 count or WHO clinical staging. It is however important to maintain ART after delivery and the completion of breastfeeding for life. The preferred regimen is TDF + 3TC (or FTC) + EFV.

This recommendation supersedes the previous 2013 guidelines (option B), whereby treatment was only continued after the completion of breastfeeding, if the mother was eligible for ART for her own health.

Exposed babies should receive a course of medication linked to the ARV drug regimen that the mother is taking and the infant's feeding method.

If breastfeeding, the infant should receive once-daily Nevirapine (NVP) from birth for six weeks.

If the baby is on replacement feeding, the infant should receive once-daily NVP (or twice-daily Zidovudine (AZT)) from birth for four to six weeks.

Many developing countries of the world are still practising the clinical setting (Option B) guidelines explained above. However, adopting the 2015+ WHO recommendations would require improved donor support to

developing or resource poor countries, most especially in the areas of funding and logistics.

Common HIV Co-Infections

1. TB/HIV

In 2013, an estimated 13% of the estimated 9 million people who developed tuberculosis (TB) were HIV positive. There were also 360,000 deaths from HIV-associated TB equivalent to 25% of all TB deaths. This is around 25% of the estimated 1.5 million deaths from HIV/AIDS in the same year (33). TB is the commonest opportunistic infection associated with HIV infection.

The principles of treating TB are the same for HIV-infected and uninfected patients. Patients should receive at least six months of rifampicin-based treatment. A study has reported benefits in eight to nine months of rifampicin-based treatment over the standard six months (34). The summary of treatment is as follows

1. Start TB treatment first, followed by ART as soon as possible (usually within 8 weeks of starting anti-TB).
2. Treat TB according to in-country guidelines.
3. For dual treatment of clients on rifampicin, preferred ARVs are TDF (or ZDV) + 3TC + EFV (800 mg daily for clients >60kg. If less, use 600 mg daily).
4. Avoid the use of NVP due to adverse drug reactions.
5. Avoid the use of most PIs (or substitute rifampicin for rifabutin, if you must use PIs).

For prevention, Isoniazid Preventive Therapy (IPT) can be used among co-infected clients without active TB. IPT should start 3 months after the commencement of ARVs. Use Isoniazid (INH) 5 mg/kg/day to a max of 300 mg/day for IPT. Use IPT for 6 months.

An EFV-containing regimen is the first line of treatment unless for a pregnant woman in the 1st trimester. For clients on the 2nd line drug who develop the disease, it is advisable to replace rifampicin with rifambutin.

In Immune Reconstitution Inflammatory Syndrome (IRIS), the client had improved after ARV and was later gradually getting worse. It is common when ARVs are started too early, for example in TB/HIV co-infection

most especially those with a low CD4 count. IRIS can occur within 3 months of the commencement of ARVs. It is common among TB-HIV clients as an exaggerated inflammatory response of the immune compromised person (such as PLHWA) who have recently started antiretroviral therapy) in the presence of an associated opportunistic infection.

2. HBV/HIV

Hepatitis B virus co-infections with HIV are common. The management of such a co-infection should be given priority because:

- The progression of liver disease into states such as cirrhosis and liver cancer is higher among patients with co-infection of HBV and HIV.
- The risk of post-ART initiation hepatotoxicity is higher among those co-infected than a person infected with HIV alone.

At any stage of liver disease, co-infection with HIV is an indication for ART treatments whatever the CD4 level. Available potent medications include Tenofovir, with either Lamivudine or Emtricitabine combinations. The use of Interferon alpha in the treatment of the liver disease is important to the management of this co-infection.

Preventive Art

ARVs are drugs traditionally used for the treatment of HIV infections. However, they are also useful in HIV prevention, the 3 categories include

1. Isoniazid Preventive Therapy (IPT);
2. Co-trimoxazole Preventive Therapy (CPT); and
3. Post Exposure Prophylaxis (PEP).

Post Exposure Prophylaxis

Not all HIV exposures lead to disease transmission. The risk of contracting HIV through puncture exposures is about 0.3% (35) and about 0.63% through exposure of the mucous membrane (36). However, not all body fluids are considered potentially infectious unless they are visibly bloody (37).

Rationale for PEP: Detection of HIV in regional lymph nodes and blood may take up to 72 hours and 5 days respectively (38, 39) and about 8 days to be detected in the cerebrospinal fluid (40). A window of opportunity to prevent acquisition of HIV infection thus exists following exposure in which case early ART could lead to effective viral suppression (41). A study has shown that 28 days is the optimal or ideal number of days for ARV treatments (42).

Common indications for PEP:

1. Unprotected vaginal/anal intercourse;
2. Occupational exposures;
3. Some non-occupational exposures.

Risks of PEP are those of drug side effects and drug resistance.

Time to start PEP: The earlier that PEP is initiated within the first 72 hours of exposure, the better it is for treatment effectiveness and outcomes. Evidence-based health guidelines of the New York State recommended that PEP should be given within 36 hours and within 2 hours of exposure respectively for both non-occupational and occupational exposures (43). Data from an animal study (44) have also shown evidence of increasing failure rates if PEP is not given within 48-72 hours after exposure. The general consensus was that PEP is the recommended treatment for a duration of four weeks based on an animal study (44).

PEP drug regimen: the preferred regimen for PEP is a drug combination of TDF + FTC + either raltegravir or dolutegravir. This regimen is well tolerated, potent and easy to administer.

The preferred alternative is TDF + FTC + ritonavir-boosted darunavir, atazanavir, or fosamprenavir.

Other alternatives are:

1. Tenofovir + Emtrictabine[b] + Zidovudine;
2. Tenofovir + Emtricitabine[b] + Lopinavir/ritonavir;
3. Zidovudine + Lamivudine[c] + ritonavir-boosted protease inhibitors.

Zidovuine is no longer recommended in PEP.

In addition to HIV serologic screening, the source patient should be encouraged to do plasma HIV RNA testing, and PEP should be continued until the results of the plasma HIV RNA assay are available:

The preferred PEP regimen for sexual assault and rape is the same as that for other types of non-occupational exposures and occupational exposures. Occupational exposure to HIV can be classified into two groups depending on the extent of exposure. These are

1. Low risk: solid needles are involved, superficial exposures, intact skin, a small volume of blood or a drop seem to come out, and the source of infection is asymptomatic;
2. High risk: a large bore needle prick, deep injury sustained, a large volume of blood has oozed out, and the source of infection is symptomatic.

For low risk, only 2 drugs were advocated while the full HAART complement containing 3 drugs is advocated in high risk exposures. While a TDF-based regimen is advocated in treatment, it is advisable that all exposures should be assumed to be high risk.

If at the point or time of exposure, the victim (e.g., a health care worker) is HIV positive, it is unlikely to be occupational exposure and the victim was probably already infected. If the victim is negative, or the source is either positive or negative (because of the window period) as at the time of exposure, then post exposure prophylaxis is indicated and advised. Though amenable to the use of HAART, pre-exposure to HIV has numerous ethical and legal implications.

ART Monitoring, Effectiveness and Follow Up

Monitoring should ideally be done at least during the 4 periods below

1. At baseline (entry into HIV care);
2. The pre-ART period;
3. Starting ART;
4. Maintaining ART.

Laboratory evaluation should include CD4 testing, FBC every 3 months, viral load every 6 months, LFT, Electrolytes and Urea, lipid profile, renal function tests every 6 months, TB screening, urinalysis, paps smear, syphilis, hepatitis, etc.

Other monitoring includes

(a) Clinical monitoring: whether symptoms are improving;
(b) Adherence monitoring: whether the client is adhering to the treatment regime. Indices for assessing this include but are not limited to the volume of drugs left, observations, pharmacy pick-up records, self-reported adherence or calculated adherence (>95%);
(c) Response to therapy; whether the client is failing on treatment or not. There are 3 types of failure:
    1. Virologic response: this is the primary goal of ART, and it is the suppression of the viral load to a level that it is no longer detectable (<50 copies per ml). The inability to achieve this goal within or by 24 weeks after starting HAART constitutes virologic failure.
    2. Immunologic response: an increment in CD4 count is a reliable way of measuring ART effectiveness. Viral suppression on ART in the absence of a corresponding increase in CD4 counts is termed immunologic non-response or immunologic failure.
    3. Treatment failure goes by worsening clinical or treatment staging of HIV.

For children, monitoring should in addition specifically address the following:

Growth monitoring, Developmental assessment, Nutritional assessment,

Co-morbidities, and Anthropometry.

Children should be seen more regularly, for example 2 weeks after initiating ART, monthly for the first 6 months and 3 months thereafter.

ARV Toxicity and Adverse Drug Reactions (ADRS)

ARV toxicities are common, as shown in Table 1 above.

An Adverse Drug Reaction (ADR) is a response (mild to severe) to drugs that is unintended and occurs at normal doses. Though these should be generally prevented, they may be unavoidable. Mild ones may not require the discontinuation of ARVs but the severe or life-threatening category may require discontinuation. Mild toxicity: may also not require the substitution of ARVs, but may require symptomatic treatment such as anti-histamine. Moderate toxicity: may require the substitution of drugs, while

severe toxicity: may require the discontinuation of ARVs + giving supportive therapy.

Like ART, most (other) drugs are metabolized via the Cytochrome P450 pathway, and their concentrations may increase or decrease the ARV level thus causing some adverse drug reactions. There are 2 mechanisms of such interactions

1. ARV-ARV drug interaction e.g., ZDV/d4T antagonistic interactions;
2. Non-ARV-ARV drug interaction e.g., rifampicin decreases the plasma level of all PIs by about 75%, and decreases the plasma level of EFV by about 25% and NVP by 37%. Similar trends were found with rifambutin.
   Another example is between ketoconazole and NVP.

Management of common medical conditions and opportunistic infections among PLWHA

Table 2: Common opportunistic infections in HIV

Name of infection	Likely causative organisms	Treatments in addition to ARVs
Bacterial pneumonia	Strep pneumonia, Staph aureaus, Klebs pneumonia and H. influenza	Ampiclox, Amoxicillin-clavulanic combination, cephalosporins
Acute pharingo-tonsillitis	Respiratory viruses, Strep pneumoniae, Klebs pneumonia and H. influenza	Amoxicillin-clavulanic combination Cephalosporins
Acute otitis media	Strep pneumonia, Staph aureaus, Klebs pneumonia and H. influenza	Ampiclox, Amoxicillin-clavulanic combination, cephalosporins
Acute watery diarrhoea	Rota viruses, E. coli, Campylobacter spp.	Rehydration + antibiotics
Malaria	P. falciparum	Arthemisinin Combination Therapy as per the country's guidelines
Candida infections	Candida Albicans	Oral Nystatin

Oral thrush, Oesophagitis		Oral Fluconazole
Pneumocystis pneumonia (PCP)	Pneumocystis jiroveci	Trimethioprin, Dapsone, Clindamycin
Oral herpes	HSV types 1 and 2	Acyclovir, Mild analgesic
Herpes zoster (Shingles)	Varicella zoster	Acyclovir, Mild analgesic
Toxoplasmosis	T. Gondii	Pyrimethamine Sulphadiazine, Clindamycin
Cryptococcal meningitis	Cryptococcus neoformans	Flucytosine, followed by Amphotericin B, and Fluconazole
Mycobacterium Avium Complex	M. avium spp.	Clarithromycin, Ethambutol
Tuberculosis	Mycobacterium TB	Treatment of TB with DOTs, and prophylaxis as per the country's guidelines
Aspergillosis	Aspergillusspp	Amphotericin B
Cryptococcus meningitis	Cryptococcus neoformans	Amphotericin B Fluconazole
Cryptosporidiosis	Cryptosporidium parvum	Rehydration Azithromycin
Histoplasmosis	H. Capsulatum	Amphotericin B
Cytomegalovirus infections	Cytomegalovirus	Acyclovir

The Future of ARVs and the Feasibility of HIV Vaccines

It may be difficult to truly predict the future of HIV management using drugs. Newer ARVs are being developed; some of them belong to existing classes of drugs and some to entirely new classes. The greatest fear of ARVs remains their toxicity and side effects when taken either on a short-term or long-term basis. There is a need for researchers and scientists to invest more purposeful time and proposals in the development of ARVs while Governments and other stakeholders step up the funding of such research efforts. The newer ARVs appear to be more effective and less toxic and easier to consume compared to the older traditional ARVs.

Several clinical trials are ongoing at various phases to test the efficacy of more and newer ARVs considering the high unmet needs for ARVs in many countries.

Though an HIV cure is desired, only the "Berlin patient" is known to the author to be (potentially) cured so far, and the patient has been off treatment since 2006 with no detectable virus (44). This was achieved through two bone marrow transplants that replaced his immune system with a donor's that did not have the CCR5 cell surface receptor.

Recently, two infants were reported to have been cured of HIV (45), presumably because treatment was initiated within hours of infection, thus preventing HIV from establishing a deep reservoir (37).

Vaccines are generally accepted as the most effective public health intervention for controlling viral epidemics, and in this case such a vaccine has to teach the immune system how to create protective immune responses against HIV. The development of a vaccine to prevent HIV infection is especially challenging because of:

- the diversity of HIV subtypes;
- the changing epidemiology of the disease;
- viral mutations in which the vaccine would be able to address the different strains of the virus.

The widely reported Thai RV144 trial of 2009 (46) showed that individuals who received a vaccine were 31% less likely to become infected with HIV than people who received a placebo. It is, however, important for the scientific world to look beyond the conventional ARVs and vaccines and consider or study other forms of treatment. These include:

- Immune boosters – drugs that may not interfere directly with the HIV virus, but rather they are intended to increase the number of CD4 and other immune cells, thereby boosting the general body’s immune function.
- Therapeutic vaccine – these are vaccines that would serve both as vaccine and treatment modality, leading to an improved ability of the immune system to fight the HIV virus.
- The use of microbiocides: research is still evolving, ongoing.

So far, the results of studies of immune boosters and therapeutic vaccines have been disappointing. Although there is no successful HIV vaccine yet, some candidate vaccines have been shown to protect against AIDS to an extent among animal models. All hope is not lost and the struggle will continue until a zero incidence and prevalence rates of HIV are achieved.

With the emerging concepts in the pharmacology of HIV arising from recent research and presentations at international meetings and conferences, the world is now moving towards the "HIV Test and Start" approach. This means that all HIV-positive clients should commence ART immediately once they are diagnosed HIV positive. This approach has numerous advantages including early viral suppression, but it is not without limitations and consequences most especially for developing countries where ARVs may not be readily available. In these countries, ARVs are largely donor dependent, host countries may not be able to contribute counter-part funds to purchase drugs and consumables to guarantee no stock-out. The HIV self-testing and the test-retest approaches also have implications for encouraging HIV testing services as well as for HIV programming.

References

1. Fauci AS. Toward an AIDS-free generation. *JAMA*, 2012; 308(4): 343-347.
2. Smyth RP, Davenport MP, Mak J. The origin of genetic diversity in HIV-1.*Virus Res*. 2012; 169(2): 415-29.
3. Sangeeta D, Patel Dipa M Kinariwala, and Tanuja B Javadekar. Clinico-microbiological study of opportunistic infection in HIV seropositive patients. *Indian J Sex Transm Dis*. 2011; 32(2): 90-93
4. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med.* 2007; 120(8): 713-9.
5. Moore RD, Chaisson RE. Natural History of Opportunistic Disease in an HIV-Infected Urban Clinical Cohort. *Annals of Internal Medicine.* 1996; 124(7): 633.
6. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS*. 1999; 13: 1933-1942.
7. Danel C, Moh R, Gabillard D, Badje AN, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *The New England Journal of Medicine*. 2015; 373(9): 808-822.

8. US Department of Health and Human Services DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (PDF). US Department of Health and Human Services, April 2015.
9. Salzburg Statement on Shared Decision Making. Salzburg Global Seminar, Accessed November 2015. Available at: http://e-patients.net/u/2011/03/Salzburg-Statement.pdf.

Accessed 14 April 2017.

10. Beach MC, Duggan PS, Moore RD. Is patients' preferred involvement in health decisions related to outcomes for patients with HIV? *Gen Intern Med*. 2007; 22: 1119-1124.
11. Gardner EM, Burman WJ, Steiner JF, Anderson PL and Bangsberg D. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS*. 2009; 23(9): 1035-1046
12. Horn T. Activists Protest Stribild's $28,500 Price Tag. *AIDS Meds*. Available at commons.lib.jmu.edu/cgi/viewcontent.cgi?article=1154&context=honors201019. Accessed 1 November, 2016.
13. Beardsley T. Coping with HIV's ethical dilemmas. *Scientific American*. 1998; 279(1): 106-7.
14. Kitahata MM, Gang S, Abraham AG, Merriman B, Saag M S, Justice AC, et al Effect of early versus deferred antiretroviral therapy for HIV on survival. *The New England Journal of Medicine*. 2009; 360(18): 1815-1826.
15. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015; 373: 795-807.
16. Kelley CF, Kitchen CM, Hunt PW, Rodriguez B, Hecht FM, Kitahata M, et al. Incomplete Peripheral CD4+ Cell Count Restoration in HIV-Infected Patients Receiving Long-Term Antiretroviral Treatment. *Clinical Infectious Diseases*. 2009; 48(6): 787-794.
17. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008; 22(16): 2143-2153.
18. Deek SG. The end of AIDS: HIV infection as a chronic disease. *The Lancet*. 2013; 382(9903): 1525-1533.
19. WHO. Guidelines: HIV. World Health Organization. Available at www.who.int/hiv/pub/guidelines/en/. Accessed 16th November 2015.
20. Wensing AM, van Maarseveen NM; Nijhuis M. Fifteen years of HIV protease inhibitors: Raising the barrier to resistance. *Antiviral Research*. 2010; 85(1): 59-74.

21. Bai Y, Xue H, Wang K, Cai L. Covalent fusion inhibitors targeting HIV-1 gp41 deep pocket. *Amino Acids the Forum for Amino Acid, Peptide and Protein Research*, 2013; 44(2): 701-13.
22. Marin B, Thiébaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS*. 2009; 23: 1743-1753.
23. Ho JE, Deeks SG, Hecht FM. Initiation of antiretroviral therapy at higher nadir CD4+ T-cell counts is associated with reduced arterial stiffness in HIV-infected individuals. *AIDS*. 2010; 24: 1897-1905.
24. Uy J, Armon C, Buchacz K Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr*. 2009; 51: 450-453 [PubMed] .
25. Quinn TC, Wawer MJ, Sewankambo N. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000; 342: 921-929.
26. Lewden C, Chene G, Morlat P. HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr*, 2007; 46: 72-77.
27. Darbyshire J. Perspectives in drug therapy of HIV infection. *Drugs*. 1995; 49(1): 38-40.
28. Harrington M, Carpenter CC. Hit HIV-1 hard, but only when necessary. *The Lancet*. 2000; 355(9221): 2147-52.
29. WHO. WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2013, 38.
30. Violari A, Lindsey JC, Hughes MD, Mujuru H, Barlow-Mosha L, Kamthunzi P. Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-infected Children. *New England Journal of Medicine*. 2012; 366(25): 2380-2389.
31. United States DHHS. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. US: DHHS, 2015.
32. Guay LA, Musoke P, Fleming T. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet*. 1999; 354(9181): 795-802.
33. Global Tuberculosis Control 2014. Available at www.who.int/tb/publications/global_report/. Accessed November 12, 2016.

34. Khan FA, Minion J, Al-Motairi, et al. An update of systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. *Clinical Infectious Diseases*. 2012; 55(8): 1154-63.
35. Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. *Am. J. Med*. 1997; 102(5B): 9-15.
36. Ippolito G, Puro V, De Carli G. The risk of job occupational human immune-deficiency virus infection in health care workers. *Arch Intern Med*. 1993; 153: 1451-1458.
37. Kuhar DT, Henderson DK, Struble KA, Heneine W, Thomas V, Cheever LW, et al. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for post-exposure prophylaxis. *Infect Control Hosp Epidemiol*. 2013; 34(9): 875-92.
38. Pinto LA, Landay AL, Berzofsky JA, Kessler HA, Shearer GM. Immune response to human immunodeficiency virus (HIV) in health care workers occupationally exposed to HIV-contaminated blood. *Am J Med*. 1997; 102(5B): 21-24.
39. Spira AI, Marx PA, Patterson BK, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. *J Exp Med*. 1996; 183(1): 215-225.
40. Valcour V, Chalermchai T, Sailasuta N, et al. Central nervous system viral invasion and inflammation during acute HIV infection. *J Infect Dis*. 2012; 206(2): 275-282.
41. Bourry O, Mannioui A, Sellier P, et al. Effect of a short-term HAART on SIV load in macaque tissues is dependent on time of initiation and antiviral diffusion. *Retrovirology*. 2010; 7: 78.
42. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med.* 1997; 337(21): 1485-1490.
43. New York State Department of Health AIDS Institute. HIV Prophylaxis Following Non-occupational Exposure. New York, NY: HIV Clinical Resource, 2008. [Accessed November 12, 2016]. Available at: http://www.hivguidelines.org/clinical-guidelines/post-exposure-prophylaxis/hiv-prophylaxis-following-non-occupational-exposure-including-sexual-assault/.
44. Rosenberg T. The Man Who Had HIV and Now Does Not. *New York Magazine* 2011. Available at

integral-options.blogspot.com/2011/.../new-york-magazine-man-who-had-hiv-and.ht. Retrieved December 23, 2016.
45. McNeil Donald. Early Treatment Is Found to Clear HIV in a 2nd Baby. *New York Times*, 2014. Available at https://issuu.com/wuhcpenn/docs/wuhc_march_newsletter_final. Retrieved December 23, 2015.
46. Rerks-Ngarm S. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *New England Journal of Medicine,* 2009; 361(23): 2209-2220.

CURRENT CONCEPTS IN HIV: LABORATORY INVESTIGATIONS

ADEREMI VICTOR ADEWALE
MBBS, MPH, MSC

HIV/AIDS remains a disease with significant public health implications, globally. Today, newer methods and approaches are being developed to aid diagnosis and treatment initiation and to monitor therapy response including resistance to the commonly used antiretroviral agents. With regard to such developments, healthcare workers, especially in less developed and developing economies, would do well to keep themselves up to date with respect to such developments for a better service delivery. The aim of this review is to identify laboratory investigation tools and approaches that are currently available for the ease of diagnosis and management of HIV/AIDS patients. A search of Medline, PUBMED, Global Health, AJOL and online Google Scholar yielded a number of relevant scholarly articles from which current laboratory investigative modalities for HIV diagnosis, initiation, treatment, monitoring of metabolic complications and resistance to therapy were identified.

Depending on the cultural context and availability of investigative tools, guidelines have been developed for HIV diagnosis and Anti Retroviral Therapy (ART) initiation globally (1-3). What is common to all is an emphasis on pre- and post-testing counselling. Together, these two (counselling and testing) are crucial to achieve adequate prevention, care and interventional supports in the fight against HIV (4). To ensure that false negatives and false positives are substantially minimized, given the very serious social, economic and medical implications of incorrect HIV diagnosis in an individual (4, 5), any positive result following the initial screening is often subjected to confirmatory testing. In Africa, the need for re-testing and/or confirmatory testing is to be appreciated in the fact that there are appreciably high rates of HIV misdiagnosis. For instance, Shank and others noted, upon re-testing, that approximately 10% and 7% of persons previously diagnosed HIV positive were misdiagnosed in the

Democratic Republic of Congo and Ethiopia respectively (6). A somewhat similar but more pathetic scenario was observed in Malawi in 2011 when a case of a 43-year-old previously diagnosed HIV-positive woman was reported as being HIV-negative after having been placed on ART for over 2 years and the patient had developed complications from ART (7). With the recent proposal by the World Health Organization (WHO) for self-testing (8), feasible and accurate diagnostic tests become more crucial for ensuring adequate prevention and proper treatment of HIV cases (4).

In Nigeria, several test kits are available for the rapid diagnosis of HIV. Chembio HIV-1/2 Stat-Pak, Alere Determine™ HIV-1/2, and Core HIV-1/2 and Uni-Gold are examples of the most commonly employed rapid diagnostic tests (RDTs) (9). These RDTs are currently in use because they meet the WHO standards for a minimum test sensitivity of 99% and a specificity of 95% (10). Other RDTs which are also used in Nigeria include SureCheck, Double-CheckGold, and Bundi (10).

HIV Testing: what categories of people should be targeted?

Following adequate pre-test counselling, it is recommended that HIV testing be done routinely for some at-risk individuals, for example, men having sex with men, intravenous drug users, individuals with a history of STIs, immigrants from highly endemic areas, etc. (1); special circumstances such as pregnancy and HBV/HCV co-infection (3); and closed settings such as prisons and facility-based settings (11). A primary school-based HIV screening has equally been recommended to ensure cases are detected early and promptly managed especially in settings of high HIV prevalence (12). These tests often include the use of RDT kits (Unigold and Determine for example), viral load estimation, CD4 counts, and other ancillary tests necessary for identifying other medical conditions that may require additional therapy and care (1, 3, 4).

HIV Testing: what investigations are needed and when are they required?

Instances where investigations are needed can be broadly categorized as follows (1, 13):

1. Investigations to establish a diagnosis – including initial screening plus confirmatory tests;

2. Investigations to initiate treatment;
3. Investigations to monitor the response to ART;
4. Investigations to identify and manage metabolic complications of HIV infection and treatment;
5. Investigations to establish genotypic/phenotypic resistance to ART.

1. Investigations to establish a diagnosis

In settings of poor or inadequate laboratory facilities, the WHO has recommended that two or three rapid diagnostic tests (RDTs) be combined in an algorithmic fashion to ensure an accurate diagnosis (8). Aside from poor laboratory facilities, the need for rapid test kits for HIV diagnosis may have arisen out of the observation that the conventional ELISA testing followed by the western blotting approach was laborious – in that some technicalities and expertise may be required in their usage and maintenance (4, 14). However, the effectiveness of the current diagnostic guidelines involving the use of RDTs is increasingly being challenged (15, 16). For instance, out of the two commonly used HIV screening algorithms, namely, the parallel rapid test algorithm and the serial rapid test algorithm, the former has been shown to be associated with variable outcomes in terms of test specificity, thus signifying a possibility of increased false positive results when such an approach is used (4, 15). Another drawback, perhaps, is that while most HIV antibody screening tests that are currently on the market can detect the presence of both HIV-1 and HIV-2, they are unable to discriminate between the two viruses (17). To confirm the presence of HIV-2, therefore, a nucleic acid test is required (17). Generally, individuals are subjected to an initial assessment to establish the presence of HIV infection. This assessment involves taking the appropriate history (sexual health, circumstances surrounding conception, and delivery, etc.) and a general physical examination to identify weight loss and telltale signs on the skin, in the oral cavity and abdomen (such as enlarged spleen and liver), anogenital regions, and the eyes (1). This is followed by CD4+ T-cell counts, a viral load estimation, and other ancillary tests including liver and kidney function tests, full blood count, tests to confirm the presence or otherwise of other viruses such as hepatitis A, B, C (1, 3). In children below the age of 18 months, the use of a virological study has been advocated, albeit its high cost and complexity (14). In the newborn, diagnosis can be rapidly made using the

Dried Blood Spot (DBS) collection technology (18). This technology allows for early infant diagnosis (EID) of HIV in infancy.

Serial versus Parallel Algorithm for HIV Diagnosis

Parallel and serial testing algorithms are the two commonly used strategies for rapid, point-of-care HIV diagnosis. In the parallel algorithm, samples are tested at the same time using two dissimilar HIV test kits whereas in serial testing, samples are first tested using a particular RDT kit, and depending on the result, an additional testing may or may not be indicated. The WHO recommended algorithm for Nigeria is serial testing (9). In serial testing, a third test kit (the tiebreaker) may be indicated in situations of discordant results between the 1st and 2nd tests (9).

2. Investigations for treatment initiation

Although it has been suggested that all adults with proven HIV-positive status be placed on highly active antiretroviral therapy (HAART), notwithstanding their levels of CD4 count, the viral load estimation and CD4 count levels are still very important before ART initiation (3, 19). In fact, CD4+ T-cell count should be done more than once before an individual is commenced on ART (20). Investigations to establish the presence of other infective conditions prior to ART initiation are equally important. Tuberculosis (TB), a chronic infectious disease that has been shown to pose a serious challenge in the treatment of HIV-AIDS, is a very good example in this regard (21). While the traditional approach of utilizing sputum AAFB, microscopy and chest X-ray for diagnosing TB has been shown to yield positive results, Lawn and others have shown in a recent South African study that the newly endorsed WHO Xpert MTB/RIF assay for TB diagnosis is associated with a higher detection of cases when compared to smear microscopy (21, 22). Additionally, Xpert MTB/RIF assay offers the advantage of detecting individuals who are resistant to rifampicin, an important anti-TB agent (21). Another newer approach for TB screening before initiating treatment in HIV-positive patients is to assay for the presence of lipoarabinomannan (LAM) in the urine, a biomarker with higher sensitivity compared with sputum microscopy, using an enzyme-linked immunosorbent assay (23).

3. Investigations to monitor the response to ART

Monitoring an individual's response to ART is an important step to ensure success in HIV management. Here, the most important monitoring tool is the HIV-1 RNA viral load, as well as the CD4+ T-cell count which is to be measured every 12 to 16 weeks or 24 to 48 weeks once the patient's condition becomes more stable clinically (3, 20, 24). The viral nucleic acid is measured in blood samples and other body fluid using Reverse Transcriptase-PCR techniques (20). The technique is particularly useful for the monitoring of the patient's response to HAART and additionally offers the advantage of detecting the presence of retroviral infection even when the individual is in the window period (1). Other tests often performed to monitor response include fasting lipid profiling, fasting blood sugar and screening for the presence or otherwise of viral hepatitis and opportunistic infections (3).

4. Investigations to identify and manage metabolic complications of HIV infection and treatment

While some may be diagnosed on clinical grounds, a few other metabolic complications associated with HIV infection and treatment often require some degree of laboratory investigations. Examples of such documented metabolic complications include alterations in fat distribution, lactic acidosis, abnormal lipid, and glucose metabolism (13). For dyslipidemia, a fasting lipid profile is generally preferred but a non-fasting lipid profile can also offer some advantages especially with regard to identifying cholesterol subsets and important drug-drug interactions (13). To establish the presence or otherwise of abnormal glucose metabolism and lactic acidosis, fasting blood sugar/oral glucose tolerance tests and the estimation of venous or arterial lactate levels are respectively indicated except that the standard precautionary measures required for venous lactate sampling must be followed to ensure that the values obtained are truly representative (13).

A high level of lactic acid in the blood (in the presence of other clinical signs and symptoms like abdominal pain, abnormal fatigue, weight loss and dyspnoea associated with exercise), the so-called symptomatic hyperlactatemia, is an emerging metabolic complication associated with ART (25). Detecting this condition requires a combination of approaches that includes the measurement of lactate in the patient's arterial blood and the use of the functional respiratory test and liver/muscle biopsies (25).

5. Investigations to identify resistance to ART

Resistance to ART is a major challenge in the management of HIV/AIDs. Establishing the presence of drug resistance in HIV-positive individuals requires the use of either a genotypic assay, which essentially targets the nucleic acid constituent of the virus and offers insight into the drugs to which the patient is resistant, or a phenotypic assay, that measures the extent to which the virus responds to ART in a laboratory setting (26). In other words, while a genotypic assay detects mutations underlying the observed resistance to ART, the phenotypic assay is used to assess the degree of susceptibility of HIV to a particular drug (27). Although genotypic assays are the most widely employed for resistance detection, because they are cheap and readily available (27), phenotypic assays remain better options to be used for patients with a proven poor response to multiple antiretroviral regimens (26). An example of the genotypic approach involves either direct PCR or viral population-based sequencing of samples from peripheral blood mononuclear cells or plasma HIV-1 RNA (27, 28). HeLa-$CD4^+$ cells-based plaque reduction and peripheral blood mononuclear cell (PBMC) assays were the two most widely used phenotypic assays until lately when two other standardized assays (from Tibotec-Virco and ViroLogic Inc.) with better throughput performances were developed (27). Sample preparations for these recombinant virus susceptibility assays are similar and essentially involve RNA extraction, reverse transcription, and PCR amplification (27).

Table 1: A summary of the investigations needed and circumstances in which they are required

Establishing diagnosis	Treatment Initiation	Monitoring response to ART	Identification and management of metabolic complications	Identification of resistance to ART
CD4 cell counts	CD4+ T-cell count	RT-PCR for viral nucleic acid measurement	Fasting lipid profile	Genotypic approach: direct PCR sequencing Viral population-based sequencing

Viral load estimation	Viral load estimation	CD4+ T-cell count	Non-fasting lipid profile	Phenotypic assays: HeLa-$CD4^+$ cells-based plaque extraction assay. PBMC assay. Recombinant virus susceptibility assays
Liver function test (LFT)	Screening for TB: Sputum AAFB Microscopy Chest X-ray Xpert MTB/RIF assay Urinary lipoarabinomanan assay	Other tests like Fasting lipid profile Fasting blood sugar Viral hepatitis and opportunistic infection screening	Fasting blood sugar/Oral glucose tolerance test	
Renal function test (RFT)	Other ancillary tests: FBC, LFT, RFT, etc.		Venous/arterial lactate level estimation	
Full blood count (FBC)			Functional Respiratory Test	
Hepatitis A, B, C screening			Liver/Muscle Biopsies	

References

1. Asboe D, Aitken C, Boffito M, et al. British HIV Association Guidelines for investigation and monitoring of adult HIV-1 infected individuals 2011. *HIV Medicine*. 2012; 13: 1-44.
2. Kansas Disease Investigation Guidelines Version 05. HIV/AIDS disease management and investigation guidelines. *HIV/AIDS*. 2013; 1-4.

3. The Korean Society for AIDS. The 2015 clinical guidelines for the diagnosis and treatment of HIV/AIDS in HIV-infected Koreans. *Infect Chemother*. 2015; 47(3): 205-211.
4. Mbachu II, Udigwe G, Joseph I, et al. The evaluation of the accuracy of serial rapid HIV test algorithm in the diagnosis of HIV antibodies among pregnant women in Southeast Nigeria. *BMC Research Notes*. 2015; 8: 557.
5. Johnson C, Fonner V, Sands A, et al. Annex 14: A report on the misdiagnosis of HIV status of the Consolidated Guidelines on HIV Testing Services. Geneva: World Health Organization, 2015. SBN-13: 978-92-4-150892-6.
6. Shanks L, Klarkowski D, O'Brien DP. False positive HIV diagnoses in resource-limited settings: operational lessons learned for HIV programmes. *PLoS One*. 2013; 8(3): e59906.
7. Mulinda N, Johnstone K, Newton K. Case Report: HIV test misdiagnosis. *Malawi Med J.* 2011; 23(4): 119-120.
8. World Health Organization. Service delivery approaches to HIV testing and counseling (HTC): a strategic HTC policy framework. 2012. Available: http://www.who.int/hiv/pub/vct/htc_framework/en/index.html.
9. Osaro M, Peterside F, Okonko IO, Ughala E, Obike-Martins V. Evaluation of commonly used rapid test kits and serological serial testing algorithm for diagnosis of HIV-1 and 2 antibodies in Port Harcourt, Nigeria. *Virol-mycol*. 2015; 4: 146.
10. Manak MM, Njoku OS, Shuts A, et al. Evaluation of the performance of two HIV 1/2 rapid tests in high and low prevalence populations in Nigeria. *J. Clin. Microbiol*. 2015; 53(11): 3501-3506.
11. World Health Organization. Consolidated guidelines on HIV testing services: 5Cs: consent, confidentiality, counseling, correct results and connection. *WHO Library Cataloguing-in-Publication Data*. 2015; ISBN 978 92 4 150892 6.
12. Ahmed S, Kim MH, Sugandhi N, et al. Beyond early infant diagnosis: case-finding strategies for identification of HIV-infected infants and children. *AIDS*. 2013; 27(2): 235-245.
13. Wohl DA, McComsey G, Tebas P, et al. Current Concepts in the Diagnosis and Management of Metabolic Complications of HIV Infection and Its Therapy. *Clin Infect Dis*. 2006; 43: 645-653.
14. World Health Organization. Guidance on provider-initiated HIV testing and counseling in health facilities. Joint United Nations Programme on HIV/AIDS, 2007; ISBN 978 92 4 159556 8.

15. Klarkowski D, Glass K, O'Brien D, et al. Variation in Specificity of HIV Rapid Diagnostic Tests over Place and Time: An Analysis of Discordancy Data Using a Bayesian Approach. *PLoS One.* 2013; 8(11): e81656.
16. Gray RH, Makumbi F, Serwadda D, et al. Limitations of rapid HIV-1 tests during screening for trials in Uganda: diagnostic test accuracy study. *BMJ*. 2007; 335(7612): 188.
17. Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children. Guidelines for the use of antiretroviral agents in paediatric HIV infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf, accessed on 25/12/2015.
18. Lofgren SM, Morrissey AB, Chevallier CC. Evaluation of a Dried Blood Spot HIV-1 RNA programme for early infant diagnosis and viral load monitoring at rural and remote healthcare facilities. *Global Health Sciences Literature Digest*. 2010; 23(18): 2459-2466.
19. Govender S, Otwombe K, Essien T, et al. CD4 Counts and Viral Loads of Newly Diagnosed HIV Infected Individuals: Implications for Treatment as Prevention. *PLoS One*. 2014; 9(3): e90754.
20. BMJ Best Practice. HIV infection. BMJ Publishing Group Limited. Last updated Jan 15, 2016.
21. Lawn SD, Brooks SV, Kranzer K, et al. Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. *PLoS Med*. 2011; 8(7): e1001067.
22. World Health Organization. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. Geneva: World Health Organization, 2010. Available: http://www.who.int/tb/laboratory/roadmap_xpert_mtb_rif_rev23dec2010.pdf. Accessed 26 January 2016.
23. Lawn SD, Edwards DJ, Kranzer K, Vogt M, Bekker L, Wood. Urine lipoarabinomanan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. *AIDS*. 2009; 23(14): 1875-1880.
24. Sanchez AM, DeMarco CT, Hora B, et al. Development of a contemporary globally diverse HIV viral panel by the EQAPOL program. *J Immuno Methods.* 2014; 117-130.
25. Gerard Y, Maulin L, Yazdanpanah Y, et al. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. *AIDS*. 2000; 14(17): 2723-2730.
26. AIDS.gov. Just diagnosed: resistance testing. *AIDS.gov*. 2009.

27. Robert WS. HIV InSite Knowledge Base. In *Assays for antiretroviral resistance*. San Francisco: University of California, 2002.
28. Santoro MM, Fabeni L, Armenia D, Alteri C, Di Pinto D, Forbici F, et al. Reliability and clinical relevance of the HIV-1 drug resistance test in patients with low viremia levels. *HIV/AIDS Clin Infect Dis*. 2014; 58(8): 1156-1164.

POLICY AND ADVOCACY IN HIV/AIDS

OLAWALE J OLADIMEJI
MBCHB, MHPOL,
BAMIDELE M BELLO
BSC, MPH, PHD,
AND FUNMITO O FEHINTOLA
MBBS, MPH, FWACP

Since the discovery of the Human Immuno-deficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS), it has continued to be a global challenge to development and a growing public health concern globally. It has attained a pandemic state with a higher burden in developing countries where it has further weakened the already existing fragile health system (1). However, some developed countries have through different policy implementations controlled the spread of the disease within their own countries (2). HIV/AIDS, being a cross-cutting issue that has multi-sectorial involvement having various impacts in a country, needs policies that would guide the robust response to its menace in a given population. Furthermore, being a cross-cutting issue makes it impossible for any government alone in a country to control its spread and effect; there is a need for other actors to advocate various stakeholders and the general population on how best way it can be controlled (3). Policy and advocacy in HIV/AIDS are intertwined at different stages and their synergistic strength is needed for a successful HIV/AIDS response. This chapter discusses policy and advocacy in HIV/AIDS by exploring policy in the HIV/AIDS response giving a brief description of health policymaking, describing global HIV policies, expatiating on National Policies in Nigeria; the National HIV policies and strategies, and the making of National Policies in Nigeria. In addition, it elaborates on advocacy in the HIV response by giving a brief description of the practice of advocacy, the roles of advocacy in the HIV response, global advocacy in the HIV response and advocacy in the HIV response in Nigeria. It

concludes by introducing the concept of policy advocacy in the HIV response.

Policy in the HIV/AIDS Response

Health Policymaking

HIV policies are domiciled in health policies though they are closely interrelated with other sectors that are outside the health system. A health policy has been defined by the World Health Organization (WHO) as "a written expression of goals for improving the health situation, the priorities among these goals, and the main directions for attaining them" (4). It has also been defined as "decisions, plans, and actions that are undertaken to achieve specific health care goals within a society" (5). Some authors have defined it as courses of action or inaction in a given population determining health outcomes (6).

The process of health policymaking is complex and different frameworks have been given to explain it. An empirical framework, the health policy triangle (7) designed by Watt and Gilson is simplified focusing on the context (political, cultural, funding, international, civil and private groups), process (the formulation stages), content (prioritization and inclusiveness) and actors (individuals, groups, and governments).

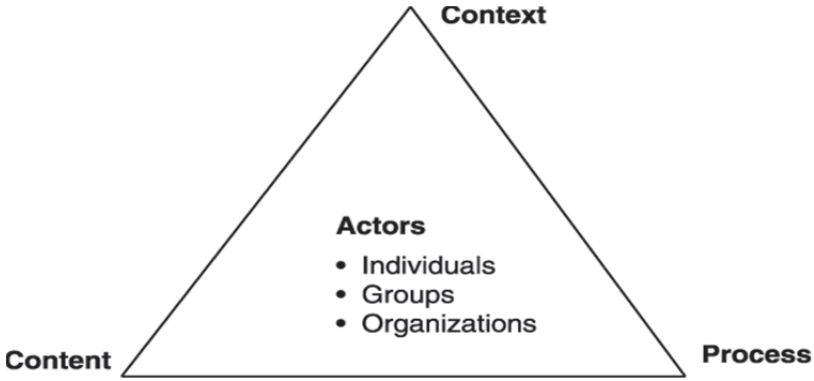


Fig 1 The Policy triangle framework
Source: Walt 1994

This policy triangle shows the different factors that may affect the making of a health policy, which also includes HIV/AIDS policies.

Another model, the Kingdon Multiple Stream Model, has been used to describe the making of health policies as an interaction between three streams (8). It explained that policies are made when the problem stream, political stream, and policy stream interact when a window opening occurs in the policy space. This model can be applied to the making of HIV/AIDS policies both internationally and nationally.

Global HIV/AIDS Policies

The global community has had a multiple policies response to HIV/AIDS since it was confirmed in the laboratory. Each of the policies has been influenced by and formulated with a central objective of controlling the spread of HIV/AIDS and halting the pandemic. The policy field of HIV/AIDS globally has many players with competing interests and different levels of influence.

The World Health Organization (WHO), being the United Nations-affiliated organization on international health, designed a policy in 1986 for the control of HIV/AIDS. This was the first global policy designed as a response to the HIV/AIDS global challenge. However, because of the increasing challenge posed by the disease, the United Nations formed another organ of its own; UNAIDS, which functions alongside the WHO on HIV/AIDS control globally. These two organizations have over the last three decades formulated policies and strategies for the HIV/AIDS response globally. They have also set and harmonized treatment standards and targets for the control of the disease globally and regionally. Moreover, they have also prioritized the population at risk and vulnerable groups in the disease control. Using quality evidence from research and systematic reviews, they have formulated and reviewed policies and strategies globally and also aligned them to other global development goals like the Millennium Development Goals and Sustainable Development Goals. The Sustainable Development Goal 3 has ending HIV/AIDS by 2030 as one of its targets. To achieve this, the WHO has set a target for 2020 by designing the "HIV Prevention 2020 Road Map" (9).

HIV PREVENTION 2020 ROADMAP

The Prevention 2020 Road Map was designed in June 2016 with a projection to achieve the 90-90-90 target by 2020 i.e., 90% of people living with HIV will be tested; 90% treated; and 90% virally suppressed (9). This means three milestones have to be achieved:

a) Reduce new HIV infections to fewer than 500,000 globally (a 75% reduction);

b) Reduce AIDS-related deaths to fewer than 500,000 globally;

c) Eliminate HIV-related stigma and discrimination.

The Road Map was prepared through a consultative process that brought together more than 40 countries and organizations, including civil society organizations, networks of people living with HIV, faith-based organizations, networks of key populations and international organizations and foundations, to chart the way forward to achieving global HIV prevention goals by 2020 (10).

The Road Map is relevant for all low- and middle-income countries, but focuses on 25 countries with high numbers of new infections in adolescents and adults in 2016. Exceptional international and national efforts are needed in these countries, which account for almost 75% of new adult HIV infections globally. All countries, however, need to intensify HIV prevention efforts to meet commitments to end the AIDS epidemic (9, 10).

The focus of the Road Map is on HIV primary prevention and the promotion and provision of effective tools to prevent HIV infections. It emphasizes the empowerment of adolescent girls, young women and key populations at risk so that they can protect themselves and stay free of infection (10).

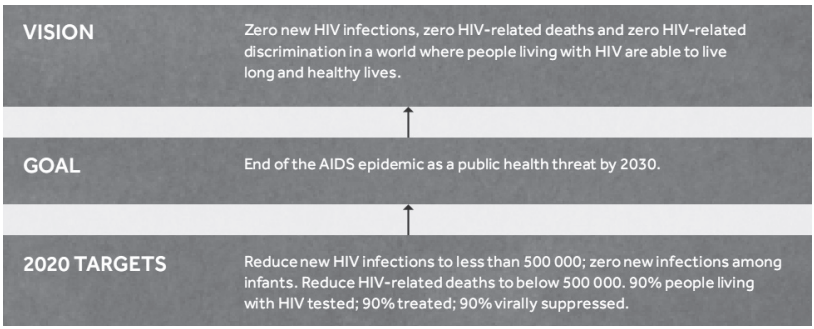


Figure 2: HIV prevention 2020 roadmap
Source: WHO 2016

Other vital global players in the HIV/AIDS response are the United States PEPFAR, the World Bank, the Global Fund, and the Bill and Melinda Gates Foundation. Each of these organizations has played a critical role in global HIV/AIDS policy, had high-level influence, made a great impact and determined the policy direction of the HIV/AIDS response globally.

National Policies in Nigeria

Nigeria has different HIV policy tools which include national policies, strategic frameworks and plans, action plans, and technical guidelines (11). Whereas the policy defines the country's long-term aspiration and intentions regarding HIV and AIDS, the Strategic Framework and/or Plan defines the approach and mechanisms towards the realization of the aspiration and elaborates on the intentions of the policy by defining strategic directions and key interventions (12). The Strategic Framework or Plan is important in the policy-to-action chain, and has become “a mainstay of AIDS responses in countries affected by the epidemic” (13). Action or Operational Plan(s), which usually span one to two years, function as the blueprints for implementation as they elaborate on the intentions of the policy and detail the dimensions of the activities relevant to the interventions identified in the Strategic Plan, and thus guide the "street-level bureaucrats" in taking relevant actions (11).

These three groups of policy instruments – the National HIV Policy, the National HIV Strategic Framework and Plan, and the National Action Plans – are intrinsically related (Figure 3) and have been developed in Nigeria periodically in the trajectory of the national HIV and AIDS response efforts (11).

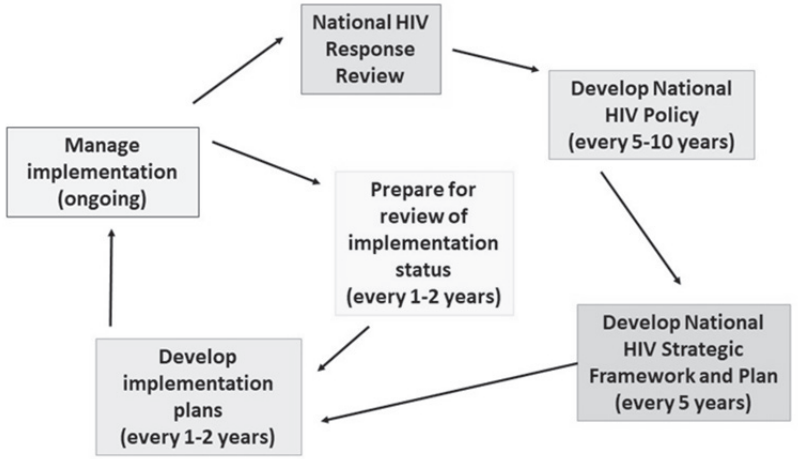


Figure 3: Nigeria policy instruments
Source: Fatusi 2018

As at 2018, Nigeria has developed ten national broad-based HIV policy documents, consisting of three National Policies specifically focusing on HIV (in 1997, 2003, and 2010), three Strategic Frameworks (in 2005, 2010, and 2016), two Strategic Plans (2010 and 2016/17) and two Action Plans (the Emergency Action Plan of 2000/2001, and the President's Comprehensive Response Plan of 2013) (11).

Making National HIV Policy

The making of HIV policy in Nigeria has been broad-based involving different stakeholders along the various stages of the process. The process that has evolved over the years has been more inclusive, more focused on priority areas and had more political commitment.

The process has gone through these different stages but not in this linear order (11):

(i) Agenda setting phase: This often is made by the Nigerian government based on need within the country or the need to align with international standards.

ii) Preparatory phase: This involves constituting a Technical Working Group by NACA, which has the over-sight function of the entire process.

(ii) Consensus-building phase: The consensus-building phase is continuous and entails organized stakeholder meetings at the initiation of the policy and at the end of the draft policy to review the document.

(iii) Technical drafting and review phase: This is undertaken by Consultants hired by NACA and also members of the TWG constituted for the policy.

(iv) Approval and enactment phase: After the TWG has finished the policy and the second stage of the consensus building is done, the document is then sent to the Federal Executive Council (FEC) for final approval, then to other organs of government.

(v) Dissemination stage: After the approval of the policy by the FEC, it would be disseminated through appropriate channels to the required places.

The National Strategic Framework III: 2016-2021

The 2016-2021 NSF (NSF III) (14) is designed in alignment with the Sustainable Development Goals (SDGs), the global agenda to end the AIDS epidemic by 2030, and with the vision of an AIDS-free Nigeria, with zero new infection, and zero AIDS-related discrimination and stigma. The strategic objectives target the following, among others, by 2021: at least 90% of people living with HIV to know their status and 90% of them having access to ARVs; at least 90% of those on antiretrovirals (ARV) achieving sustained virological suppression; and, to eliminate mother-to-child transmission of HIV.

The NSF focuses on five thematic areas: (i) Prevention of HIV among the General and Key Population; (ii) HIV Testing Services; (iii) Elimination of Mother-to-Child Transmission of HIV (eMTCT); (iv) HIV Treatment; and (v) Care, Support and Adherence. These thematic areas have related cross-cutting issues and programme enablers: (i) Gender and human rights; (ii) Health systems and community systems strengthening, and service integration; (iii) Coordination and institutional arrangement; (iv) Policy, advocacy and resource mobilization; (v) Monitoring and evaluation; and (vi) Leadership, ownership and sustainability.

Advocacy in HIV/AIDS Response

The Practice of Advocacy

Advocacy is any attempt to influence the decisions and practice of an institution (15-17). It involves the active espousal of a point of view or a course of action (18) and can include high profile legal challenges and other openly political actions, as well as less visible, more subtle processes of influence. While advocacy is primarily seen as seeking to influence government and the public sector, it can also focus on promoting changes in the private sector.

Advocacy activities may be aimed directly at the decision-makers or they may seek to influence indirectly through shaping public opinion and voter intentions or by disseminating alternative models of policy and practices. It may be a group, individual or multi-group that forms a coalition framework. It could also be present in the form of "lobbying."

Advocacy has emerged as one of the major strategies that are fundamental for ensuring highly effective HIV/AIDS response programs with improved health outcomes (19).

Roles of Advocacy in HIV response (20)

a) Ensuring Leadership Commitment;
b) Improving the Knowledge of the population on HIV Response;
c) Influencing Cultural Norms and Religious Beliefs;
d) Reinforcing Response Interventions;
e) Mobilizing Resources for HIV Response;
f) Engage in HIV policymaking, implementation and monitoring;
g) Collaborating with other actors to implement intervention programs;
h) Adapting the Legal/Legislative Framework;
i) Harnessing Global Support;
j) Targeting Behavioural Change.

Global Advocacy in the HIV Response

Advocacy in the HIV Response globally has been from different groups and with different approaches. UNAIDS has coordinated international organizations, bilateral organizations, civil society organizations and

donor groups to advocate for an HIV response. A partnership was formed in January 1999, the International Partnership for AIDS in Africa, which had resource mobilization and increasing political commitment as its core objectives (20).

Civil society organizations and non-governmental organizations have actively been involved in global advocacy for the HIV Response. These groups have been involved in agenda setting, the consultation stage, policy formulation and the implementation stage. Some of these groups have competing, while some have conflicting, interests (20). Some of these groups are faith-based, gender-based, pharmaceuticals, key populations, national groups, vulnerable groups, research groups, etc. They have functioned in the above listed roles at different periods.

Advocacy in the HIV/AIDS Response in Nigeria

Civil society groups and other organizations have been involved in advocacy in the HIV response in Nigeria. They have been involved in policy formulation where they take part in the consultation and consensus-building phase (11). They played critical roles in the HIV response in Nigeria from resource mobilization, increasing political commitment, participating in policy development, community engagement, policy implementation and monitoring, key and vulnerable population focus and legal framework (11). Some of these organizations have used various strategies to perform these roles.

It is worthy of note that JAAIDS, Journalists Against AIDS, which is an advocacy group that consists of journalist, reports and editors, uses the media (print, social and electronic) to influence HIV policy and response (21). In its advocacy strategy, JAAIDS runs an e-mail/web-based discussion forum (Nigeria AIDS e-forum) and a special media listserv to which all interested journalists have free access and through which it also organizes regular open electronic conferences on various aspects of the epidemic and the national response to it. Being a very popular forum (having a total of over 5,000 current subscribers) to which many policymakers, donors and activists subscribe, it has become a major avenue for eliciting the input of civil society, researchers and PLWHA into AIDS policymaking. It also serves the media well in receiving information on new research findings, policy developments, and current debates on various aspects of the epidemic especially on-going programs and services.

Other advocacy groups have engaged the government, policymakers, donor organizations, key populations, vulnerable populations, faith-based organizations, traditional leaders and community groups in different forums during the period of policy development, implementation and monitoring in Nigeria.

Conclusion

Policy and advocacy in HIV/AIDS are critical intertwined concepts that work synergistically to ensure the achievement of the set objectives of controlling HIV/AIDS. The concept of policy advocacy is a strategy or approach targeted at effecting change by starting, directing, and implementing a process that engages with policymakers (22). It encompasses different advocacy strategies but is directed solely to effect change in a policy. This is needed in the HIV/AIDS response especially in Nigeria where the burden of HIV/AIDS is a developmental challenge. It is a continuous process that ensures that both the policymakers and advocacy groups work together to achieve set objectives. It is a process that starts from the agenda-setting stage, through the formulation, implementation and evaluation stages of policies. This is a process that is essential if the 90: 90: 90 goal of 2020 is to be accomplished globally and especially in Nigeria which has a high burden of HIV/AIDS.

References

1. UNAIDS and AIDS Strategy and Action Planning (ASAP). Preparing National HIV/AIDS Strategies and Action Plans – Lessons of Experience, 2007. Available at www/worldbank.org/asap.
2. UNAIDS. Enhancing results by applying the Paris Declaration at sector level: Progress update and Lessons Learnt from Aid Effectiveness in AIDS Responses, UNAIDS, August 2008. http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/report/2008/20081023_accraprogressupdate_en.pdf.
3. Kam CC, Goodridge G, Moodie R. Strategic Planning, Program Design and Management. In: Lamptey PR, Gayle HD (eds). *HIV/AIDS Prevention Care Resource – Constrained Settings: A handbook for the design and management of programs*. Arlington, Family Health International, 2001. http://mr19.qeh.ox.ac.uk/sphere/pdf/common/fhi/hivaids-prevention-care.pdf.
4. World Health Organization. Health Policy, 2000

(http://www.who.int/topics/health_policy/en/).
5. Simmons R, et al. Policy Flow analysis. *Western Political Quarterly* 1974; 465.
6. Ikelegbe AO. *Public Policy making and Analysis*. 2nd edition. Benin: Uri Publishing Ltd, 1996.
7. Walt G, Gilson L. 1994. Reforming the health sector in developing countries. *Health Policy and Planning* 9(4): 353-370.
8. Kingdon JW. Agendas, alternatives and public policies. Boston and Toronto: Little, Brown and Company, 1984.
9. World Health Organization. HIV prevention 2020 roadmap, 2016.
10. World Health Organization. Global strategy for the health sector on the 2020 road map, 2016.
11. Fatusi AO, Jolayemi O, Oladimeji OJ, Afolayan M. Influences of Policies and Strategies in Nigeria. In Prosper A, Idoko JA, Odutolu O (eds.), *AIDS in Nigeria*. Unpublished, USA: Harvard University Press, 2018
12. Health Policy Initiative. The Art of Moving from Policy to Action: Lessons Learned from the USAID/Health Policy Initiative (2005–2010). Washington, DC: Futures Group, Health Policy Initiative, 2010.
13. Family Health International. The AIDS Control and Prevention (AIDSCAP) Project, 1996. http://pdf.usaid.gov/pdf_docs/pdabn592.pdf.
14. NACA. National HIV/AIDS Strategic Framework 2016-2021, 2016.
15. Kumah OM. Advocacy for Population and Reproductive Health: Key Concepts and Their Implications for Emerging Information and Communication Technologies (ICT). In *Technical Report on the UNFPA International Seminar, ICPD Advocacy in the Global Information and Knowledge Management Age: Creating a New Culture*, Ankara, 1998.
16. Casey John and Mehrotra Apurva. New York City Nonprofit Advocacy Case Studies (series of three case studies and a background paper). New York: Baruch College, Center for Nonprofit Strategy and Management, 2011. www.baruch.cuny.edu/spa/researchcenters/nonprofitstrategy/CaseStudies.php.
17. Jenkins J Craig. Nonprofit Organizations and Policy Advocacy. In Powell Walter W, and Steinberg Richard (eds.), *The Nonprofit Sector: A Research Handbook*, 2nd edition. New Haven, CT: Yale University Press, 2006.

18. Ainsworth M, Teokul W. Breaking the silence: setting realistic priorities for AIDS Control in less-developed countries. *The Lancet* 356, Issue 9223.
19. Cadwell J. Rethinking the AIDS Epidemic in Africa. *Population and Development Review*. March 2000; 26, No. 1.
20. UNFPA Report of the planning meeting on strategic options of HIV/AIDS Advocacy in Africa, 2005.
21. Ahonsi B. Presentation on Working on SRH Promotion through a Human Rights Lens in Nigeria. Ford Foundation 2018 review.
22. Young E, Quinn L. Making research evidence matter: A guide to policy advocacy in transition countries, 2011.

List of Contributors

Ibukun Peter Oyeyipo, PhD

Akinlolu G Omisore, MBCH.B, MPH, FWACP

Adeola Fowotade, MB; BS, MSC, PHD, FMCPATH

Victor O Mabayoje, MBBS, FWACP

Adedayo Damilare Adekomi, PhD

Ahmad Adekilekun Tijani, MBBS, M.Sc, PhD

Emmanuel O Farinloye, MD, FWACS

Michaeline A Isawumi, MBBCh, FMCOph, FWACS, MSC- CEH, FICS

Mustapha B Hassan, MBBS, FMCOph, FWACS, FICS

Adedayo O Olaosun, MBCHB, DLO, FWACS, MPH, MSC, CERT (ORG. LEADERSHIP)

Adetunji A Haastrup, MBBS, FWACS, FICS

Abiona Oluwadamilola Odeyemi, MBBS, FMCP

Patience O Akinwusi, BSC MBCHB FWACP, FAHA, FESC

Rasaaq A Adebayo, MBCHB, MPA, FWACP, Cert Interventional Cardiology (Alexandria Univ, Egypt)

Victor O Adeyeye, MBCHB MPA, FMCP, FWACP

Michael O Balogun, BSC,MBCHB, FMCP,FWACP, FRCP (GLASG), FSM, FESC

David A. Ofusori, PhD

BA Falana, PhD

Oyebisi Olayanju Oyekunle, MBBS, FMCP

Alebiosu Christopher Olutayo, BSC, MBCHB, FWACP

Adebimpe Olukemi Yusuf, MBCHB, FMCP

Babatope Kolawole, MBCHB, FWACP, FACP, FACE

Asekun-Olarinmoye Esther Olufunmilayo, B.Sc, MD, FWACP

Adedire Elizabeth Bunmi, MBBS.MPH,FWACP

Dare, Babatunde Joseph, PhD

Olubukunola Omobuwa, MBCHB, MPH, FWACP

Akingbola Alexander Ojo, BDS

Olubayo Abiodun Fasola, BDS, MSC, DIP Ethics, FWACS, FICD

Wasiu Olalekan Adebimpe, FWACP, PhD

Henry C Anyabolu, MBBS, FWACPaed

Jerome B.E Elusiyan, FWACPaed

Najemdeen A Adeleke, MBBS, FWACS

Moses O Abiodun, MBBS, FWACS, FMCOG

Adekunle Fatai Mustapha, MBBS, MSc, FMCP

Oluyemi Mary Adebanjo, MBCHB, MWACP

Julianah Temilola Mosanya, MBBS, FWACP

Sunday O Olarewaju

Oluwapelumi D Adeyera

Aderemi Victor Adewale, MBBS, MPH, MSC

Olawale J Oladimeji, MBCHB, MHPOL

Bamidele M Bello, BSC, MPH, PhD

Funmito O Fehintola, MBBS, MPH, FWACP

INDEX