Guidelines for **Antiretroviral Therapy** for the **Prevention** and **Treatment** of **HIV** in **Zimbabwe**

National Medicine and Therapeutics Policy Advisory Committee (NMTPAC)
and
The AIDS and TB Directorate, Ministry of Health and Child Care

December 2013

Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe, 2013

Published by:

- The National Medicine and Therapeutics Policy Advisory Committee (NMTPAC) and
- The AIDS and TB Directorate, Ministry of Health and Child Care (MOHCC), Harare

Further copies may be obtained via the AIDS and TB Directorate, Provincial Medical Directorate offices, NMTPAC, or the Directorate of Pharmacy Services, MOHCC, P.O. Box CY 1122, Causeway, Harare, Zimbabwe. Comments can be forwarded to the AIDS and TB Directorate (atp.director@ymail.com) or the Directorate of Pharmacy Services (dps@mohcc.gov.zw).

The information presented in these guidelines conforms to current medical, nursing, and pharmaceutical practice. It is provided in good faith, and hence, whilst every effort has been made to ensure that the medicine doses are correct, no responsibility can be taken for errors or omissions.

Original cover design: Regina Gapa and Charon Lessing

CONTENTS

APPENDIX

I. FOREWORD

HIV and AIDS remains a major public threat in the country with a prevalence of 15% among the adult population. The introduction of antiretroviral therapy (ART) has revolutionised the care and management of HIV and AIDS and has transformed the disease from being life-threatening infection into a chronic and manageable condition. Whilst ART does not cure HIV and AIDS, and should therefore be taken for life, it dramatically reduces mortality and morbidity if used appropriately. Recent evidence supports HIV treatment as a prevention intervention for HIV transmission and hence underscores the importance of ART.

The national ART roll-out programme continues to register successes in terms of wide national coverage for treatment to those in need despite a difficult marco-environment. Through continued decentralization of ART services more people are now able to access such services closest to their homes. The government remains committed to offering ARVs free of charge to PLHIV at public institutions as a policy in order to overcome potential economic access challenges. The rational use of such medicines is imperative if we are to reach more of those in need of this life-saving therapy. There is also continued need to use the public-health approach for the management of HIV and AIDS. Health-care workers need to have simplified treatment regimens as exemplified by our current national ART guidelines as well as the widely used Essential Medicines List of Zimbabwe. Using guidelines simplifies clinical decision making which allows the use of other cadres and not just doctors in the delivery of ART as well as in the associated monitoring.

We should all pursue and promote a standardised approach to treatment to minimise the development of HIV medicine resistance and ensure the sustainability of our programme. The guidelines are meant for use in the public and private sectors. These guidelines will be regularly updated as new information and evidence becomes available. I encourage you to make use of the latest edition of the guidelines. You will find this easy given that we use a different colour for the cover each time we produce a new version. Again, note that some recommendations might change in the future as evidence and resources dictate.
We hope you will use these guidelines consistently.

Dr P. D Parirenyatwa
Minister of Health and Child Care, Zimbabwe 2013

II. ACKNOWLEDGEMENTS

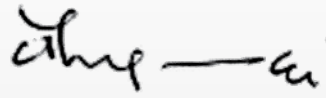
We are grateful to those people currently involved in the national ART and research programmes for sharing their experiences as well as best practices and thus contributing to the revision of these guidelines. Special thanks are extended to those who developed the original guidelines, whose basis remains the backbone of this current edition, as well as to the World Health Organization (WHO) for continually updating its ART guidelines (latest revision 2013) and allowing them to be adapted freely by national programmes.

The following people and organisations were actively involved in the current guideline revision and hence deserve special mention:

- Dr. C. Chakanyuka, National Professional Officer, HIV and Tuberculosis, WHO Country Office, Zimbabwe
- Dr. H. Mujuru, Paediatrician, UZCHS
- Professor. M. Borok, Physician, UZCHS
- Dr A. Mushavi, PMTCT and Paediatric HIV, Care and Treatment Coordinator, MOHCC
- Dr A. T. Makadzange, Infectious Diseases Specialist, UZCHS
- Dr T Nyamundaya, Elizabeth Glaser Paediatric AIDS Foundation
- Dr. T. Mutasa-Apollo, Deputy Director, HIV & AIDS and STIs, MOHCC
- Dr. J. Murungu, Deputy ART Programme Coordinator, MOHCC
- Mr F. Mudzimu, Deputy Director of Pharmacy Services, MOHCC
- Dr. F. Taziwa Deputy Medical Coordinator MSF Spain, Zimbabwe
- Dr Nandita Sugandhi, Clinical Advisor, CHAI Global Clinical Support Team
- Mr Tichakunda Mangono, Country Analyst, CHAI Zimbabwe
- Ms. Ana Svoren, Senior Laboratory Analyst, CHAI Zimbawe.
- Mr Alexio – Zambezi Mangwiro, Country Director, CHAI Zimbabwe.

We also like to acknowledge CHAI, EGPAF and the Global Fund for their financial support in printing these guidelines.
Thank you.

Dr. C.E. Ndhlovu
MMedSc (Clin Epi), FRCP
Chairperson, NMTPAC



Dr. O. Mugurungi
MBChB, MSc
Director, AIDS and TB Programmes

III. LIST OF ACRONYMS/ ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARVs	Medicines for treating HIV
ATV	Atazanavir
AZT	Zidovudine
BCG	Bacille Calmette-Guérin
BHIVA	British HIV Association
CHAI	Christian Health Access Initiative
CHBC	Community- and home-based care
CD4	Cluster of differentiation 4
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
D4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic acid
EFV	Efavirenz
EID	Early infant diagnosis
FCH	Family and child health
FDC	Fixed-dose combination
FP	Family planning
GI	Gastrointestinal
HBIG	Hepatitis B immune globulin
HBV	Hepatitis B virus
HCW	Health Care Worker
HIV	Human immunodeficiency virus
HL	Hodgkin's Lymphoma
HPV	Human papilloma virus
ICP	Intracranial pressure
IDV	Indinavir
IRIS	Immune reconstitution inflammatory syndrome
LA	Latex agglutination
LFA	Lateral flow assay

LFT	Liver function test
LPV	Lopinavir
MCAZ	Medicines Control Authority of Zimbabwe
MOHCC	Ministry of Health and Child Care
NADCs	Non-AIDS defining cancers
NMTPAC	National Medicine and Therapeutics Policy Advisory Committee
NGO	Nongovernmental organisation
NHL	Non-Hodgkin's Lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OI	Opportunistic infection
PCP	Pneumocystis jirovecii pneumonia
PCR	Polymerase chain reaction
PI	Protease inhibitor
PITC	Provider-initiated testing and counselling
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission of HIV
RNA	Ribonucleic acid
RTV	Ritonavir
SEQAAAR	Safe, efficacious, quality, affordable, accessible, available, rationally used
SQV	Saquinavir
STI	Sexually transmitted infection
TB	Tuberculosis
TDF	Tenofovir
USA	United States of America
UZCHS	University of Zimbabwe College of Health Sciences
VCT	Voluntary counselling and testing
VEN	Vital, essential, necessary
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine
ZNMP	Zimbabwe National Medicine Policy

IV. PROCESS OF UPDATING THE GUIDELINES

Chapters were allocated to members of the National Medicines and Therapeutics Policy Advisory Committee(NMTPAC) according to their areas of expertise or interest. Furthermore, other experts e.g. working with the World Health Organization (WHO), EGPAF as well as the national programmes for the HIV & AIDS and TB programmes were consulted. Use was made of the latest WHO recommendations[1] as well as the comments from the report of a Consensus meeting held on 23-24 September 2013 in Harare which was convened by the AIDS and TB Directorate to enable a discourse on the 2013 WHO ART for Prevention and HIV treatment recommendations. This meeting was attended by various stakeholders including the Steering Committee that had been set up by the AIDS and TB Directorate to adapt the newly released WHO guidance as well as people living with HIV.

The NMTPAC also convened a special meeting on 23 October 2013 where members reviewed the chapters allocated to them. Some of the recommendations were based on the ongoing evidence-informed discussions that the NMTPAC members had been having over the past years whilst awaiting the WHO's revision of their guidelines. The PMTCT recommendations were already known as the country had recently adopted the recommendation to use lifelong antiretroviral therapy i.e.Option B+ - providing ARVs to all pregnant and lactating women after the release of the WHO 2012 PMTCT programmatic update.

The principles of applying the "essential medicines" concept were maintained, and the need to maintain evidence-informed recommendations as well as the rational use of medicine was paramount. The recommendations had to be deemed cost-effective and feasible in our health-care delivery. Essential medicines are those medicines that satisfy the needs of the majority of the population and therefore should be available at all times. Relevant ART guidelines and in particular the latest WHO guidance informed the revision process. The aim was to have an evidence-informed consensus view of the acceptability, affordability, and feasibility of implementing the recommendations within the Zimbabwean healthcare delivery system.

The Zimbabwean health delivery system can be divided into four levels: primary care, first referral level (district hospital), second referral level (provincial hospital), and third referral level (central hospital). Selection of medicines is based on SEQAAAR (i.e., safety, efficacy, quality, affordability,

[1] Consolidated guidelines on the Use of Antiretroviral Medicines for Treating and Preventing HIV infections: recommendations for a public health approach, WHO, June 2013

accessibility, availability, and rational use). Medicine availability is also classified by the level of prescribing—that is, S (specialist), A, B, or C. S medicines require special expertise and/or diagnostic tests before being prescribed. A medicines should be prescribed only at the central or provincial levels.

B medicines are prescribed from the district level upward, and C medicines should be the only medicines freely available at the rural primary care level. B-level medicines can be made available at the C level with the consent of the district medical officer. ARV medicines are classified as C and therefore can be available at primary care level. The VEN (vital, essential, necessary) classification allows for priority setting for medicine selection, procurement, and availability: V medicines are vital, given first priority, and supposed to be available 100% of the time; E medicines are essential and given second priority; and N medicines are necessary or nonessential and last on the list of priority needs. The Essential Medicine List of Zimbabwe categorizes the medicines selected for Zimbabwe by level as well as by VEN classification. These classifications are reviewed from time to time to correspond to the country's current needs.

NMTPAC's overall objective is to oversee the implementation of the specific objectives of the Zimbabwe National Medicine Policy (NMP). The overall goal of the NMP is to provide quality health care for most of the population through the provision of safe, effective, good-quality, and affordable medicines.

Rational use of medicines is enhanced by the development, distribution, and use of treatment protocols and hence the need to keep revising our guidelines while taking into cognisance the feasibility of implementing the desired recommendations within our health care delivery system.

NMTPAC is responsible for reviewing the Essential Medicines List and treatment guidelines as well as monitoring the rational use of medicines in Zimbabwe. NMTPAC is a multidisciplinary team of health-care workers who provide voluntary service for the committee. Including its secretariat i.e. the Directorate of Pharmacy Services, the current NMTPAC membership has HIV experts, physicians, paediatricians, public-health specialists, pharmacists, and regulatory officers and is as follows:

Name of Member	Designation/Institution
Bakasa C, Mrs	Deputy Director, Non-Communicable Diseases, MOHCC
Borok M Z, Professor	Physician, UZCHS
Chakanyuka CC, Dr	National Programme Officer, HIV/TB,WHO
Hove R, Mrs	Pharmacist, Directorate of Pharmacy Services
Khoza S, Dr	Clinical Pharmacologist, UZCHS
Manyame S, Dr	Obstetrician and Gynaecologist, UZCHS
Maunganidze A J, Mr	Surgeon, UZCHS
Mhazo A, Mr	Pharmacist, Directorate of Pharmacy Services
Moyo T, Mr	Pharmacist, Pharmaceutical Manufacturers Association
Mudzimu F, Mr	Pharmacist, Directorate of Pharmacy Services
Mudzura-Samukange E, Mrs	Regulatory Officer, MCAZ
Mungwadzi G, Dr	President , College of Primary Care Physicians of Zimbabwe
Mujuru H A, Dr	Paediatrician, UZCHS
Mushavi A, Dr	Paediatrician, PMTCT and Paediatric HIV Care and Treatment, MOHCC
Mutasa-Apollo T, Dr	Deputy Director, HIV & AIDS and STIs
Ndhlovu C E, Dr	Physician, UZCHS
Ndlovu M, Mr	Pharmacist, Directorate of Pharmacy Services
Nyamayaro R T T, Dr	Anaesthetist, Parirenyatwa Central Hospital
Nyatsambo C, Dr	Physician, Harare City Health Department
Sifeku F, Mrs	Pharmacist and Managing Director, National Pharmaceutical Company
Torongo M, Mrs	Pharmacist, Retail Pharmacists Association
Vuragu D N, Mr	Chief Pharmacist, Parirenyatwa Central Hospital
Wellington M, Dr	Public Health Specialist, Newlands Clinic

1. INTRODUCTION

Antiretroviral therapy is an integral part of the provision of comprehensive services for HIV and AIDS prevention, treatment, care, and support. The goal of ART is to reduce morbidity and mortality due to HIV and AIDS as well as to improve the quality of life of people living with HIV and AIDS. The ultimate aim is to provide "universal access" to ART to those who need it by 2015. According to the 2011 National HIV Estimates, it is estimated that 962,779 people including 104,937 children are in need of ART in Zimbabwe in 2013 (based on a CD4 ≤ 350). It is projected that the number of people in need for ART will increase to 1,308,321 and 1,373,879 in 2014 and 2015 respectively with the adoption of earlier ART initiation at a higher CD4 threshold of ≤500. According to the World Health Organization (WHO), "Universal access means establishing an environment in which HIV prevention, treatment, care and support interventions are available, accessible and affordable to all who need them. It covers a wide range of interventions that are aimed at individuals, households, communities and countries."

1.1 ART entry points

Patients have many opportunities to enter Zimbabwe's ART programme. The well-developed ART entry points include outpatient departments and clinical wards as well as the following services: client-initiated testing and counselling (CITC) or voluntary counselling and testing (VCT), provider-initiated testing and counselling (PITC), prevention of mother-to-child transmission and early infant diagnosis (PMTCT/EID), Expanded Programme on Immunization (EPI), TB, sexually transmitted infection (STI), family planning (FP), and community- and home-based care (CHBC).

1.2 ART programme

Zimbabwe initiated its national ART programme in April 2004, and since that time the benefits of such therapy have been widely documented in the country. The scaling up of the ART programme is facilitated by the identification and approval of ART-initiating sites using standardized assessment tools and simplified treatment guidelines that employ the public-health approach as well as the family-centred approach. It is now widely accepted that even resource-poor countries using a public-health approach to HIV and AIDS care and treatment can achieve similar effectiveness with these antiretrovirals (ARVs) as observed in more affluent settings.

The national Zimbabwe Opportunistic Infection (OI) / ART review of 2012

noted that although a rapid scale-up of ART had occurred generally, treatment of adolescents and children was still lagging behind. There is thus a need to scale up the delivery of ART to this group. The increase in patient volume over time has resulted in the need for the available human resources to multitask to enable the ART programme to achieve universal access. Decentralization of services will need to continue to allow clients to have ART facilities nearer to their homes. Capacity building through health-care worker training and the use of treatment guidelines have allowed the dramatic scaling up of ART in Zimbabwe. Thus, with effective management of HIV and AIDS, people living with HIV and AIDS should continue to live quality and productive lives.

The achievements and sustainability of the national ART programme will depend on the rational use of available medicines as well as the appropriate monitoring of patients to ensure medication adherence and thus limit the emergence of ARV medicine resistance and avoid adverse medicine events.

At all levels of care, appropriate initiation of ART using the recommended first-line regimen should be emphasised. The first-line regimen has good efficacy and careful adherence support, monitoring for side-effects, and OI management should result in a large number of patients remaining on this regimen for many years to come. The 2013 WHO guidelines emphasise the need to consider the quality of life of those on ART by using safer medicines as well as starting ARVs earlier. Thus the CD4 count threshold for starting ART will be raised to 500.

Highlights from the revised guidelines include the following:

ART must be started in all those with WHO clinical stages III and IV of HIV disease. Do not insist on seeing a CD4 lymphocyte count result in such patients. Where CD4 count testing is available, ART should be started at CD4 counts of less than or equal to 500 cells/mm3 in all adults and adolescents, whilst some patients groups will start ART regardless of CD4 count.

Prioritisation for ARVs will occur as follows:

- **Regardless of the CD4 count:**
    - **ART for all HIV +ve pregnant and lactating women**
    - **All HIV+ve partners in sero-discordant couples**
    - **ALL HIV +ve children below 5 years old**
- The preferred first-line regimen for adults, adolescents, and older children will be Tenofovir, Lamivudine and Efavirenz

- ART will be offered to the HIV-infected partner in a sero-discordant relationship irrespective of the level of their CD4 count.
- Life long ART for HIV positive pregnant and lactating women (Option B+) will be given for PMTCT even without a CD4 count.
- Early infant diagnosis using dried blood spots continues.
- Early initiation of ART in HIV-infected children under 5 years of age regardless of immunological or clinical status.
- Apart from exclusive breastfeeding for the first 6 months, prolonged breast feeding up to 2 years continues to be recommended.
- First-line regimens for infants under 3 years will include the use of a protease inhibitor (PI).
- Gradual phasing in of viral load monitoring

Given the maturation of our ART programme, an increasing number of clients will require both second-line and third-line regimens, but those numbers can be kept low if ART is delivered with due care.

1.3 Adherence

ART services are no longer primarily focused on the potency of the treatment regimens; adherence to the regimens is extremely important. We must provide support for adherence so that high adherence rates are achieved. By minimising the pill burden through the use of fixed-dose combination (FDC) regimens, we have simplified treatment regimens. The lower the frequency of medicine taking, the better—once a day is better than twice a day, and so on. We should take advantage of the literacy of our clients and provide them with reading materials and posters.

1.4 Primary and secondary prevention strategies

Despite the availability of numerous chemotherapeutic agents effective in reducing the viral load in persons with HIV infection, there are still only a limited number of combinations available to us. Treatment and care of people with HIV and AIDS must now go hand in hand with prevention. Primary prevention focuses on remaining HIV-negative, whereas secondary prevention is directed to those who are already infected and aims to reduce the transmission of HIV to others, including unborn children. HIV infection remains incurable, and thus control of the epidemic using primary prevention remains vital (Table 1).

Services for HIV should be linked or integrated with other services in the health sector, including those for TB, sexual and reproductive health,

maternal and newborn health and child health. They should also be linked or integrated with services provided by other sectors, such as education and social welfare, and with those provided within homes and communities by families, international and national nongovernmental organisations (NGOs), community-based organisations, faith-based organisations, and groups or networks of people living with HIV. All such services should be provided as close to clients' homes as possible—hence the need to continue decentralising such services.

Table 1: Primary and Secondary HIV Prevention Strategies and Related Activities

Strategy	Activities
Public health education	• Inform and educate the public about the nature of HIV and other STIs, including dangers of infection, complications, modes of transmission, methods of prevention, and treatment
Promote safer sexual behaviour (behaviour change)	• Encourage the following: ° Abstaining from sexual activity altogether ° Delaying first sexual experience ° Avoiding situations that may promote casual sexual liaisons ° Avoiding multiple concurrent partnering ° Using condoms correctly and consistently • Promote and provide condoms widely
Promote early STI-care seeking	• Promote good STI-care-seeking behaviour • Make STI services accessible and acceptable
Promote testing and counselling for HIV and AIDS	• Increase access to testing and counselling for HIV and AIDS • Scale up PITC and VCT/CITC
Prevent mother-to-child transmission of HIV	• Strengthen PMTCT activities • Prioritise provision of lifelong ART to pregnant and lactating women
Promote male circumcision	• Promote male circumcision • Provide male circumcision services
Promote ARVs	• Promote early access to ARVs • Promote ARVs in sero-discordant couples

2. PRINCIPLES OF ANTIRETROVIRAL THERAPY

The guiding principles for effective ART include potency of regimens chosen, minimum adverse events, reduced pill burden, and accessibility and affordability of the medicine combinations. The reduced pill burden will be achieved by using FDCs of antiretroviral medicines. Although the potency (efficacy) of the regimen is important, adherence to a simple regimen will ensure that the ongoing viral replication is maximally suppressed, thus allowing the immune status to recover. Plasma viral load (VL) measures viral replication, whereas the effect of ART on the immune system is monitored using the CD4 lymphocyte count in most patients or CD4 percentage in children under five years.

Health-care personnel will need to receive continuing medical education to remain up to date on ART recommendations. Guidelines change as new evidence emerges from clinical trials and lessons are learnt from programme experiences. The need for those involved in managing patients on ART to undergo frequent retraining and evaluation cannot be overemphasised. ART requires in-depth knowledge about antiretroviral agents, their side effects, and issues such as immune reconstitution inflammatory syndrome (IRIS). Being able to detect and manage OIs, knowing when to initiate ART, and knowing when to change medicines as toxicities occur or when to switch to second-line or even third-line therapy, as well as counselling abilities, are all necessary skills. Such skills can be acquired with the relevant training and experiential learning. Clinical attachments and clinical mentoring are tools to improve health-care worker skills in all disciplines, including ART delivery.

Adherence to treatment regimens and schedules is crucial to the success of this therapy. Without high adherence rates, viral resistance to the medicines emerges readily. Hence, there is need to be vigilant and monitor patients during ART for adherence rates, side effects, and treatment failure. Treatment failure should alert the health-care worker on the need to switch to second-line or third-line therapy.

Switching to second-line therapy will be based on a combination of clinical monitoring plus at a minimum laboratory testing (CD4 count). Hence, there is need to be vigilant. Access to VL testing is not yet widely available but should be considered when having to switch to second or third line therapy. Given the maturing ART programmes, third-line therapy will shortly become necessary. The use of such third-line regimens will require close consultations with those specialists who have experience treating clients who are “ART experienced.”

2.1 Characteristics of available ARVs

Medicines in use in most of our programmes belong to the following classes:

- Nucleoside reverse transcriptase inhibitors (NRTIs). These medicines block the HIV reverse transcriptase enzyme and prevent the copying of the viral RNA into the DNA of infected host cells by imitating the building blocks of the DNA chain. The resulting DNA chain is incomplete and cannot create new viruses.
- Nucleotide reverse transcriptase inhibitors (NtRTIs). These medicines act at the same stage of the viral life cycle as do NRTIs but have a better resistance profile.
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs). These medicines also block the HIV reverse transcriptase enzyme, but have a different mechanism of action than the NRTIs and the NtRTIs.
- Protease inhibitors (PIs). These medicines block the enzyme protease and prevent the assembly and release of HIV particles from infected cells.

These additional classes of ARVs are not yet in use in Zimbabwe:

- *Integrase inhibitors (IIs).* These medicines target HIV's integrase protein, blocking its ability to integrate its genetic code into human cells.
- *Fusion inhibitors (FIs)*. These work by preventing HIV from entering healthy CD4 cells by blocking proteins on the surface of CD4 cells.
- *CCR5 inhibitors.* These block the CCR5 co-receptor that HIV uses to enter and infect the cell. CCR5 works specifically against CCR5-tropic HIV. Before treating a patient with a CCR5 inhibitor, a test to determine the strain of virus is necessary.

Table 2 on the following page shows the different categories of ARVs.

Table 2: Classes of ARVs

Nucleoside Reverse Transcriptase Inhibitors	Non-nucleoside Reverse Transcriptase Inhibitors	Protease Inhibitors
Tenofovir (TDF) (NtRTI)	Nevirapine (NVP)	Lopinavir/ritonavir (LPV/r)
Zidovudine (AZT, ZDV)	Efavirenz (EFV)	Atazanavir/ritonavir (ATV/r)
Lamivudine (3TC)	Etravirine	Darunavir
Emtricitabine (FTC)		Ritonavir(RTV)
Abacavir (ABC)		
Didanosine (ddI)		
Stavudine(d4T)		
Fusion Inhibitor		
Enfuvirtide		
Integrase Inhibitor		
Raltegravir		
CCR5 Inhibitor		
Maraviroc		

By prescribing and dispensing FDCs, we can reduce the patient's pill burden and improve medication adherence. Use a boosted PI (a PI plus ritonavir) where a PI is indicated.

2.2 Efficacy and safety

Regimens based on two NRTIs plus one NNRTI are efficacious, are less expensive, have generic formulations, and are available as FDCs. PIs should generally be preserved for second-line or third-line therapy and for infants.

The preferred first line regimen of Tenofovir, Lamivudine and Efavirenz has relatively few adverse effects and is taken once daily. Zidovudine (as an alternative to Tenofovir) can cause anaemia but is less likely to cause peripheral neuropathy.

Stavudine is being phased out and should only be used where either Tenofovir or Zidovudine cannot be tolerated. Patients on Stavudine should be closely monitored for side effects.

Efavirenz has less adverse effects compared to Nevirapine. Nevirapine can cause a rash and hepatotoxicity and thus should be used with caution when initiating ART at higher levels of CD4 counts (e.g., in women with CD4 counts greater than 250 and in men with CD4 counts greater than 400).

All ARVs have class-specific side effects, and individual medicines may cause specific side effects (see Table 14 in Section 7.3). In addition, significant medicine interactions and toxicities may occur when using some ARVs in combination with each other and with other medicines such as TB medicines.

3. INITIATION OF ANTIRETROVIRAL THERAPY IN ADULTS AND ADOLESCENTS

3.1 Goals of ART

The aims of ART are as follows:

- Maximal and durable suppression of replication of HIV
- Restoration and/or preservation of immune function
- Reduction of HIV-related morbidity and mortality
- Improvement of quality of life
- Prevention of mother-to-child transmission of HIV (vertical transmission)
- Reduction of transmission of HIV from infected to uninfected individuals through use of ARVs by the infected individual now commonly known as 'Treatment as prevention'

Prior to starting ART, patients should be assessed for readiness to take ARVs; the ARV regimen; dosage; and scheduling; the likely potential adverse effects; and the required monitoring. Both medical and psychosocial issues need to be addressed before initiating ART. Patients should be adequately counselled about adopting appropriate lifestyle measures such as safer sex practices (including use of condoms), and any other psychosocial problems that may interfere with adherence (e.g., alcohol, psychiatric disorders) should be addressed. At each clinic visit, always screen for tuberculosis using a TB symptom checklist, advise patients about adequate nutrition and the importance of medicine adherence and regular follow-up care. People taking ARVs should also be regularly asked on whether they are taking other medications including herbal remedies that may interfere with the efficacy of ARVs.

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. Increasing evidence also indicate that untreated HIV may be associated with the development of severe non-AIDS defining conditions including cardio-vascular disease, kidney disease, liver disease and neurocognitive disorders. Recent results from the HPTN 052 study strongly support the use of ART to prevent HIV transmission among sero-discordant couples .

3.2 Medical criteria for initiating ART in adults and adolescents

ART should be provided to all eligible people with confirmed HIV diagnosis and with a CD4 count of ≤ 500 cells/mm3.

As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count less or equal to 350 cells/ mm3. It is also recommended to initiate ART in the following categories of patients regardless of CD4 cell count:

- Active TB disease
- Pregnant and breast-feeding women with HIV
- Individuals with HIV in sero-discordant relationships
- HBV co-infection with severe chronic liver disease

Patients with CD4 <100

Patients with low CD4 below 100 should be fast-tracked for treatment initiation. They should be screened for symptomatic TB and cryptococcal disease (see section 4.5). They should receive Cotrimoxazole and INH prophylaxis like all other patients and should be closely monitored for 3 months as this is their highest risk period for bacterial infections and TB or crypto IRIS. Health workers should educate them and their families to report immediately to a health facility if they are unwell whilst their CD4 is< 100.

See Table 3 and the WHO clinical staging system (Appendixes I and II).

Table 3: Treatment Decisions (adapted from WHO 2013 Consolidated Guidelines for the Use of Antiretroviral Drugs for Prevention and Treatment of HIV Infection)

Adults and Adolescents – with a documented positive HIV test and meeting any one of the following criteria:	
Criteria	**Treatment Decision**
Severe or advanced symptomatic HIV infection (WHO clinical stage 3 or 4)	Treat all regardless of CD4 cell count
Asymptomatic/mild HIV disease	Treat CD4 ≤ 500 cells/mm3 (CD4 ≤ 350 cells/mm3 as a priority)
HIV sero-discordant couples	Treat infected partner regardless of CD4 cell count
TB co-infection	Treat all HIV Positive TB patients regardless of CD4 cell count
Hepatitis B co-infection	Treat regardless of CD4 count in presence of chronic severe liver disease
HIV positive Pregnant and lactating women	Treat all regardless of CD4 cell count

The revised medical criteria of initiating ARVs at CD4 count ≤ 500 cells/ mm3 means that many more PLHIV will be eligible for ART and that will include many healthier people. Given our limited resources as a country, not all these eligible patients may be able to receive ARVs immediately. Hence there will be need to prioritize as indicated above. The AIDS and TB Directorate of the MOHCC will regularly advise you on availability of funds to procure ARVs, so as to ensure that those started on ARVs are maintained on them to reduce the potential development of HIV medicine resistance.

3.3 Psychosocial criteria for initiating ART

Consider the following psychosocial criteria when initiating ART:

- Has the patient completed the prescribed counselling session(s)?
- Is a treatment partner available and/or has disclosure been made to that treatment partner (strongly encouraged)?
- Is there an easy method of following up on the patient?
- Is the patient ready to take medications indefinitely?

STARTING ART IS GENERALLY NOT AN EMERGENCY. PATIENTS SHOULD BE ADEQUATELY PREPARED FOR IT.

3.4 Reasons for deferring ART

A patient may be deferred (delayed) from starting therapy if the patient

- has cryptococcal meningitis,
- needs further psychosocial counselling (e.g., for alcohol problems),
- has TB (defer starting ART for at least 2 weeks)
- needs further information on HIV and AIDS,
- is terminally ill and unable to swallow oral medication (palliative care is then offered to such a patient).

Such patients should be offered continued monitoring and close follow-up as well as counselling so that ART can be commenced at an appropriate time.

3.5 Adherence to ART

WHO defines treatment adherence as 'the extent to which a person's behaviour- taking medications, following a diet and/or executes lifestyle changes' corresponds with agreed recommendations from a health care provider.

Efforts to support adherence should start before ART initiation and should include basic information about HIV, the ARV medicines, expected adverse events, preparations for long-term ART. Many factors affect adherence to treatment. Patients may just forget to take their ARVs, be away from home, be depressed or may abuse alcohol. Medication factors may include adverse events, pill burden, dietary restrictions. Health care factors include medicine stock outs, long distances to health facilities and costs related to care.

Effective adherence support interventions include client-centred behavioural counselling and support, support from peer educators trained as "expert patients," community treatment supporters and mobile text messaging. High quality evidence from randomized trials has shown that text messages contributed to reduced non-adherence and unsuppressed viral load. Other interventions involve encouraging people to disclose their HIV status and providing them with adherence tools such as pill boxes, diaries, and patient reminder aids. During follow-up, patients should be assessed for adherence to whatever treatment plan has been agreed upon (Integrated HIV training curriculum, MOHCC).

3.6 ART in adolescents

Who is an adolescent?

WHO defines an adolescent as a child between the ages of 10 and 19 years. This period of life encompasses many physiological and psychological changes that should be taken into account when treating an adolescent.

HIV Testing and Counselling in Adolescents

It is important to increase uptake for HIV testing and counselling by adolescents. Special attention should be given to:

- Post-test counselling; appropriate and successful linkage to prevention, treatment and care services; and consent and confidentiality, which are major concerns for adolescents
- Understanding that adolescents testing positive for HIV, who do not yet require treatment, do need care and retention within the health system

Principles of ART in adolescents

The principles of therapy are similar to those in adults and children. However, one should bear in mind specific issues when monitoring and treating HIV-positive adolescents, which are discussed in the following sections.

Dosage of ART

Decisions regarding dosage for adolescents should take the following factors into account:

- The age at which to start adult dosing can be difficult to determine.
- Stunting and wasting which are common among HIV-positive adolescents.
- It is recommended that those under the weight of 25 kg should be dosed according to paediatric dosing guidelines. Thus, all adolescents—regardless of age—should be weighed before commencing ART.

Staging HIV-positive adolescents and criteria for starting ART

HIV-positive adolescents are at risk not only of the HIV-associated infections typically used to stage HIV-positive adults but also of chronic non-infective complications typically used to stage paediatric HIV. These specifically include chronic lung disease, lymphoid interstitial pneumonitis (stage 3) and HIV-associated cardiomyopathy/nephropathy and stunting (stage 4).

Such conditions should be taken into account when staging HIV-positive adolescents and when considering when to start ART.

Monitoring of HIV disease

In monitoring adolescents, remember the following:

- Stunting and pubertal delay are common.
- As well as CD4 count and Viral load monitoring, clinical monitoring should include measurement of height and weight at every clinic visit as well as evaluation of pubertal stage using Tanner staging every six months.
- Girls should specifically be asked about menstruation, including age of menarche and timing of menstrual cycles.

Chronic complications

As well as looking for and treating OIs, clinicians should monitor patients for chronic complications such as heart failure, lung and skin infections.

Disclosure

Lack of knowledge of HIV status can result in poor adherence to ART. Adolescents should be involved in the discussion about HIV testing, and their HIV status should be disclosed to them. Do not assume that adolescents are aware of their HIV status. Unless exceptional circumstances make it difficult for an adolescent to understand his or her HIV status (severe mental disability), it is strongly recommended that HIV status be disclosed before the patient starts ART. Disclosure is a gradual process and should be carried out with the involvement of the guardian, a counsellor, and the doctor.

Adherence

Adherence is particularly problematic in adolescents. Particular attention should be paid to assessing adherence at every visit and to providing adherence support. Counselling on adherence should include exploring specific reasons that may contribute to poor adherence. Adolescents face many psychosocial issues that can affect their adherence, and those should be assessed:

- In particular, ways of supporting attendance at clinic appointments and taking medicines while at school (especially for those at boarding schools) should be addressed.
- Patients should be encouraged to identify a family member who will help support their treatment.

- Peer support at the clinic level can be very helpful in encouraging adherence.
- Counselling should be adolescent-friendly, and counselling patients on their own without the presence of guardians/parents is recommended whenever possible. This ensures that patients can talk about personal issues that affect their ability to take medicines.

Education and information on sexual and reproductive health

Education about sexual and reproductive health should be part of the counselling and treatment of HIV-positive adolescents. Education and information should be tailored according to the patient's own knowledge and maturity. This clearly varies across the age group and should be assessed during counselling.

Specific information that should be given to adolescents includes information on

- Avoiding onward HIV transmission, including delaying sexual relationships and using condoms;
- Specific modes of HIV transmission (it is a common misconception that kissing and non-sexual physical contact can transmit HIV); and
- Where to access family planning services and STI treatment and how to seek help in cases of sexual assault.

4. RECOMMENDED TREATMENT REGIMENS FOR ADULTS AND ADOLESCENTS

The choice of medicine regimen is based on the "essential medicine" concept and the rational use of medicine. To maximise adherence, use of FDC medicines is strongly encouraged.

An essential medicine or medicine is defined as follows:

Essential medicines are those medicines that satisfy the healthcare needs of the majority of the population, at a price they and the community can afford; they should therefore be available at all times and in adequate amounts, and in appropriate dosage forms (WHO Expert Committee on Essential Medicines, December 1999).

The rational use of medicines is defined as follows:

The rational use of medicines requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community. (WHO Conference of Experts, Nairobi, 1985)

The national ART programme is moving towards using simplified and user-friendly fixed-dose combinations for ARVs. The following FDCs will be used for the first line regimens:

Dual combinations:

- Tenofovir (TDF) 300mg+ Lamivudine (3TC)300mg
- Zidovudine (AZT) 300mg + Lamivudine (3TC) 150mg

The above dual FDC should be used in combination with single formulation of:

- Efavirenz (EFV) 600mg
- Nevirapine (NVP) 200mg

Triple combinations:

- Tenofovir (TDF) 300mg+Lamivudine (3TC) 300mg+Efavirenz(EFV) 600mg
- Zidovudine (AZT) 300mg + Lamivudine (3TC) 150mg + Nevirapine (NVP) 200mg

Please note that the national ART programme has phased out Stavudine-based regimens. Limited stocks will be available for those patients who do not tolerate Tenofovir or Zidovudine based regimens for whatever reason.

Tenofovir (TDF) plus Lamivudine (3TC) plus Efavirenz (EFV) is the preferred first-line regimen, which obviously would necessitate a change in the currently used second-line regimens. Since the ART programme has stocks of Tenofovir/Lamivudine/Nevirapine, this combination will have to be used until most of the stocks are exhausted.

During the transition phase of implementing the revised guidelines, Tenofovir/ Lamivudine/Efavirenz combination (ideally a single pill a day in the evening) will be reserved for pregnant and breast-feeding women and TB/HIV co-infected patients until such a time as when the TDF/3TC/NVP combinations are exhausted.

Meanwhile, the National ART programme will provide guidance on the availability of TDF/3TC/EFV combinations to cater for the general population.

4.1
Table 4 First-line regimen for adults and adolescents

		Alternative Regimens
Adolescents (10-19 years) ≥ 25kg Adults including pregnant & breastfeeding women, TB/HIV, HBV/HIV	TDF + 3TC + EFV	TDF + 3TC + NVP AZT + 3TC + EFV/NVP TDF + FTC + EFV/ NVP

A. Preferred First-line regimen

Tenofovir + Lamivudine and Efavirenz will be taken once a day. There is no need for a starter pack when using TDF/3TC/EFV.

Initiation and Maintenance
Triple combination of Tenofovir (300mg) + Lamivudine (300mg)+ Efavirenz (600mg)

Caution: Tenofovir (TDF)
TDF may be associated with acute kidney Injury or chronic kidney disease as well as reduced bone mineral density in pregnant women.

Clinical considerations when using TDF

- Laboratory monitoring is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring may be used to assess for hypertension.
- Urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without diabetes using TDF-containing regimens.
- If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating TDF regimens.

Calculation of GFR or Creatinine clearance in ml/min using Cockcroft Gault Equation

Male: $\frac{1.23 \times (140-age) \times wt\ in\ Kg}{Creatinine\ (in\ micromols/L)}$

Female: $\frac{1.04 \times (140-age) \times wt\ in\ kg}{Creatinine\ (in\ micromols/L)}$

- Do not initiate TDF when the estimated glomerular filtration rate is <50 ml/min, or in long term diabetes, uncontrolled hypertension and renal failure.

B. Alternative first-line regimen
When Tenofovir, Lamivudine and Nevirapine is used; there is need for a starter pack and ideally this FDC should be prescribed as follows:

Two-Week Starter Pack	
Morning Dose	**Evening Dose**
Dual combination of Tenofovir (300mg) + Lamivudine (300mg)	Nevirapine (200mg)

After the starter pack has been completed, if there are no adverse events such as rashes, “step up” the dose of the Nevirapine. “Stepping up” means giving Nevirapine twice a day plus FDC Tenofovir + Lamivudine once daily as in the table below.

Step Up After the First Two Weeks	
Morning Dose	**Evening Dose**
Combination of Tenofovir (300mg) + Lamivudine (300mg)+ Nevirapine (200mg)	Nevirapine (200mg)

Caution: When Nevirapine is used as 1st line ART; introduce the Nevirapine gradually (i.e., a leading-in dose). Patients are more likely to develop adverse medicine reactions such as Stevens-Johnson syndrome or hepatitis if started on the full regimen including Nevirapine twice a day. If the patient has been using Efavirenz and needs to change to Nevirapine, just start using the Nevirapine at twice-a-day dosing (i.e. no need for the leading-in dose).

A. Starter pack (2 weeks):

- Dual Zidovudine 300 mg plus Lamivudine 150 mg orally twice a day

plus

- Nevirapine 200 mg orally once a day

B. Stepping up, after the first two weeks:

Give triple combination of Zidovudine (300mg) + Lamivudine (150g) + Nevirapine (200mg) twice a day.

Substitution in the event of medicine toxicity / adverse events and unavailability (see Appendix III)

If the patient has suspected adverse medicine events, therapy should be altered as follows (change of a single medicine in a multimedicine regimen is permitted—that is, the offending medicine may be replaced, preferably with an alternative medicine of the same class):

- Given Zidovudine adverse events such as anaemia or neutropenia, Zidovudine will be replaced by Tenofovir.
- If a patient reacts to Nevirapine, he or she should be switched to Efavirenz 600 mg orally once daily at night.
- In the event of lactic acidosis, the current ARVs should be discontinued and ART restarted after checking for normalization of the lactate levels.

- In case of severe psychiatric reaction on EFV give NVP.
- In case creatinine clearance is known and < 50 ml/min give AZT.

(See Section 7.3 on monitoring medicine side effects.)

An alternative to Lamivudine (3TC) is emtricitabine (FTC); these medicines are considered pharmacologically equivalent. In the event that you come across a patient on Tenofovir/Emtricitabine /Efavirenz, you may substitute emtricitabine with Lamivudine.
For patients presenting with renal impairment; consult/ refer for specialist opinion.

4.2 Second-line treatment recommendation for adults and adolescents

Ideally, patients who fail to respond to first-line treatment should be treated with a different regimen that contains medicines that were not included in the first line regimen. The second-line regimen will still consist of two NRTIs but with the addition of a PI. The second-line regimen should be initiated only after assessing for treatment adherence and failure and in consultation with a specialist in HIV and AIDS treatment or the clinical mentorship team at the OI/ART clinic. Clinical mentors should be consulted where there is doubt about what to do. More adherence counselling will be required in preparation for the planned new therapy. (To diagnose treatment failure see Section 7.9.)

Table 5: Preferred second line regimens for adults and adolescents including pregnant and breastfeeding women

Target Population	**Preferred second line regimens**	
Adolescents ≥10 years, Adults, Pregnant and Breastfeeding women	If TDF was used in first line ART	AZT + 3TC + ATV/r or LPV/r
	If AZT was used in first line ART	TDF + 3TC + ATV/r or LPV/r
HIV and TB co-infection	Patients receiving Rifampicin	Same NRTI backbone as recommended for adults and adolescents plus double dose LPV/r (800mg/200mg BD
HIV and HBV co-infection	AZT + TDF +3TC + ATV/r or LPV/r*	

Note: * ATV/r is the preferred PI in all cases

- Those patients with Hepatitis B infection will always need Tenofovir and Lamivudine among their medicines.
- Patients currently on abacavir plus didanosine plus a PI should be transitioned to the above regimens.
- For adults who cannot tolerate both TDF and AZT use ABC/3TC and ATV/r or LPV/r
- Abacavir /Lamuvudine 600 mg /300mg orally once daily

plus

- Atazanavir/ritonavir one daily or Lopinavir/ritonavir twice daily

4.3. Third-line treatment recommendation for adults and adolescents

Those failing second-line therapy will need to be referred for Specialist assessment which may include viral load and genotype testing prior to recommending the third-line medicines. Adherence needs to be reinforced all the time. In adults, raltegravir (400mg) twice a day and darunavir (800mg)/ ritonavir (100mg) once daily will be used as well as any other medicines as determined by the laboratory tests where available. You will need to be advised by the Paediatricians regarding doses for children.

4.4. Use of ARVs in patients with TB (refer to the latest national TB guidelines or the TB/HIV guidelines)

TB is the most common OI encountered among people with HIV infection in Zimbabwe. Since the advent of the pandemic of HIV infection, TB has remained a serious public-health problem. Studies have shown that up to 50% of people with HIV infection develop TB and that up to 85% of patients with TB have HIV infection. In addition, TB accounts for a third of HIV-related deaths. There is a need to integrate the HIV and TB services, as TB and HIV co-infection is common. Rifampicin interacts adversely with some antiretroviral agents such as PIs and Nevirapine. The preferred regimen for HIV positive TB patients is Tenofovir plus Lamivudine and Efavirenz.

Patients with TB who are not yet on ART

In patients who have HIV-related TB but are not yet on ART, treatment of TB takes priority. ART should be started at least two weeks after the start of TB therapy i.e. during the intensive phase when the patient has stabilized on TB treatment regardless of their CD4 count status. TB/HIV co-infected patients with severe immunosuppression such as CD4 count less than 50

cells/mm3, should receive ART early i.e. within the first 2 weeks of initiating TB treatment. Cotrimoxazole prophylaxis should have been provided with the commencement of the TB therapy if the patient is not on it already.

Patients who develop TB when already on ART

Treat TB as per national TB guidelines.

4.5 Treatment of Cryptococcal disease

Prevention of Cryptococcal Disease

Patients initiating ART with undiagnosed cryptococcal disease are at higher risk of early mortality than patients who are pre-emptively diagnosed and treated for cryptococcal disease. All patients initiating ART should be clinically screened for evidence of symptomatic cryptococcal disease – headache, neck stiffness, fever, focal neurologic signs, confusion, altered mental status. All those who screen positive should be referred for further diagnostic work up for meningitis. Screening of asymptomatic ART naïve individuals with CD4 count <100cells/mm3 is recommended and should be done with a Cryptococcal neoformans antigen test (CrAg)using latex agglutination tests (LA) or lateral flow assays (LFA) on serum, plasma or CSF. A lumbar puncture should be offered to individuals who screen positive for cryptococcal antigen, as a positive cryptococcal antigen may precede the onset of clinical cryptococcal meningitis by many weeks.

Individuals who are screened for cryptococcal disease should be managed as indicated in Table 6.

Table 6: Treatment decisions for asymptomatic cryptococcal disease

Serum CrAg negative	No LP necessary. No fluconazole required. Initiate ART.
Serum CrAg positive	If available recommend LP:
	If CSF CrAg positive, manage for cryptococcal meningitis
	If CSF CrAg negative treat with Fluconazole 800mg orally once daily for 2 weeks, then Fluconazole 400mg orally daily for 8 weeks, followed by maintenance therapy with Fluconazole 200mg orally daily until CD4>200 cells/mm3 for 6 months

Timing of ART for individuals with asymptomatic cryptococcal antigenemia is unknown. We recommend initiation of ART 2-4 weeks after initiation of antifungal therapy in individuals who screen positive for serum CrAg without any evidence of disseminated cryptococcal meningitis.

Treatment of cryptococcal meningitis

Cryptococcal meningitis remains a major cause of death in HIV infected patients. Early diagnosis and prompt treatment of cryptococcal meningitis is critical to improve clinical outcomes. The mainstay of treatment is rapid diagnosis, prompt initiation of appropriate antifungal therapy and management of raised intracranial pressure. Patients at greatest risk of cryptococcal meningitis are those with low CD4 counts and clinical suspicion must be high for all patients presenting with headaches, confusion, altered mental status.

Diagnosis of cryptococcal meningitis must be made by lumbar puncture. Opening pressure must be measured. If a manometer is not available, intravenous tubing may be used and a tape measure used to measure the column of CSF fluid. CSF samples must be tested for cryptococcus by india ink staining and/or CSF cryptococcal antigen test. Sensitivity and specificity for india ink staining are not as high as cryptococcal antigen testing, and a negative test does not exclude cryptococcal meningitis in the right clinical setting.

Treatment of cryptococcal disease must be with amphotericin B based regimens. Ideally amphotericin B must be combined with flucytosine.

However flucytosine is typically not available in resource limited settings, including Zimbabwe. Combination therapy with amphotericin B and fluconazole is strongly recommended. In the absence of amphotercin B, high dose fluconazole can be used as alternative therapy (See Table 7). Therapy is characterized by a 2 week induction phase, followed by an 8 week consolidation phase, and maintenance therapy which is continued until adequate immune reconstitution is achieved.

Table 7: Recommended therapy for cryptococcal meningitis

	Treatment phase	**Regimen**	**Duration of therapy**
Preferred	Induction phase	Amphotericin B 0.7-1mg/kg/day IV + Fluconazole 800mg orally once daily	2 weeks
	Consolidation phase	Fluconazole 800mg orally once daily	8 weeks
	Maintenance/ Secondary prophylaxis	Fluconazole 200mg orally once daily	Until CD4 count >200 cells/mm3 for 6 months
Alternate	Induction Phase	Fluconazole 1200mg orally daily	2 weeks
	Consolidation Phase	Fluconazole 800mg orally daily	8 weeks
	Maintenance/ Secondary prophylaxis	Fluconazole 200mg orally once daily	Until CD4 count >200 cells/mm3 for 6 months

Management of Raised Intracranial pressure

Mortality and morbidity from cryptococcal meningitis is high with a significant proportion attributable to raised intracranial pressure. Management of raised ICP is critical to ensure good clinical outcomes. If the intracranial pressures is >25cm of water, remove 10-30ml of CSF and continue with daily lumbar punctures until CSF pressures have normalized (<25cm of water).

Failure to adequately manage intracranial pressures can result in persistent headache, cranial nerve abnormalities which include hearing loss, vision loss, and death.

A repeat lumbar puncture at 2 weeks after initiation of appropriate induction antifungal therapy is not necessary except in the setting of persistently elevated intracranial pressure and evidence of poor clinical response. Cryptococcal latex agglutination titres are not indicated for monitoring response to therapy.

Management of Amphotericin B associated toxicities

Amphotericin B, particularly amphotericin deoxycholate is associated with renal tubular toxicities and can lead to electrolyte abnormalities such as hypokalemia and hypomagnesemia. It can also result in anaemia and administration related febrile reactions.

- Amphotericin B is often provided as a powder and should be mixed with 5% dextrose water. It should never be mixed with normal saline or half normal saline as this will result in precipitation of the amphotericin B. To minimize renal toxicities, amphotericin B must be administered slowly over 4 hours. Initial therapeutic doses should be given as Amphotericin B 1mg/kg/day.

- Prehydration with 500ml-1L of normal saline with 20mEq of potassium chloride is recommended based on the volume status of the patient.

- Patients must receive oral potassium supplementation – e.g. 1200mg twice a day. The potassium supplementation minimizes the extent of hypokalemia that can develop. Where available supplementation with magnesium trisilicate 500mg orally twice daily is also recommended.

- Renal function must be monitored at baseline. U & Es should be measured twice weekly.

If the creatinine doubles a dose of amphotericin B can be omitted, and prehydration increased to 1L of normal saline every 8 hours and creatinine rechecked. If creatinine normalizes, prehydrate with IL normal saline with 20mEq KCL and restart at amphotericin B (0.7mg/kg/day) given over 4 hours. Monitor renal function twice weekly.

If repeat creatinine remains elevated or continues to increase, amphotericin B should be discontinued and high dose fluconazole 1200mg orally once daily initiated (Table 7).

Monitoring of haemoglobin at baseline and weekly is also recommended.
Timing of ART in cryptococcal meningitis

The timing of the initiation of ART in patients with cryptococcal meningitis is still uncertain. Early initiation of ART is recommended for all OIs except for intracranial OIs such as TB meningitis and cryptococcal meningitis. In cryptococcal meningitis ART can be initiated 2- 4 weeks after initiation of antifungal therapy with amphotericin B based regimens. In patients who are predominately treated with fluconazole monotherapy, ART should be initiated at least 4 weeks after initiation of antifungal therapy.

ART should not be commenced at the same time that amphotericin B and/or fluconazole therapy is commenced for cryptococcal meningitis.

5. Preventing Mother-to-Child Transmission of HIV (PMTCT)

Mother-to-child transmission is responsible for more than 90% of HIV infection in children, and at least two-thirds of such infections occur during pregnancy, and delivery, whilst the remainder occur during breastfeeding. It is therefore critical to identify HIV-positive pregnant and lactating women and manage them appropriately.

The PMTCT programme is an entry point into care for the family. It is the beginning of a lifelong therapeutic relationship for the HIV-positive mother and her children, and it is essential to reinforce the importance of HIV follow-up care for mother and her children, as well as her partner.

When to start ART in HIV positive pregnant and breastfeeding women (Adapted from WHO 2013 guidelines Chapter 7)

- All HIV infected pregnant and breastfeeding women should initiate lifelong antiretroviral treatment (ART) irrespective of their CD4 count or WHO clinical stage (Option B+).
- Women who are not yet ready for lifelong ART should be initiated on triple ARVs (ART),which should be continued at least for the duration of breastfeeding to prevent further risk of mother-to-child transmission of HIV through breast milk.
- HIV infected lactating women meeting treatment eligibility criteria (CD4 500 or less) should continue lifelong ART according to criteria for adult non-pregnant populations as it would be inappropriate for them to discontinue ART after the breastfeeding period.

N.B. Pregnant and breastfeeding women who were initiated on Zidovudine prophylaxis should be discontinued and commenced on lifelong ART (Option B+).

Being on lifelong ART will necessitate ongoing counselling of HIV positive pregnant and breastfeeding women to support retention and adherence and to minimize loss to follow-up.

- Emphasise modes of HIV transmission and prevention, PMTCT, and access to care and treatment.
- Encourage the importance of skilled birth attendance, clean and safe delivery, and newborn care.
- Counsel on infant and young child feeding and maternal nutrition. Emphasize exclusive breastfeeding (no mixed feeding) for the first six

months of an infant's life and safe introduction of complementary foods from six months of age.

- Counsel on sexual and reproductive health including family planning and the need for dual contraception (reliable hormonal contraceptive plus barrier method like male or female condoms)
- Make an appointment for family planning at six weeks postpartum.
- Stress the need for condom use for prevention of STIs and HIV during pregnancy and in the postpartum period. New HIV infections during pregnancy and lactation pose additional risk of HIV transmission to the infant.
- **Retest previously negative women in 3rd trimester of pregnancy and/ or at delivery, 6 weeks post natally and 6 monthly thereafter.**
- Stress the importance of follow-up for the HIV exposed infant
  - ° Commence cotrimoxazole prophylaxis from 6 weeks of age
  - ° Collect Dried Blood Spot (DBS) for HIV DNA PCR test at 6 weeks of age i.e.Early Infant Diagnosis (EID).
  - ° Infants should be re-tested at the end of the breast-feeding period

Table 8: Timing of Initiation of ART for Mother and ARV Prophylaxis for Infant (PMTCT)

Pregnancy	**Labour**	**Post delivery (breastfeeding and non breastfeeding)**
Maternal		**Infant (Birth to six weeks)**
Preferred first line		
Tenofovir + Lamivudine +Efavirenz		BW<2500: NVP 10mg daily BW ≥2500: NVP 15mg daily
Alternative First line		
Zidovudine +Lamivudine + Efavirenz		BW<2500: NVP 10mg daily BW≥2500: NVP 15mg daily

When using ARVs in pregnant women, certain precautions should be kept in mind:

Efavirenz (EFV)

Previously there was a recommendation not to use Efavirenz during the first trimester and in women at risk of becoming pregnant. However, WHO issued an evidence based update on Efavirenz safety in pregnancy in 2011 which recommends it to be safe for use even in the first trimester.

Health education needs for pregnant mothers

When dealing with pregnant women, health-care providers should take the following steps:

- Provide routine counselling and blood testing, including HIV testing in pregnancy, haemoglobin level, blood group, hepatitis screen and syphilis.
- Pregnant women of unknown HIV status who present in labour and delivery should be tested for HIV and commenced on ART if they test positive. The baby should be commenced on NVP prophylaxis for 6 weeks.
- If a woman tests positive postnatally, the baby should be given 6 weeks of Nevirapine (NVP) and have DNA PCR done to exclude infection in the baby.

Infant and young child feeding recommendations

In order to give HIV exposed infants the greatest chance of HIV-free survival, the recommendation is to promote and support breastfeeding, while providing maternal lifelong ART and infant Nevirapine (NVP) prophylaxis.

All mothers whether known to be infected with HIV or not should exclusively breastfeed their infants (no mixed feeding) for the first 6 months of life, introducing safe, adequate and nutritious complementary foods thereafter, with continued breastfeeding up to 24 months and beyond.

For an effective postpartum MTCT prevention strategy

The HIV infected mother who is breastfeeding and on lifelong ART should receive continued counseling and support for adherence to minimize the risk of HIV transmission through breast milk.

With increasing antenatal coverage of ARV medicines for PMTCT, the relative proportion of infants infected with HIV in the post delivery period may be increasing because of inadequate ARV medicine coverage during breastfeeding. Thus the need to emphasize the importance of testing breastfeeding women of unknown HIV status and re-testing women who were previously HIV negative in ANC to pick up new HIV infections in breastfeeding women. Such women who test HIV positive during lactation should be commenced on lifelong ART.

ARV prophylaxis in an HIV-exposed infant
HIV-exposed infants whose mothers are on lifelong ART should be commenced on Nevirapine prophylaxis for six weeks.

Table 9: Infant Nevirapine prophylaxis

Age	**Nevirapine dosage**
Birth to six weeks	BW <2500*: 10mg once daily BW ≥ 2500: 15mg once daily

Always remember to change the dose when baby gains weight.

***For very low birth weight babies below 2000g dose of NVP is 2 mg/kg once daily for 6 weeks**

For non breastfeeding infants NVP as above or AZT 4mg/kg 12 hourly for 6 weeks

6. ANTIRETROVIRAL THERAPY IN CHILDREN

More than 90% of HIV-infected children acquire their infection through mother to child transmission of HIV (vertical transmission). **Thus, elimination of new HIV infections among children through effective PMTCT interventions should be prioritized**. HIV disease progression occurs very rapidly in the first few months of life in infants acquiring HIV in utero, often leading to death. The importance of early infant diagnosis (EID) of HIV infection and early initiation of ART can therefore not be overemphasised.

6.1 Early infant diagnosis (see Appendix X)

All infants should have their HIV-exposure status established at their first contact with the health system, ideally before six weeks of age. Check for HIV exposure status on the child health card, or enquire from the mother or caregiver. Where the mother is available and was not tested during pregnancy, perform a rapid HIV test on the mother and if she is positive, then her infant is HIV exposed and needs to have a DBS collected for HIV DNA PCR.

At 9 months of age, most infants (93%) no longer possess maternally transferred antibodies. Prior to the age of 18 months, a DNA polymerase chain reaction (PCR) test for HIV is more reliable. A DNA PCR test should be offered to all exposed infants from six weeks of age. If the DNA PCR test is negative before the age of 18 months, the infant does not have HIV infection but is at risk of infection if breastfeeding is continued.

In an infant, *outside* the window period (three months after last exposure - labour/delivery, or breastfeeding) and rapid HIV test is negative, then the infant has not been infected with HIV and can be considered definitively negative.

If an infant is still *within* the window period, and rapid HIV test is negative then the infant is still considered to be HIV exposed and may be infected and should be managed as an HIV-exposed infant.

Where virological testing is not available for children less than 18 months, a presumptive diagnosis of severe HIV disease should be made if the infant is confirmed HIV antibody positive and:

1. Diagnosis of any AIDS-defining condition(s) can be made, or
2. The infant is symptomatic with two or more of the following:
    1. Oral thrush
    2. Severe pneumonia
    3. Severe sepsis

Infants under 18 months of age with clinically diagnosed presumptive severe HIV should be started on ART. Confirmation of HIV diagnosis should be obtained as soon as possible.

Recommendations for antibody testing in infants

Antibody tests (rapid and laboratory-based ELISA) are the preferred method of diagnosis for HIV infection for children over 18 months of age.

In a child under 18 months who has never been breastfed and HIV antibody tests are *negative*, this child is uninfected and virological testing is indicated only if clinical signs or subsequent events suggest HIV infection.

In a child under 18 months who has not breastfed for more than six weeks, HIV antibody tests that are negative mean the child is uninfected.

HIV antibody tests that are positive at any age under 18 months identify those infants who need virological tests (i.e., the child is HIV exposed but needs definitive test with HIV DNA PCR to confirm HIV infection).

6.2 Care of an HIV-exposed infant

Initial care

Care for HIV-exposed infants should include the following:

- Make sure HIV-exposed infants are entered into the “HIV exposed follow-up register”.

- All HIV-exposed infants should have HIV DNA PCR testing performed from six weeks of age or at the earliest possible time thereafter if 6 weeks testing is missed.

- Cotrimoxazole prophylaxis should be given from six weeks of age until the HIV status of the infant is known. If the HIV infection is confirmed, continue cotrimoxazole and commence on ART.

- Monthly follow up visits are recommended, but more frequent visits may be needed if problems are detected.

During these visits the following services should be provided:

- *Growth monitoring and promotion*
- *Developmental assessment (see appendix VI, VII, VIII.)*

Counselling on infant and young child feeding:

- Counselling and support for the HIV infected mother to adhere to ART is crucial.
- Weaning should not be abrupt, but rather should be gradual over a one month period.
- HIV-infected infants diagnosed by virological testing or infants with symptoms suggestive of HIV should continue breastfeeding for as long as possible.
- Immunisations should be given according to the national guidelines. The BCG vaccination should still be given at birth, but BCG should not be given to children with symptomatic HIV infection.
- Always look for and treat opportunistic infections.
- Be aware of and watch for potential medicine interactions. The management of TB in HIV-infected children and the treatment of severe HIV infection with ARVs is complicated by the potential for multiple medicine interactions. Refer to TB treatment guidelines or cross-reference with appropriate chapter.
- Counselling on safer sex behaviour, including the use of condoms during the breastfeeding period is recommended to minimize risk of maternal sero-conversion during breastfeeding.
- Counsel on family planning (see PMTCT section)

6.3 Management of an HIV-infected child using ARVs

Infants and young children have an exceptionally high risk of poor outcomes

from HIV infection. Up to 52% of children die before the age of two years in the absence of any intervention. By five years of age as much as 75% of HIV positive children will be dead if they are not initiated on ART.

The goal of ART for children is to increase survival and decrease HIV-related morbidity and mortality.

Criteria to initiate ART in children

1. **All children below 5 years of age MUST be commenced on ART irrespective of their CD4 count.**

2. All children 5 years and above with paediatric WHO clinical stage 3 or 4 disease MUST be commenced on ART irrespective of CD4 percentage.

3. Children ≥5 years with WHO clinical stage 1 or 2 and a CD4 count less than 500 should be commenced on ART (see Appendix II for clinical staging)

Table 10 Recommendations on when to start ART in children (Adopted from WHO 2013 HIV guidelines)

Age	**When to start**
Infants (<1yr)	Treat all individuals
1 year to less than 5 years	Treat all individuals (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 or CD4 %<25% as a priority)
5 years and above	WHO stage 3 or 4 or CD4 ≤500 (CD4 ≤350 as a priority)

Issues to consider in initiating ART in children

Psychosocial factors: It is important to identify and counsel at least one dedicated caregiver who can supervise and/or give medicines. Disclosure to another adult in the same household (secondary caregiver) is encouraged to assist with medication.

Disclosure: The process of disclosure to the child should be initiated as early as possible, usually from as early as 5 – 7 years of age. Adherence is good in children who know their status and are supported to adhere to medicines.

Adherence: Continued support for good adherence

Recommendations for ART in children need to take into consideration the following:

- Age and weight of the child
- Availability of paediatric formulations of the medicines
- Palatability of the medicines
- Effect of food on the absorption of the medicines
- PMTCT regimens used

6.4 Table 11 Recommended first-line treatment for children

First line treatment		**Alternative first line treatment**
Children < 3years	AZT + 3TC + LPV/r	AZT + 3TC + NVP ABC + 3TC + LPV/r ABC + 3TC + NVP
Children 3 - <10 years and adolescents <35kg	AZT + 3TC + NVP	ABC + 3TC + EFV
Special circumstances*	d4T+ 3TC + LPV/r d4T+ 3TC + NVP	

* use d4T for children with anaemia or other contraindication to use AZT

Monitoring children on ART

- Check haemoglobin if on Zidovudine after at least 6-8 weeks
- Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and/or serum creatinine when on Tenofovir
- Alanine aminotransferase (ALT) for Nevirapine
- CD4 count every 6 months
- Viral load once every year or when clinical signs are suggestive of treatment failure

6.5 Recommended second-line treatment for children

Definition of treatment failure in children

Clinical Failure: New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment

Immunological failure: Younger than 5 years - Persistent CD4 levels below 200 cells/mm3 or CD4 percentage <10%
Older than 5 years - Persistent CD4 levels below 100 cells/mm3

Virological failure: Plasma viral load above 1000 copies/ ml based on two consecutive viral load measurements after 3 months, with adherence support.
OR
If using dry blood spot technology, a viral load above 3000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support.

Table 12 RECOMMENDED SECOND LINE ART REGIMENS

Second line ART			Preferred	Alternative
Children	If AZT used for 1st line then use ABC containing 2nd line, if ABC is used then use AZT		ABC+3TC+LPV/r	
	If PI based first line regimen used	<3yrs	No change from first line regimen used	ABC +3TC + NVP
		3yrs to <10yrs	ABC +3TC + EFV	TDF+ 3TC NVP ABC+3TC+NVP

Discuss the child with your mentor IF NOT SURE OF SECOND LINE TREATMENT

6.6 Starting ART in children using FDCs

Refer to dosing table and also see Appendix IX. Keep the following factors in mind with regard to dosing:

- Medicine doses must be adjusted as the child grows.
- Dosing is by weight.
- Overdosing up to 10% is acceptable.
- Scored tablets may be divided into two equal halves
- Tablets may be crushed and mixed with a small amount food or water and administered immediately.
- Give clear explanation to the caregiver.
- Use pillboxes if available.
- Standardization is important to safely dispense correct doses.

Medicine	Strength of tablet or sprinkle sachet or capsule	No. of tablets or sprinkle capsule/sachets by weight band											
		3-5.9kg		6 -9.9kg		10-13.9kg		14-19.9kg		20-24.9kg		25-34.9kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC/NVP	60mg/30mg/ 50mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	4	4
LPV/r sprinkles	40mg/10mg	2	2	3	3	4	4	5	5	6	6		
ABC/3TC/LPV/r	30mg/15mg/ 40mg/10mg	2	2	3	3	4	4	5	5	6	6		
AZT/3TC/LPV/r	30mg/15mg/ 40mg/10mg	2	2	3	3	4	4	5	5	6	6		
DRV/r	240/40mg	-	-	-	-	1	1	1	1	2	1		
ATV/r	100/33mg	-				1		1		2			
ABC/3TC	120/60mg	1		1.5		2		2.5		3			
TDF/3TC	75mg/75mg					1.5		2		2.5		3-3.5	
TDF/3TC/EFV	75mg/75mg/1 50mg					1.5		2		2.5		3-3.5	
TDF/3TC adult double scored	300mg/300mg					One third		One half		Two thirds		1	
TDF/3TC/EFV adult double scored	300mg/300mg/ 600mg					One third		One half		Two thirds		1	

3 tablets for 25-29.9kg and 3.5 tablets for 30-34.9kg
TDF tablets are scored to break into half or third.

7. MONITORING PATIENTS ON ANTITRETROVIRAL THERAPY

Patients on ART need close monitoring to assess adherence to the treatment regimen, tolerance, the side effects of the medications, and the efficacy of the treatment. Give the patient an ART card for documenting his or her treatment and visits (available from the AIDS and TB Directorate). Adolescents have special needs that go beyond just delivery of ART; counsellors will need to be aware of the need for specialized counselling. Adolescents' growth, including puberty and schooling, may be delayed, and these issues will need to be managed carefully if they are to become well-adjusted individuals later in life (see Section 3.6 on adolescents).

7.1 Initial evaluation

Before commencing ART, all patients should have a detailed history taken, a physical examination carried out, and basic laboratory tests performed. Prior to commencing ART, the patient should have a confirmatory HIV test, plus it is essential to test for TB in all patients. Document the patient's WHO clinical staging in his or her file or card.

It is preferable in most instances to perform the following baseline tests:

- Full blood count (especially if Zidovudine will be used)
- Alanine transaminase test
- Serum creatinine test (if Tenofovir will be used)
- Mantoux test (useful in children)
- GeneXpert test or Chest X-ray (to exclude TB)

If possible, perform the following tests also prior to commencing ART:

- CD4 lymphocyte count (or CD4 percentage for children under 5 years)
- Syphilis serology test
- Hepatitis B and C virus screening
- Pregnancy test

7.2 Monitoring adherence to treatment

Strict adherence (which is at least 95% adherence) to recommended treatment regimens is important for treatment to be effective. Counselling and the provision of accurate information to all patients (treatment literacy) is an important determinant of treatment adherence. Information on side effects should be provided, and patients should be told what to expect from

the treatment. An adherence card should be provided, and patients/carers instructed on how to fill out the card. Counselling should be provided at each visit. Patients should be encouraged to seek help between visits as needed. Patients should be instructed to bring all medications and containers at each visit. Providers should carry out an adherence assessment to determine whether the medications have been taken as per schedules agreed upon.

7.3 Monitoring adverse medicine events or medicine side effects

A patient on ART may develop new symptoms whilst on treatment. Such symptoms may be indicative of inter-current illnesses, adverse medicine events, or immune reconstitution inflammatory syndrome. All patients should be examined carefully at each visit. Any inter-current illness should be treated appropriately. If in doubt, refer the patient to your clinical mentor or higher-level OI/ART clinic.

The patient should be seen every two weeks for the first month after initiating treatment, and thereafter monthly for another three months. After the first four months, the patient can be seen every three months. The patient should be provided with written and verbal information on potential side effects and should be requested to report immediately for examination should side effects occur. See Appendix III for the grading of side effects. There is a need to watch out for common side effects such as anaemia, renal impairment, peripheral neuropathy, and lactic acidosis as well as lipodystrophy or fat redistribution.

Anaemia

Check haemoglobin after the first month of Zidovudine use.

Lactic acidosis

Lactic acidosis is characterized by non-specific symptoms and signs such as shortness of breath, hyperventilation, fatigue, weight loss, abdominal pain, vomiting, and tachycardia. Lactate levels are currently not routinely available, but one needs to have a high index of suspicion. Use a full urea and electrolytes screen with bicarbonate levels as a surrogate marker. The treatment for this is to stop all ARVs and keep the patient well hydrated. When the patient's symptoms have settled down, restart an ARV regimen that contains Tenofovir. Referral to a higher level of care or a specialist is encouraged.

Lipodystrophy / fat redistribution

With longer duration of use of ART, cosmetic problems such as loss of fat in the face or limbs and buttocks or increasing breast size and abdominal fat accumulation will be encountered more frequently. If the patient is on a Zidovudine -containing regimen, consider changing to Tenofovir, but counsel the patient appropriately.

Central nervous system toxicities

Hallucinations, abnormal dreams, depression, mental confusion and convulsions can occur especially with Efavirenz. These events tend to occur within the first month. Patients should be warned about them but if the symptoms do not settle down, consider using Nevirapine. However, if both NNRTIs cannot be tolerated use boosted PIs.

Metabolic abnormalities

Hyperglycaemia i.e. development of diabetes and hyperlipidaemia should be anticipated with the long-term use of ARVs. Check blood sugar and lipid levels at least with every CD4-level check or when clinically indicated.

Other side effects

Mild side effects such as headache, fatigue, gastrointestinal upsets, and diarrhoea occur fairly frequently, but serious side effects occur rarely. Mild side effects usually occur early in treatment and often wear off and should be treated symptomatically. Side effects of medicines are summarized below

Table 14: Some Important Side Effects of Antiretroviral Agents

Medicine	Side Effects	Action to Be Taken
Nucleotide/ Nucleoside reverse transcriptase inhibitors		
Tenofovir	Gastrointestinal (GI) symptoms, rash, and renal complications, decreases in bone mineral density	Monitor creatinine. Substitute with Zidovudine
Zidovudine	Anaemia, neutropenia, headache, myopathy, lactic acidosis, lipoatrophy or lipodystrophy	Monitor full blood count; if severe anaemia, change to Tenofovir or abacavir.
Lamivudine	Usually nil	
Abacavir	Severe hypersensitivity reactions	Withdraw medicine immediately; give alternative like Tenofovir or Zidovudine. Do not restart medicine, as this can be fatal.
Stavudine	Peripheral neuropathy, abdominal pain, fatigue, lactic acidosis, pancreatitis, lipodystrophy	Monitor and withdraw medicine if symptoms are severe or unacceptable to client.
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine	Fever, fatigue, nausea, mild or severe skin rashes (e.g., Stevens-Johnson syndrome [rare]), liver toxicity, abnormal liver function tests (LFTs)	If LFTs are suggestive of hepatitis or if jaundice is present, discontinue; if rash is severe, discontinue and replace with Efavirenz.

Efavirenz	Central nervous system symptoms (confusion, headache, sleep disturbance, abnormal dreams) usually during the first three weeks and then resolve	Monitor; withdraw medicine if symptoms persist.
Protease inhibitors		
Atazanavir	Jaundice, nausea, diarrhoea, headache, hyperbilirubinaemia	Monitor; withdraw medicine if symptoms are severe.
Lopinavir/ritonavir	Lipodystrophy, GI intolerance, diarrhoea, hyperglycaemia, hyperlipidaemia	Give loperamide for the diarrhoea.
Ritonavir	Lipodystrophy, pancreatitis, hepatitis, skin sensitivity, circum-oral paraesthesia, nausea, vomiting, diarrhoea	Monitor; withdraw medicine if symptoms are severe.
Integrase inhibitor		
Raltegravir	Mood changes, depression, myopathy. skin reactions e.g., Stevens-Johnson syndrome, hypersensitivity	Discontinue if severe skin reaction occurs

7.4 Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is characterized by a clinical deterioration after starting ART. It is the immune system interacting with latent infections. This syndrome should be considered if the following occur within 2 to 12 weeks of commencing ART:

- Patients with advanced HIV disease, particularly those with a CD4 count of less than 50, may become ill with IRIS. Typical symptoms are fever, sweats, loss of weight, and occasionally skin rash and lymphadenopathy.
- Immune reconstitution illnesses occur when improving immune function

unmasks a previously occult OI (an infection that was present in the patient's body but was not clinically evident).
- Common immune reconstitution illnesses in Zimbabwe are TB and cryptococcal meningitis as well as recurrent herpes simplex virus.

An immune reconstitution illness is not indicative of treatment failure or medicine side effects. It is not a reason to stop ART or to change the ARV regimen, but the emerging OI must be treated.

7.5 Monitoring effectiveness of ART

The effectiveness of ART may be monitored by assessing clinical improvement, immunologic function (CD4 count/CD4%), and HIV viral load (VL). It is necessary to make an assessment of response to treatment through regular careful clinical examinations backed where possible by simple laboratory tests.
WHO is recommending VL testing as the gold standard for monitoring response to ARV medicines as it is more sensitive and can detect adherence problems and treatment failure much earlier than CD4 count testing. Given reduced access to VL testing in Zimbabwe, CD4 testing should be conducted regularly at six-monthly intervals.

7.6 Clinical monitoring

Monitoring ART in adults and adolescents

The following clinical indices suggest that the patient is responding to ART:
- The patient feels better and has more energy to perform daily tasks.
- The patient is gaining weight (record the patient's weight at each visit).
- There is an improvement in symptoms and signs of the original presenting illness.
- Infections such as oral thrush, hairy leukoplakia, genital herpes, skin rash, and molluscum contagiosum have improved.
- There has been an improvement in chronic diarrhoea.
- There has been an improvement in Kaposi's sarcoma.
- The patient is free of new moderate or severe infections.

Monitoring of ART in children
In children, growth and development are important clinical monitoring indicators and are assessed using growth charts. Laboratory indices of

CD4 lymphocyte counts and HIV VL levels may also be used in assessing response to therapy, noting that sometimes the VL will come down but may still not be undetectable.
Clinical assessment involves the following:

- Always check the child's and caregiver's understanding of ART as well as anticipated support and adherence to ART.
- Always check for symptoms of potential medicine toxicities.
- Always assess for treatment failure (i.e. reassessment of clinical stage).

Important signs of infants' and children's response to ART include the following:

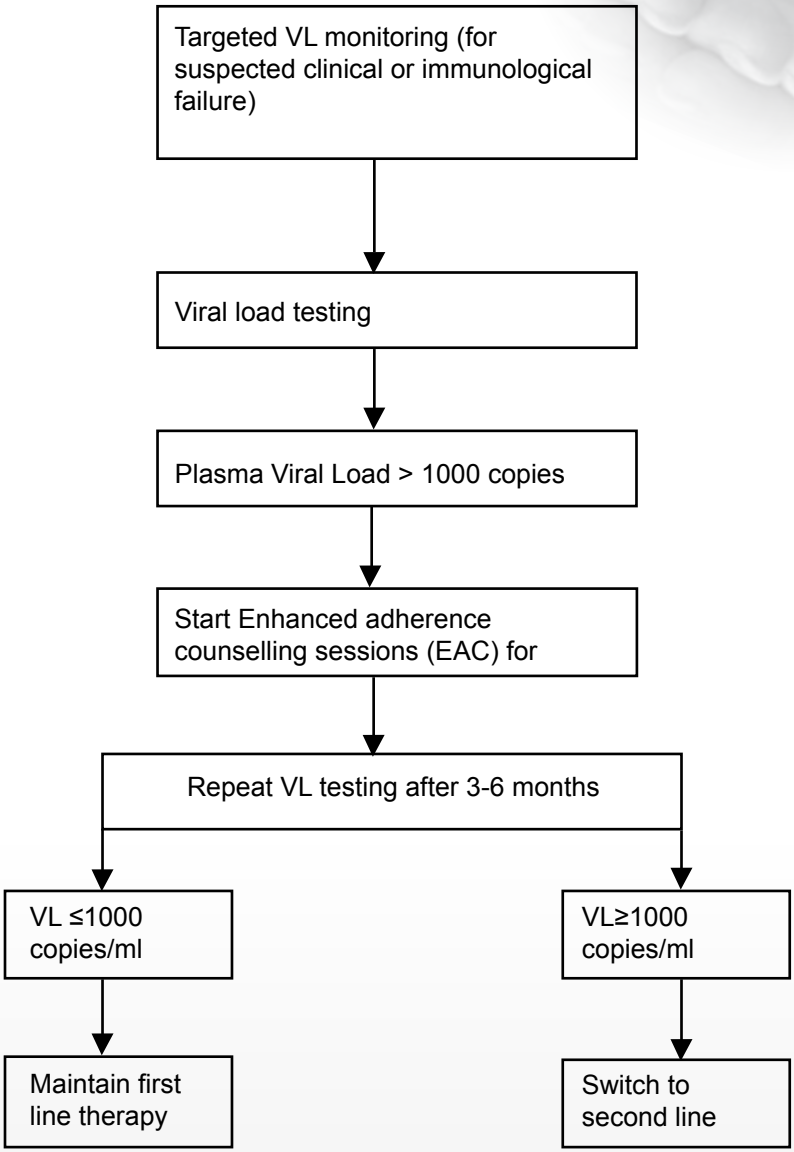
- Improvement in growth—in children who have been failing to grow
- Improvement in neurological symptoms and development—in children with encephalopathy or who have been demonstrating delay in the achievement of developmental milestones
- Decreased frequency of infections (bacterial infections, oral thrush, and/or other OIs)

7.7 Virological (HIV viral load) monitoring

The VL usually decreases to undetectable levels within six months of greater than 95% adherence to ART i.e. plasma viral load less than 1000 copies per ml OR viral load less than 3000 copies per ml if using dry blood spot technology. However, this response also depends on the initial pre-treatment VL. The VL measurement is useful in assessing treatment failure. If there has been a threefold increase in the VL from the lowest point following treatment, it is an indication of treatment failure. In such situations, one must review the treatment regimen and consider changing the regimen.

WHO is recommending VL testing as the gold standard for monitoring response to ARV medicines and this should be done routinely once a year. Due to limited resources, Zimbabwe will do targeted VL testing until such a time when the country can afford routine VL testing. Below is an algorithm for targeted VL testing

Figure 1: Viral Load testing strategies to detect or confirm treatment failure and switch in adults, adolescents and children



7.8 Immunological monitoring (CD4 count)

With successful ART, the CD4 lymphocyte count increases. The rate of increase depends on the initial CD4 count. Persistently declining CD4 counts (as measured on two occasions, at least three to six months apart) and clinical deterioration as described above are suggestive of treatment failure. CD4 count testing should be performed six-monthly, particularly after the first two years of initiation of ART. More frequent testing should be performed if immunological failure is suspected. In Zimbabwe since viral load testing is not readily available, CD4 testing will continue to be used for some time. Guidance will be provided by the ART programme on when VL can be used as a routine test.

7.9 Treatment failure

Clinical criteria that suggest treatment failure

Before diagnosing treatment failure, one must assess adherence to treatment. The decision to switch from first-line to second-line or even third-line therapy should not be taken lightly. Treatment failure can be determined clinically (this tends to result in delayed switching to second-line therapy), immunologically using CD4 trends over time, or virologically (e.g., VL greater than 1000 copies/ml based 2 consecutive VL measurements 3-6 months apart with adherence support).

Table 5: Treatment Failure (WHO. 2013)

Clinical failure	**Children:** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO stage 3 and 4 clinical conditions with exception of TB) after 6 months of effective treatment **Adults and Adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO stage 4 clinical condition) after 6 months of effective treatment
Immunological failure (CD4 failure)	**Children** Decrease to pre-therapy CD4 count/percentage Younger than 5years – Persistent CD4 level below 200 cells/ mm3 or CD4% < 10% Older then 5 years - Persistent CD4 levels below 100 cells/mm3
	Adults and adolescents CD4 counts falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm
Virological failure	Viral load greater than 1,000 copies/ml based on two consecutive VL measurements after 3 months with adherence support

Note: A second-line regimen should be started only after consultation with an appropriate specialist in HIV and AIDS care/treatment or your mentor.

Treatment failure in children

Consider the following before switching ART regimens:

- The child should have received the regimen for at least 24 weeks (six months).
- Adherence to therapy should be assessed and considered to be optimal.
- Any inter-current OIs should have been treated and resolved.
- Before considering changing treatment due to growth failure, ensure that the child is receiving adequate nutrition.

In children on ART, the main clinical indications to switch therapy are the development of new or recurrent stage 3 or 4 events at least 24 weeks (six months) after starting therapy with a first-line regimen. Of note are

- a lack of or decline in growth rate in children who showed an initial response to treatment (moderate or severe unexplained malnutrition not adequately responding to standard therapy despite adequate nutritional support and without other explanation); loss of neurodevelopmental milestones (see Appendix VI) or development of encephalopathy; or
- occurrence of new OIs or malignancies or recurrence of infections, such as oral candidiasis that is refractory to treatment or oesophageal candidiasis.

Note: A second-line regimen should be started only after consultation with a specialist in HIV and AIDS care/treatment or your mentor.

8. PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS AND NON-COMMUNICABLE DISEASES

Various opportunistic infections(TB, cryptococcosis) co-infections (hepatitis B or C), co-morbidities and other health conditions are common among people living with HIV and have implications for the treatment and care, including the timing and choice of antiretroviral medicines HIV is also associated with cancers such as Kaposi Sarcoma, Non-Hodgkins' Lymphoma, invasive cervical cancer as well as non-communicable diseases such as diabetes, cardiomyopathies and chronic kidney disease. This section provides a brief overview of the most common and important conditions.

COTRIMOXAZOLE PREVENTIVE THERAPY

Immunosuppressed people are prone to develop OIs such as Pneumocystis jirovecii pneumonia, toxoplasmosis, and lower respiratory tract bacterial infections and bacterial skin infections.

Cotrimoxazole prophylaxis can potentially prevent the following OIs:

- Streptococcus pneumoniae pneumonia
- Nontyphoid salmonelloses
- Pneumocystis jirovecii pneumonia (PCP)
- Cerebral toxoplasmosis
- Nocardiosis
- Isosporiasis

Cotrimoxazole prophylaxis should be given to the following:

- All patients with WHO clinical stages II, III, and IV disease
- All patients with CD4 counts of less than 350 cells/mm3
- Pregnant women with CD4 counts of less than 350 cells/mm3
- All children born to HIV-positive mothers at six weeks of age until they are tested and confirmed to be negative

Cotrimoxazole prophylaxis should be started *as soon as any of the above conditions are suspected*; this should be done at every entry point and not just be left to the OI clinics.

<u>Cotrimoxazole prophylaxis in adults</u>

Cotrimoxazole (sulphamethoxazole 800 mg and trimethoprim 160 mg) should be given once daily orally.

Cotrimoxazole prophylaxis in children
Give once daily orally according to the following table.

Age	Dose (ml)		
	Suspension (240 mg / 5 ml)	**Adult tablets (480 mg)**	**Paediatric tablets (120 mg)**
0 to 6 months	2.5	¼	1
6 months through 3 years	5	½	2
Over 3 years	10	1	3

Notes on the provision of cotrimoxazole to adults and children

Health-care providers should keep the following recommendations in mind when offering cotrimoxazole prophylaxis:

- Cotrimoxazole prophylaxis should be commenced at least one to two weeks before the commencement of ART. This allows time to identify those who might be allergic to cotrimoxazole.
- This prophylaxis should be continued indefinitely
- For patients who are allergic to cotrimoxazole, consider desensitization (see Appendix IV).

8.1 TB/HIV COLLABORATIVE ACTIVITIES

The association between TB and HIV is well documented with an estimated 72% of TB patients in Zimbabwe co-infected with HIV. Management of TB and HIV requires close collaboration between the NTP and AIDS programmes. This will help reduce the burden of TB in HIV and the burden of HIV in TB patients.

HIV care settings should implement the three I's strategy:

- Intensified TB case- finding
- Isoniazid Preventive Therapy (IPT)
- Infection control at all clinical encounters.

The activities to be undertaken in the management of TB/HIV co-infected persons are summarised below.

Summary of management of TB/HIV co-infection:

1. HIV testing and counselling should be routinely offered to all persons

suspected or known to have TB.

2. HIV-related prevention, care and support services should be routinely offered to all persons suspected or known to have TB.
3. Case definitions and anti-TB treatment regimens are the same for HIV-positive and HIV-negative TB patients, and medicine dosages in mg/kg are also the same.
4. In TB/HIV co-infection the first priority is to initiate anti -TB treatment followed by cotrimoxazole, and then ART
5. All TB patients co-infected with HIV should be given co-trimoxazole preventive therapy (CPT) for the whole duration of TB treatment.
6. All people living with HIV with active TB disease, irrespective of CD4 cell count and the site of TB disease, should be initiated on ART as soon as practicable (Refer to Section 4.4)
7. All PLHIV should be screened for TB at every contact with health services. Patients should be screened for current cough, fever, night sweats and loss of weight.
8. PLHIV who develop TB should be started on anti-TB treatment immediately.
9. TB/HIV patients benefit from the use of steroids for the same indications as found in HIV-negative TB patients (refer to TB National Guidelines)

Use of ARVs in patients with TB (see section 4.4)

Use of ARVs in cryptococcal disease (see section 4.5)

8.2 Kaposi Sarcoma and other cancers

HIV infected individuals are at greater risk of developing cancer than the general population. Certain cancers have been termed 'AIDS-defining cancers' (ADC):

- Kaposi sarcoma (KS)
- Non-Hodgkin lymphoma (NHL)
- Invasive cervical cancer

With the advent of effective combination antiretroviral therapy (ART) the rates of some of these cancers have declined significantly eg. KS.

Other cancers have been associated with HIV and the rates of these non-AIDS-defining cancers (NADCs) are rising. Sites for these NADCs include:

- Head and neck including squamous conjunctival carcinoma
- GIT including anus

- Lung, liver, genito-urinary tract and kidney
- Hodgkin lymphoma (HL)
- Glioma
- Leiomyosarcoma in children

The reasons for this increase are poorly understood and may include increased susceptibility to cancers known to be associated with oncogenic viruses, decreased tumour surveillance with HIV-associated immune suppression and the fact that patients with HIV are now living much longer on ART. Anal, penile, cervical, vaginal, vulval, oral, laryngeal and nasopharyngeal cancers are associated with HPV infection; HL is associated with Epstein-Barr virus infection; liver cancer is associated with hepatitis B and C infection.

Patients with HIV and cancers should be treated for the HIV infection and for the cancer. In addition, palliative care with meticulous attention to symptom control from the time of diagnosis is vital, especially in patients with advanced HIV disease.

Overlapping toxicities of ART and chemotherapy medicines or biological agents used to treat cancer may be a problem. Timing of the ART and the cancer treatment is critical as immune reconstitution may be associated with worsening of the cancer. Chemotherapy can deplete the CD4 count by up to 50%. Most patients will require consultation with a specialized referral unit in order to develop a treatment plan.

8.2.1 Kaposi Sarcoma

KS is a spindle cell tumour, related to infection with human herpesvirus-8 (HHV8) or Kaposi sarcoma herpes virus (KSHV). KS presents with multifocal purplish-red macules, plaques or nodules on the skin. Typical sites include the tip of the nose, around the ear, antero-medial part of the thigh, instep of the foot, but any part of the skin can be affected. KS also affects the mouth and the oropharynx; palate disease may indicate lung involvement, although any of the viscera may be affected. KS involves the lymph nodes and may present with lymphoedema, even in the absence of overt cutaneous disease. It can occur at any CD4 count, but most patients have a CD4 <200 cells/μL.

Staging

Staging may be clinical or according to the AIDS Clinical Trials Group (ACTG) system.

Clinical staging:

1 – indolent, local disease, <5 lesions, long history

2 – locally aggressive, regional lymphadenopathy

3 – generalised cutaneous, generalised lymphadenopathy

4 – visceral, palatal, abnormal CXR, positive endoscopy

Plus A or B – without/with systemic symptoms of significant LOW, fever, sweats

ACTG staging:

TIS staging (tumour, immune status, systemic illness – poor performance status, prior or current OIs). Staging is recorded as 0 (good prognosis) or 1 (poor prognosis)

- Extent of tumour – (T)

– T0 'good' prognosis – skin macules, plaques and nodules, minimal oral plaques (flat on palate), lymph nodes

– T1 'poor' prognosis – lymphoedema, ulceration/fungating nodules, extensive oral disease, visceral disease

- Immune status – I0 > 200 or I1 < 200 cells/μL
- Severity of systemic symptoms – (S)

– S0 – no symptoms

– S1 – some symptoms

Diagnosis

This is clinical, preferably confirmed by biopsy.

THE TIMING OF ART INITIATION AND SPECIFIC THERAPY FOR THE KS IS CRITICAL.

Early or trivial KS may respond to ART alone but many patients present late and with a heavy tumour burden. Thus these patients need chemotherapy to reduce the tumour burden and then ART. Immune reconstitution with ART occurs and may worsen the KS dramatically.

Treatment may be local or systemic:

- Local therapy can be used for scanty or cosmetically disfiguring skin disease. Local radiotherapy, intra-lesional chemotherapy and cryotherapy are possible alternatives.
- Systemic therapy consists of intravenous chemotherapy (first-line is usually a combination of vincristine, bleomycin and doxorubicin, second-line chemotherapy is paclitaxel). Other therapies include interferon-α, thalidomide and other biological agents.

Survival

In the pre-ART era, survival was 4%. This has improved markedly although resolution of KS may be a slow, gradual process which invariably requires chemotherapy in addition to ART.

8.4 LYMPHOMAS

HIV positive patients have an increased incidence of high-grade NHL, including primary B-cell lymphoma of the brain. Lymphoid tumours generally have an aggressive course in HIV positive patients. This also applies to HL (often mixed cellularity or lymphocyte depleted) and CNS lymphoma.

Treatment

Combination chemotherapy is used; there is evidence that the same doses as for HIV negative patients may be used but this requires aggressive supportive measures to be available for complications of treatment such as myelosuppression. Modified/low dose chemotherapy may be more applicable in low-resource settings though there is no definitive study to guide treatment in terms of chemotherapy medicines, dose intensity and scheduling. There are no guidelines as to timing of ART versus chemotherapy but patients should have proper HIV VL suppression with ART. CNS prophylaxis with intrathecal chemotherapy is standard practice.

8.5 CERVICAL CANCER

All HIV positive women need regular check-ups for cervical cancer as they are at a higher risk of pre-cancer and invasive cervical cancers. Refer all women for PAP smears or visual inspection using acetic acid (VIAC). Such reviews should be offered at least annually. Patients should be on fully suppressive ART. Immediate management of pre-cancerous and cancerous lesions should be offered.

8.6. Non-AIDS Defining Cancers (NADCS)

Each tumour should be treated on its own merit, Patients should be on fully suppressive ART.

8.7 Other non-communicable diseases

HIV is becoming a chronic disease now that mortality is being averted with ART. Patients will be living longer and hence are at risk of dying from non-communicable diseases. Apart from assessing patients for the traditional risk factors for cardiovascular disease such as hypertension, chronic kidney disease, diabetes, obesity and hyper-lipidaemia, there is need to be aware of the risk posed by the antiretroviral medicines themselves. Antiretroviral medicines, in particular, the protease inhibitors tend to make patients have hyperglycaemia and hyperlipidaemia.

- Monitor the blood pressure, glucose, lipid levels and renal function at least annually or more frequently in those who already have abnormalities. (Refer to the latest EDLIZ).
- Interventions such as nutrition assessment, dietary counselling and support, smoking cessation, promoting exercise as part of HIV care provide opportunities for reducing the risks of NCDs among PLHIV

9. POST-EXPOSURE PROPHYLAXIS

In people who have been accidentally exposed to HIV through needle-stick inoculation or through contamination of mucous membranes by secretions, it has been shown that administration of ARVs within 72 hours of exposure reduces the likelihood of HIV infection being transmitted. In this situation, ART needs to be continued for one month. The following guidelines should be followed in the event of accidental occupational exposure to material (i.e., blood, secretions, excretions) that may contain HIV. Occupational exposure to potentially infectious material may occur through an injury with a sharp object that has been used on a patient or through the contamination of mucous surfaces with patients' blood or secretions.

The following types of exposures should be considered for post-exposure prophylaxis:

- Needle-stick injury or injury with a sharp object used on a patient
- Mucosal exposure of the mouth or eyes by splashing fluids
- Broken skin exposed to a small volume of blood or secretions such as may occur with sexual abuse
- Sexual assault (rape)

The exposure can be classified as high risk or low risk for HIV infection, as follows:

Low risk:

- Solid, such as surgical needle, superficial exposure on intact skin
- Small volume (e.g., drops of blood) on mucous membranes or non intact skin
- Source patient asymptomatic or with VL less than 1,500 copies/ml

High risk:

- Large-bore needle, deep injury
- Large-volume splash on mucous membranes or non intact skin
- Source patient symptomatic or with high VL levels

9.1 Prevention of occupational exposure in health facilities

All health facilities in the private and public sector should adopt a policy for the prevention of occupational accidental exposure to blood-borne pathogens. Universal precautions (i.e., the use of disposable latex gloves when handling bodily fluids, single-use equipment, and proper management of sharp and

contaminated materials) should be observed by all levels of health-care workers. Universal precautions are designed to prevent transmission of HIV, hepatitis B virus (HBV), and other blood-borne pathogens when providing health care. Under universal precautions, the blood and certain body fluids of all patients are considered potentially infectious for HIV, HBV, and other blood-borne pathogens.

Universal precautions involve the use of protective barriers such as gloves, gowns, aprons, masks, or protective eyewear, which can reduce the risk of exposure of the health-care worker's skin or mucous membranes to potentially infective materials.

Health facilities should implement universal precautions for the prevention of exposure to potentially infectious material. The programme should include the training of all employees in the handling and disposal of infectious material. All personnel should be made aware of the risks involved in improper handling of such material, and the steps necessary for preventing exposure should be clearly displayed in posters.

The greatest risk of accidental exposure is in the handling of sharp objects that have been used on patients. All personnel should be taught how to safely handle and dispose of sharp objects. Messages should promote the avoidance of recapping needles, using "sharps bins" for disposing of sharps, and taking care in performing procedures.

Health personnel should also be conscious that blood and secretions from patients may be infectious and that simple contamination of unbroken skin does not comprise a significant risk, but contamination of intact mucous surfaces of the mouth and eyes does. The health facility should ensure the continuous supply of personal protective equipment, educational materials, disposable syringes and needles, and sharps bins. Health facilities should ensure the availability and accessibility of medicines for post-exposure prophylaxis.

9.2 Procedure to be followed in the event of injury with a sharp object

In the event of an injury with a sharp object, such as a needle or scalpel, that has been used on a patient or in the event of a mucous surface being contaminated with blood or secretions from a patient, the following steps should be followed:

1. Wash the exposed area thoroughly with soap and water.

2. Rinse the eye or mouth with plenty of water if contaminated.
3. Report the injury to a senior member of staff or the supervisor.
4. Start the ARVs recommended for post-exposure prophylaxis immediately—these should be started within 1 hour if possible and at the latest within 72 hours of the exposure.
5. Ascertain the HIV status of the patient and the injured health worker after providing appropriate counselling—the standard rapid HIV antibody tests should be used and the results of tests obtained as quickly as possible. Offer viral DNA or RNA testing if source is suspected to be in the window period.
6. Depending on the results of the HIV tests, the following actions should be taken:
    - If the source patient is HIV-negative, no further post-exposure prophylaxis is necessary for the exposed health worker. There will be need to consider exposure to other infections such as hepatitis B.
    - If the exposed health worker is HIV-positive, no further post-exposure prophylaxis is necessary for the health worker. The health worker should be referred for further counselling and the long-term management of his or her HIV infection, which would have occurred prior to the exposure.
    - If the health worker is HIV-negative and the source patient is HIV-positive, continue ARVs for a period of one month; repeat the health worker's HIV tests at three months and at six months after the initial test. If the health worker should seroconvert during this time, provide appropriate care and counselling and refer for expert opinion and long-term treatment.
    - If the health worker refuses to be tested, he or she may have no claim for possible future compensation.
7. If it is not possible to determine the HIV status of the source patient, then assume that the source is positive and proceed according to the guidelines in the previous bullets.
8. In the event of HIV infection exposure to the HCW, the greatest risk of transmission to other individuals is in the first six weeks. The exposed Health Care Worker should be instructed to use measures to reduce the potential risk of HIV transmission to others, e.g. condom use, abstinence and refraining from blood transfusion until the 6 month serologic test is negative.
9. Healthcare workers who are breastfeeding should consider discontinuing breastfeeding following exposure to HIV. This avoids infant exposure to ARVs and HIV in breast milk should the mother be infected.
10. Post-exposure prophylaxis with hepatitis B immune globulin (HBIG) and/or hepatitis B vaccination series should be considered for occupational

exposure (within 24 hours) after evaluating the hepatitis B status of the source patient and the vaccination status of the exposed person. Hepatitis B vaccine and HBIG can be given at the same time but using different injection sites. Routine pre-exposure hepatitis B vaccination should be offered to all health-care workers.

9.3 Post-exposure prophylaxis after rape or sexual assault

It is recommended that a victim of rape or sexual assault presenting within 72 hours of exposure be counselled and provided with the medicines recommended for post–occupational exposure prophylaxis. It is important to try to determine the HIV status of the perpetrator. If that is not possible, it may be assumed that the perpetrator is HIV-positive, and the victim is provided with the treatment as listed in the preceding section. Refer the client to the nearest support centre for sexual assault survivors.

9.4 ARVs to be used in post-exposure prophylaxis

Immediately after exposure, all exposed adult individuals should take the following:

- Zidovudine 300 mg orally twice daily
  plus
- Lamivudine 300 mg orally once daily
  Plus
- Atazanavir (300mg)/ ritonavir 100mg orally daily

The above regimen is given for one month.
The dosage for children is as follows:

> 40 kg and/ or > 6 yrs: TDF/3TC +ATV/r
< 40 kg and/ or < 6 yrs: AZT/3TC + LPV/r

The exposed individuals should be counselled regarding side effects prior to receiving the medicines. If the source is HIV-negative, medicine administration should be discontinued.

Special note
All health care workers on atazanavir/ritonavir should have a baseline liver function test and a repeat at two weeks. If there is any derangement in transaminases urgent advice must be sought. Please note that atazanavir causes hyperbilirubinaemia which is a normal part of treatment. Patients on atazanavir may develop a rash. If this happens urgent advice must be sought.

If a health care worker is on Zidovudine, a baseline full blood count should be done. It should be repeated at two weeks.

APPENDIX I. CLINICAL STAGING FOR ADULTS AND ADOLESCENTS

(Adapted from WHO, WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children, 2007. Available at: http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html.)

Clinical Stage 1
• Asymptomatic • Persistent generalized lymphadenopathy
Clinical Stage 2
• Moderate unexplained weight loss (< 10% of presumed or measured body weight) • Recurrent upper respiratory tract infections (sinusitis, bronchitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulcerations • Papular pruritic eruptions • Seborrhoeic dermatitis Fungal nail infections
Clinical Stage 3
• Unexplained severe weight loss (> 10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month) • Persistent oral candidiasis • Oral hairy leukoplakia
• Pulmonary TB • Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis • Unexplained anaemia (< 8 g/dL) and/or neutropenia (< 1,000/mm3) and/or thrombocytopenia (< 50,000/ mm3) for more than 1 month

Clinical Stage 4
• HIV wasting syndrome • Pneumocystis pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital, or anorectal of more than 1 month's duration) or visceral at any site • Oesophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) • Extrapulmonary TB • Kaposi's sarcoma • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis • Disseminated nontuberculous mycobacteria infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis • Chronic isosporiasis • Cytomegalovirus (CMV) infection (retinitis, or CMV infection of other organs) • Disseminated mycosis (e.g., extrapulmonary histoplasmosis, coccidiomycosis) • Recurrent septicaemia (including nontyphoidal salmonella) • Lymphoma (cerebral or B-cell non-Hodgkin's) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

APPENDIX II. REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION

(Adapted from WHO, WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children, 2007. Available at: http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html.)

Primary HIV Infection
• Asymptomatic • Acute retroviral syndrome
Clinical Stage 1
• Asymptomatic • Persistent generalized lymphadenopathy
Clinical Stage 2
• Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Extensive wart virus infection • Extensive molluscum contagiosum • Recurrent oral ulcerations • Unexplained persistent parotid enlargement • Lineal gingival erythema • Herpes zoster • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) • Fungal nail infections
Clinical Stage 3
• Moderate unexplained malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5° C intermittent or constant, for longer than 1 month) • Persistent oral candida (outside first 6 to 8 weeks of life) • Oral hairy leukoplakia • Acute necrotizing ulcerative gingivitis/periodontitis • Lymph node TB • Pulmonary TB • Severe recurrent presumed bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis • Unexplained anaemia (< 8 g/dL), neutropenia (< 500/mm3), or chronic thrombocytopenia (< 50,000/mm3) • HIV-associated cardiomyopathy or HIV-associated nephropathy

Clinical Stage 4
• Unexplained severe wasting, stunting, or severe malnutrition not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe presumed bacterial infections (e.g., empyema, pyomyositis, bone or joint infection, or meningitis, but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) • Extrapulmonary TB • Kaposi's sarcoma • Oesophageal candidiasis (or candida of trachea, bronchi, or lungs) • Central nervous system toxoplasmosis (outside the neonatal period) • HIV encephalopathy • Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month • Extrapulmonary cryptococcosis, including meningitis • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis) • Chronic cryptosporidiosis • Chronic isosporiasis • Disseminated nontuberculous mycobacteria infection • Acquired HIV-associated rectal fistula • Cerebral or B-cell non-Hodgkin's lymphoma • Progressive multifocal leukoencephalopathy

APPENDIX III. GRADES OF ADVERSE EVENTS

Grade 1 (Mild)	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Grade 2 (Moderate)	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3 (Severe)	Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization possible
Grade 4 (Life-threatening)	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable

APPENDIX IV. RAPID COTRIMOXAZOLE DESENSITIZATION PROTOCOL

(Adapted from Zimbabwe Ministry of Health and Child Welfare, HIV/AIDS Standard Treatment Guidelines, 2004)

Suitable for prophylactic-dose cotrimoxazole or high-dose cotrimoxazole for treatment of *Pneumocystis jirovecii* pneumonia

Desensitization can be offered rapidly or over a longer period of time. Do not desensitize anyone who has had an anaphylactic reaction to cotrimoxazole or a severe skin rash such as Stevens-Johnson syndrome. Desensitization is usually about 60% effective. Rapid desensitization ideally should be performed during the day in a setting where emergency resuscitation can be provided and adrenaline can be given. Observations during rapid desensitization should take place every 30 minutes, before each dose is given, and should include temperature, pulse, and blood pressure.

If only mild rash or pruritus occurs, administer antihistamine (e.g., chlorpheniramine or promethazine) and continue. If more serious side effects occur, such as severe wheeze, severe or symptomatic hypotension, severe rash, and so on, discontinue desensitization, manage appropriately, and do not try to restart desensitization.

Once cotrimoxazole has been started, it can be continued indefinitely as long as no reactions are noted, but if the medicine is stopped at any time, there may be a risk of reaction when it is restarted.

Using a 1 ml syringe, put 0.5 ml of paediatric cotrimoxazole 240 mg / 5 ml syrup in 1,000 ml of 5% dextrose and mix well.

Give as follows:

Minutes	Quantity of Above Mixture Given Orally
0	1 ml (use 10 ml syringe)
30	10 ml (use 10 ml syringe)
60	100 ml (use 10 ml syringe)
90	0.5 ml
120	5 ml
150	480 mg tablet
180	Start full prophylactic or therapeutic dose.

APPENDIX V. SOME IMPORTANT MEDICINE INTERACTIONS

Avoid giving the following medicines together:

Medicines Involved	Effects of the Interaction
Avoid giving Nevirapine and ketoconazole together.	Both medicines are toxic to the liver. The level of Nevirapine is increased while that of ketoconazole is reduced.
Use alternative contraception with Nevirapine.	ARVs can make oral contraceptives less effective. Encourage dual methods of contraception (including using condoms).
Avoid giving Efavirenz and diazepam together except in an emergency that requires diazepam.	Efavirenz increases the levels of diazepam in the blood.
Avoid giving Stavudine and Zidovudine together.	Both medicines work to prevent the virus from entering the CD4 lymphocyte. They antagonize each other when given together.

APPENDIX VI. DEVELOPMENTAL MILESTONES

Age	Psychosocial	Gross Motor	Fine Motor / Visual	Communication/
Hearing				
1 month	Follows faces to the midline	Moves all extremities equally; lifts head when lying on stomach	Opens hands spontaneously	Startled by loud sounds; cries; quiets when fed and comforted
2 months	Follows faces past midline; smiles responsively	Lifts head up 45 degrees when on stomach	Looks at own hand	Makes baby sounds (cooing, squealing, gurgling)
3 months	Recognizes mother; smiles responsively	Supports head for a few seconds when held upright	Opens hands frequently	Responds to voices; laughs
4 months	Follows an object with eyes for 180 degrees; regards own hand; anticipates food on sight	Bears weight on legs; good neck control when pulled to sitting; lifts chest and supports self on elbows when pulled to sit	Brings hands together in midline (clasps hands); grabs an object (such as a rattle); reaches for objects	Turns head to sound
6 months	Reaches for familiar people	Rolls from stomach to back or back to stomach; sits with anterior support	Plays with hands by touching them together; sees small objects such as crumbs	Responds to name; babbles

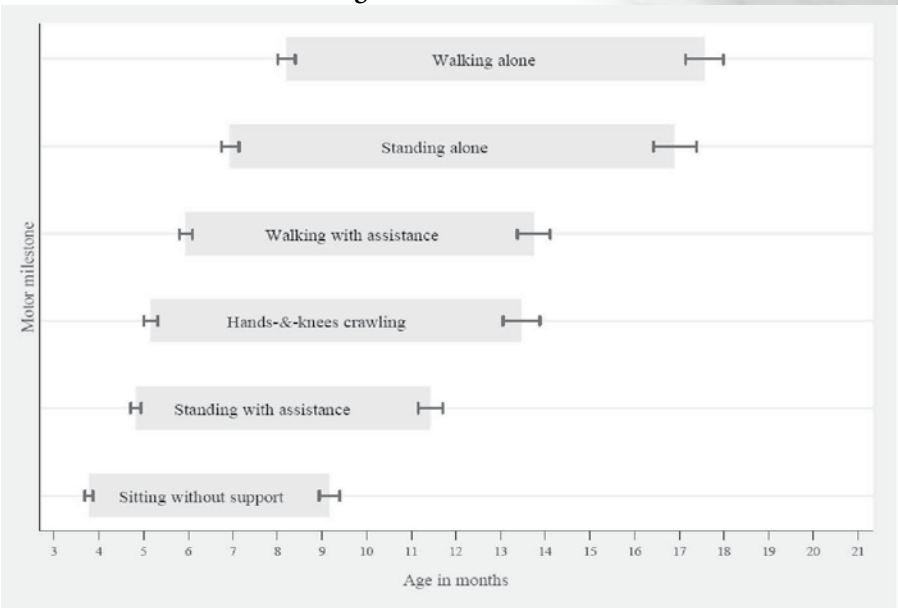
9 months	Indicates wants; waves bye-bye; has stranger anxiety	Can sit without support; creeps or crawls on hands and knees	Looks for a toy when it falls from his or her hand; takes a toy in each hand; transfers a toy from one hand to the other	Responds to soft sounds such as whispers
12 months	Has separation anxiety; social interactions intentional and goal directed	Pulls self up to standing position; walks with support	Points at objects with index finger	Says at least one word; makes “ma-ma” or “da-da” sounds; locates sounds by turning head
15 months	Imitates activities; finds a nearby hidden object	Can take steps by himself or herself; can get to a sitting position from a lying position	Can stack one cube on top of another	Able to say mama and dada to respective parents
18 months	Initiates interactions by calling to adult	Walks without help	Takes off own shoes; feeds self	Says at least 3 words
2 years	Does things to please others; engages in parallel (imitative) play	Runs without falling	Looks at pictures in a book; imitates drawing a vertical line	Combines 2 different words

APPENDIX VII. DEVELOPMENTAL RED FLAGS

Birth to 3 months	• Failure to alert to environmental stimuli • Rolling over before 2 months (hypertonia) • Persistent fisting at 3 months
4 to 6 months	• Poor head control • Failure to smile • Failure to reach for objects by 5 months
6 to 12 months	• No baby sounds or babbling • Inability to localise sounds by 10 months
12 to 24 months	• Lack of consonant production • Hand dominance prior to 18 months (contralateral weakness) • No imitation of speech and activities by 16 months
Any age	• Loss of previously attained milestones

APPENDIX VIII. SIX GROSS MOTOR MILESTONES

Windows of achievement for six gross motor milestones



Reference: WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatrica Supplement 2006:450:86-95.

Source: WHO Mulitcentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatrica Supplement 2006; 450:86-95.

APPENDIX IX. ARVs PAEDIATRIC DOSING CHART

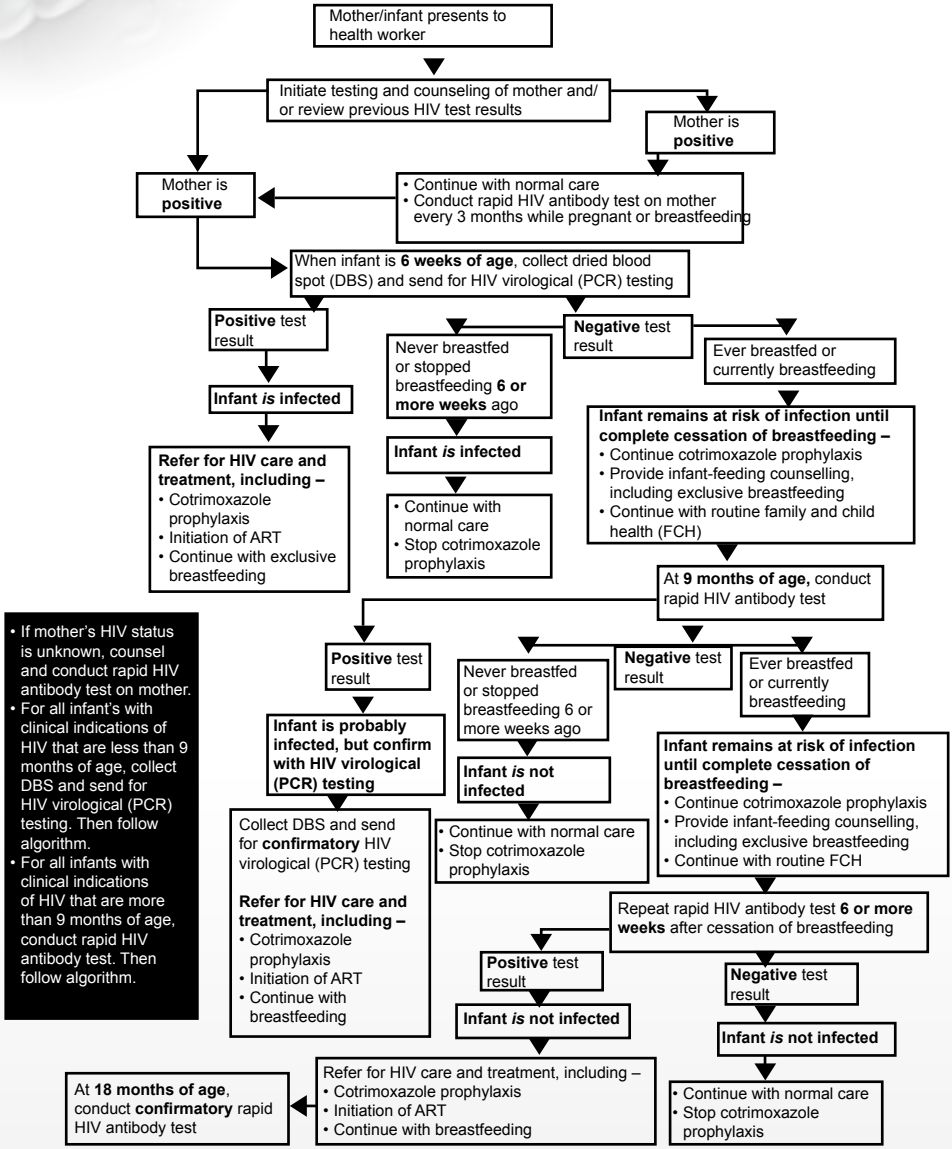
Medicine	Strength of paediatric tablet (mg) or liquid (mg/ml	Number of tablets or ml by weight band (AM + PM)					Strength of adult tab (mg)	Number of tablets by weight band (AM + PM)	
		Children 6 weeks of age and over							
		3–5.9 kg AM + PM	6–9.9 kg AM + PM	10–13.9 kg AM + PM	14–19.9 kg AM + PM	20–24.9 kg AM + PM		25–29.9 kg AM + PM	30–34.9 kg AM + PM
	6/30	1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	30/150	1 + 1	1 + 1
	12/60	0.5 + 0.5	1 + 0.5	1 + 1	1.5 + 1	2 + 1			
		1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	30/150 /200	1 + 1	1 + 1
		0.5 + 0.5	1 + 0.5	1 + 1	1.5 + 1	2 + 1			
NVP	200; 10 mg/ml	5 ml + 5 ml	8 ml + 8 ml	10 ml + 10 ml	1 + 0.5	1 + 0.5	200	1 + 1	1 + 1
AZT	60	1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	300	1 + 1	1 + 1
AZT	300; 10 mg/ml	6 ml + 6 ml	9 ml + 9 ml	12 ml + 12 ml	0.5 + 0.5	1 + 0.5	300	1 + 1	1 + 1
AZT/3TC	60/30	1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	300/150	1 + 1	1 + 1
AZT/3TC /NVP	60/30 /50	1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	300/150 /200	1 + 1	1 + 1
ABC	60	1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	300	1 + 1	1 + 1
ABC	300; 20 mg/ml	3 ml +3 ml	4 ml + 4 ml	6 ml + 6 ml	0.5 + 0.5	1 + 0.5	300	1 + 1	1 + 1
ABC/3TC	60/30	1 + 1	2 + 1	2 + 2	3 + 2	3 + 3	600/300	1 + 0	1 + 0
Lop/r	100/25	n/r	n/r	2 + 1	2 + 2	3 + 2	100/25 (paed)	3 + 3	3 + 3

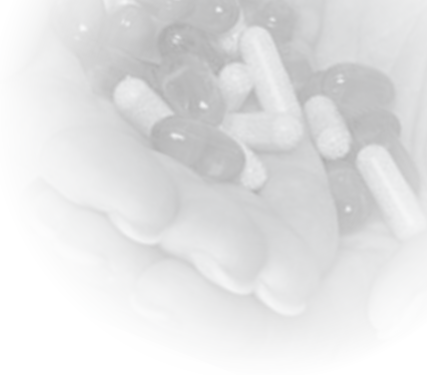
Lop/r	80/20 mg/ ml	2 ml + 1 ml	2 ml + 1 ml	2 ml + 2 ml	3 ml + 2 ml	3 mL+ 3 ml	200/50 (adult)	2 + 1	2 + 1
Note: Higher doses of Lop/r may be required when co-administered with enzyme-inducing medicines such as NVP, EFV; n/r = not recommended.									
Medicine	**Strength of paediatric tablet (mg)**	**Number of tablets by weight band once daily Children 3 years and over**					**Strength of paediatric tablet (mg)**	**Number of tablets by weight band once daily (PM dosing preferred)**	
EFV	200, 50	n/r	n/r	1x200 mg	1x200 mg +	1x200 mg +	200, 50	1.5x200 mg +	2x200 mg
					1x50 mg	2x50 mg		1x50 mg	
EFV	200, 50	n/r	n/r	0 + 1	0 + 2	0 + 3		0 + 2.5	0 + 2

(Note: Pediatric Dosing Chart on preceding page was adapted from: International Center for AIDS Care and Treatment Programs, Global AIDS Program, Baylor International Pediatric AIDS Inititative, Pediatric Antiretroviral Dosing in Resource-Limited Settings, Updated November 2006. Available at: http://www.cdc.gov/globalAIDS/pa_pmtct_pediatric.htm.)

APPENDIX X. EARLY INFANT DIAGNOSIS ALGORITHM

Algorithm for HIV Testing of Infants When Virological (PCR) Testing Is Available





NOTES

NOTES