APPROACH TO THE MANAGEMENT OF ADVANCED HIV DISEASE (AHD)

Screening, diagnosing, preventing, and treating AHD-related opportunistic infections and other AHD-related conditions

Ministry of Health

Government of Lesotho

June 2020

Contents

Foreword

Over the past 3 decades, Lesotho has made significant progress in scaling up HIV prevention, diagnosis, treatment, and care. Currently, over 230,000 people living with HIV (PLHIV) receive antiretroviral therapy (ART), which translates to an ART coverage of more than 70%, with a national viral load suppression rate of over 90%. This is evidence that substantial progress has been made towards the HIV response in Lesotho.

Advanced HIV Disease (AHD) threatens to roll back the positive impact of HIV investment and programmatic milestones made to date in Lesotho. AHD poses negative social and economic challenges to our communities and contributes to substantial costs that burden the health system.

The World Health Organisation (WHO) has recommended that a defined package care of interventions, which includes screening, treatment and prophylaxis for major opportunistic infections, rapid initiation of ART, and intensified treatment adherence support, should be provided to patients presenting with AHD to reduce associated morbidity and mortality.

This advanced HIV disease manual responds to WHO's guidance by defining and streamlining the AHD package of care in Lesotho. It has been developed to reduce AHD associated morbidity and mortality, by providing health care workers with comprehensive, clear guidelines on how to prevent, diagnose, treat, care, and follow up the most common AHD conditions in PLHIV.

Lesotho remains focused and committed to improving universal access to HIV prevention, diagnosis, and treatment. Confronting and addressing AHD remains a public health priority and is central towards ending AIDS as a public health threat by 2030.

I am confident that the guidance in this AHD manual will be used by health care workers to save the lives of many of my fellow Basotho and countrymen.

On behalf of all Basotho, I express the utmost gratitude and acknowledgement to all internal and external stakeholders that have contributed to the development of this important AHD manual.

Dr. Nyane Letsie

Director General Health Services

Ministry of Health Lesotho

Acknowledgements

The Lesotho Ministry of Health expresses sincere thanks to all its HIV/TB development/implementing partners for their contributions towards the development of this Advanced HIV Disease manual. These partners include, but are not limited to, President's Emergency Plan for AIDS Relief (PEPFAR), Centers for Disease Control and Prevention (CDC), USAID, World Health Organization (WHO), UNAIDS, Clinton Health Access Initiative (CHAI), Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), Baylor College of Medicine Children's Foundation Lesotho, Jhpiego, SolidarMed, mothers2mothers, Partners in Health (PIH), Lesotho Network of AIDS Services Organizations (LENASO), ICAP at Columbia University, and Population Services International (PSI).

In addition, the development of this AHD manual would not have been accomplished without the inputs of health personnel from both, the Government and CHAI. The Ministry therefore acknowledges their contribution to the process.

The Ministry of Health also wishes to specially acknowledge all members of the HIV/TB Advisory Committee; in particular, the following members of the writing task team who provided technical assistance and guidance during the development of this national AHD manual:

Ministry of Health (MOH): Dr. LLang Maama, Ms. Tsietso Motsoane, Dr. Tapiwa Tarumbiswa, Dr. Mpho Khoabane, Dr. Simon Marealle, Ms. Annah Moseneke-Masheane, Ms. Matsitso Mokhoanyane, Ms. Rosina Phate-Lesihla, Ms. Likabelo Mokoteli, Mr. Makhebe Khomolishoele, Ms. Itumeleng Tshabalala, Ms. Nteboheleng Tjobe, Ms. Seipati Motsei-Nchephe, Ms. Mathato Nkuatsana, Mr. Monkoe Leqheka, Mr. Muccara du Preez

Baylor Lesotho: Dr. Mosa Molapo Hlasoa, Dr. Mabene Tsotako, Dr. Teresa Steffy, Ms. Mpheng Thamae

Centers for Disease Control and Prevention (CDC): Dr. Fred Asiimwe Mugyenyi

Clinton Health Access Initiative (CHAI): Ms. Esther Mandara, Dr. Brian Ngwatu, Dr. Ikechukwu Amamilo, Mr. Shaun McGovern, Ms. Swati Kalra, Ms. Thatohatsi Sefuthi

Elizabeth Glaser Pediatric AIDS Foundation (EGPAF): Dr. Esther Tumbare, Dr. More Mungati, Dr. Mamello Sekese, Dr. Tsitsi Vimbayi Chatora, Ms. Malijane Nyabela, Ms. Kekeletso Mabeleng

ICAP: Dr. Gerald Mwima

Independent Contractors: Dr. Jill Sanders

Jhpiego: Dr. Tafadzwa Chakare

Mothers2Mothers: Dr. Hamid Mandali

Partners in Health (PIH): Dr. David Holtzman

SolidarMed: Dr. Josephine Muhairwe

USAID: Dr. Justine Mirembe

Abbreviations and Acronyms

5FC	5-fluorocytosine
AHD	Advanced HIV Disease
AmB	Amphotericin B
ART	Antiretroviral Therapy
ARV	Antiretroviral
BCG	Bacillus Calmette-Guerin
BMI	Body Mass Index
CAP	Community-Acquired Pneumonia
CDI	Clostridium Difficile-associated Infection
CM	Cryptococcal Meningitis
COPD	Chronic Obstructive Pulmonary Disease
CPT	Co-trimoxazole Preventive Therapy
CrAg	Cryptococcal Antigen
CSF	Cerebrospinal Fluid
CTX	Co-trimoxazole
DR	Drug-resistant
DS	Drug-sensitive
DST	Drug Susceptibility Testing
EPTB	Extra-Pulmonary Tuberculosis
FDC	Fixed-Dose Combination
FTT	Failure to Thrive
GI	Gastrointestinal
GRT	Genotypic Resistance Testing
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
HPV	Human Papilloma Virus
HTS	HIV Testing Services
IMAM	Integrated Management of Acute Malnutrition
IMCI	Integrated Management of Childhood Illnesses
INH	Isoniazid
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
IV	Intravenous
IYCF	Infant and Young Child Feeding
LAM	Lipoarabinomannan
L-AmB	Liposomal formulation of Amphotericin B

LEEP	Loop Electrosurgical Excision Procedure
LFA	Lateral Flow Assay
LMICs	Low- and Middle-Income Countries
LTFU	Lost to follow-up
M&E	Monitoring and Evaluation
MDD	Major Depressive Disorder
MoH	Ministry of Health
MUAC	Mid-Upper Arm Circumference
NACS	Nutrition Assessment Counselling and Support
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OI	Opportunistic Infection
PBFW	Pregnant and Breastfeeding Women
PC	Palliative Care
PCR	Polymerase Chain Reaction
PHQ	Patient Health Questionnaire
PJP	Pneumocystis Jirovecii Pneumonia
PLHIV	Persons Living with HIV/AIDs
PMTCT	Prevention of Mother-To-Child Transmission
PTB	Pulmonary Tuberculosis
RUTF	Ready-to-Use Therapeutic Food
SAM	Severe Acute Malnutrition
TB	Tuberculosis
TPT	TB Preventive Therapy
VL	Viral Load
WBC	White Blood Cell
WHO	World Health Organization
WLHIV	Women Living with HIV

1. Background: Advanced HIV Disease (AHD)

As a result of increased access to antiretroviral treatment (ART), the burden of morbidity and mortality associated with HIV infection has decreased over the past decade. However, around 1 in 3 people living with HIV (PLHIV) present to care with AHD and a growing number of PLHIV are returning to care with advanced disease following a period of treatment interruption. People with AHD are particularly at high risk of death, even after initiating ART, with this risk increasing with decreasing CD4 cell count. The most common causes of death are tuberculosis (TB), cryptococcal meningitis (CM), and severe bacterial infections.

For adults and adolescents, and children five years or older, advanced HIV disease is defined as CD4 cell count <200cells/mm^3 or with a current WHO stage 3 or 4 event. All children younger than five years of age with HIV regardless of CD4 count are considered as having AHD due to high viremia and rapid disease progression with high mortality. There is limited access to diagnostic tools, treatment, and preventative services for AHD in most low- and middle-income countries (LMICs), leading to high mortality rates. The World Health Organization (WHO) in 2017 released clear, evidence-based guidelines to countries on the package of services required to appropriately screen, optimally treat, and prevent AHD-related opportunistic infections (OIs).

In Lesotho, of those previously diagnosed with HIV and not on ART, about 23% have a CD4 count <200cells/mm^3 (LePHIA 2017). Even still, of those on ART, approximately 9% on treatment still have a low CD4 count, requiring intervention. Another study conducted in Berea and Motebang hospitals in 2019 revealed a high AHD prevalence of 27.7% among patients initiating ART. Patients without access to an AHD package of care are more likely to be susceptible to opportunistic infections and ultimately, without intervention, are likely to die. This susceptibility to opportunistic infections is reflected in national data that shows that one in five PLHIV have been diagnosed with TB during their lifetime in Lesotho. And surprisingly, despite improvements in access to ART, HIV-related mortality remains high in Lesotho, with over 6,000 patients still dying annually from AIDS-related complications (UNAIDS 2019 AIDSinfo Database). Among Eastern and Southern Africa, Lesotho has the highest percentage of AIDS-related mortality among PLHIV.

2. Introduction

2.1 Approach to the Management of AHD

The 2017 WHO guidelines on management of advanced HIV disease recommend a package of interventions including screening, treatment, and/or prophylaxis for major opportunistic infections, rapid ART initiation, and intensified adherence support interventions to everyone presenting with AHD.

Even though national HIV and TB treatment guidelines in Lesotho have highlighted the need to provide differentiated packages of care for opportunistic infections, a specific guideline document devoted entirely to managing the major opportunistic infections associated with AHD and the overall approach to AHD management has never been developed or deployed.

This guiding document is intended to provide a summary of the screening, diagnosis, prevention, and treatment of major AHD-related opportunistic infections and other AHD-related disease entities. It is

intended to complement and not replace existing national guidelines on the respective OIs and disease entities. For further information on the management of the entities highlighted in this document, refer to the latest respective national guidelines documents.

2.2 Definition of AHD

Lesotho defines AHD in adults, adolescents, and children older than five years as CD4 cell count <200cells/mm^3 or with a current WHO stage 3 or 4 event. All children younger than five years of age with HIV, regardless of CD4 count, are considered as having AHD.

2.2.1 Role of CD4 testing in identifying and managing people with AHD

Lesotho recommends targeted CD4 for the identification of AHD: at baseline, for suspected treatment failure, and for those returning to care. CD4 monitoring should continue until CD4 is >350 cells/mm^3 and viral load is <1,000 copies/mL and only start again if patients meet the above criteria.

Relying on clinical staging alone risks missing substantial numbers of PLHIV with severe immune suppression. In a study from Zimbabwe, Uganda, Kenya, and Malawi, close to half the people with CD4 cell count <100 cells/mm^3 were classified as having WHO clinical stage 1 or 2 disease.[1]

2.3 Major Causes of AHD-Related Mortality

Leading causes of mortality among adults with AHD include tuberculosis, severe bacterial infections, cryptococcal meningitis, toxoplasmosis, and Pneumocystis Jirovecii Pneumonia (PJP). Among children, TB, severe bacterial infections, and PJP, are the leading causes of death. In line with the WHO's AHD recommendations, this national guideline document primarily focuses on the management of these major causes of AHD-related mortality in Lesotho, including:

2.3.1 Tuberculosis (TB)

Tuberculosis is caused by bacteria (*mycobacterium tuberculosis*) that most often affect the lungs.

- Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.
- Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and /or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB.
- Extra pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

TB is the leading cause of morbidity and mortality among PLHIV, accounting for about one-third of the estimated 770,000 people dying from AIDS-related causes globally in 2018, with most of these TB-associated deaths occurring among men. TB also remains a leading cause of HIV-associated hospitalization among adults and children living with HIV worldwide. Young children living with HIV have an especially high risk of progressing to TB disease following initial infection.

[1] REALITY trial: https://www.nejm.org/doi/full/10.1056/NEJMoa1615822

Provision of TB Preventive Therapy (TPT) to all PLHIV is a critical strategy that prevents TB.

2.3.2 Cryptococcal Disease

Cryptococcal disease is an opportunistic infection that occurs primarily among people with AHD and is an important cause of morbidity and mortality. By far the most common presentation of Cryptococcal disease is Cryptococcal Meningitis (CM), which accounts for an estimated 15% of all AIDS-related deaths globally, three-quarters of which are in sub-Saharan Africa. Less common presentations of Cryptococcal disease include pulmonary disease and skin, lymph node and bone involvement. Pre-emptive therapy for cryptococcal antigen–positive asymptomatic people is a key strategy to prevent cryptococcal meningitis. In addition, primary and secondary fluconazole prophylaxis is critical to preventing cryptococcal disease.

2.3.3 Toxoplasmosis

Cerebral toxoplasmosis is the most frequent cause of expansive brain lesions among adults living with HIV not receiving co-trimoxazole. Toxoplasmosis is a common protozoan infection among PLHIV, with the prevalence of coinfection especially high in sub-Saharan Africa. People with latent toxoplasmosis infection are at risk of developing cerebral toxoplasmosis when their CD4 count falls below 200 cells/mm^3. The diagnosis of cerebral toxoplasmosis requires imaging techniques, such as computed tomography scans, which are rarely available in most sub-Saharan African settings, and thus, knowledge of the disease burden is limited. Toxoplasmosis should be suspected in any individual with AHD and new onset focal neurologic findings. Empiric treatment can be lifesaving. About 15% of the hospitalized adults living with HIV dying from AIDS-related illnesses die from cerebral toxoplasmosis.

2.3.4 Pneumocystis Jirovecii pneumonia (PJP)

PJP is caused by a fungus, Pneumocystis Jirovecii, which is common in the environment and does not cause disease in immunocompetent people. PJP is a leading cause of mortality among hospitalized adults (13%) and children (29%) living with HIV. However, the global burden of morbidity and mortality attributable to PJP is poorly characterized because appropriate diagnostic testing is lacking in most settings.

2.3.5 Severe bacterial infections

People with AHD frequently have severe bacterial infections, including bloodstream, respiratory, central nervous system, and gastrointestinal infections. The burden of mortality and morbidity attributable to severe bacterial infections is poorly characterized largely because appropriate diagnostic facilities are lacking. Severe bacterial infections are estimated to cause more than one-third of the hospitalizations among adults and children living with HIV worldwide.

3. Summary: Primary AHD Package of Care for Lesotho

A package of interventions including screening, treatment, and prophylaxis for major opportunistic infections, rapid ART initiation, and intensified adherence support should be offered to everyone presenting with AHD at all facilities within Lesotho. The package of care is summarized in *Table 1* below. The specific aspects of management for this package of care are described in further detail in this manual.

Table 1: Components of the Package of Care for People Living with HIV

	Intervention	**CD4 Cell Count/ Eligibility Criteria**	**Adults and Adolescents**	**Children (0->10)**
Screening and Diagnosis	Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients Sputum/non-sputum – AFB, Xpert	Any CD4	Yes	Yes
	Urine TB LAM* for TB diagnosis in patients with symptoms and signs of TB	CD4 ≤100 cells/mm^3	Yes	Yes
	Cryptococcal antigen (CrAg) screening	CD4 <200 cells/mm^3	Yes	No
Prophylaxis and Pre-emptive treatment	Co-trimoxazole prophylaxis	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4 event	Yes	Yes
	TB Preventive Therapy	Any CD4	Yes	Yes
	Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis	CD4 <200 cells/mm^3	Yes	N/A (Screening not advised)
Rapid ART initiation	Rapid ART initiation	Any CD4	Yes	Yes
	Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis	Any CD4	Yes	Yes
Adherence support	Tailored enhanced adherence counselling to ensure optimal adherence to the advanced disease package, including phone calls and home visits, if feasible	Anyone with AHD	Yes	Yes
*TB LAM also recommended for patients that are seriously ill (defined as (Temp>39, Resp rate >30/min, heart rate >120/min, unable to walk unaided) irrespective of CD4 cell count				

4. Guidance on Rapid ART Initiation

Rapid ART initiation should be offered to all PLHIV following a confirmed HIV diagnosis and clinical assessment. ART initiation should be offered on the same day to people who are ready to start.

The introduction of the "treat all" recommendation (ART for all PLHIV regardless of CD4 cell count) supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation. Rapid ART start is especially important for people with extremely low CD4 cell count, for whom the risk of death is high. People should not be coerced to start immediately and should be supported in making an informed choice regarding when to start ART. The Children with HIV Early antiretroviral (CHER) randomized trial demonstrated superior benefit in clinical and immunological outcome following early ART. More recently, a randomized trial from Kenya in which HIV+ hospitalized children (median age 23 months) were randomized to ART start within 48 hours vs 7–14 days suggested there was no difference in mortality between the treatment arms, providing evidence that rapid treatment was safe and prompt initiation of ART is essential to reduce the very high mortality observed overall, with 21% of children dying during 6 months of follow-up[2]. Therefore, special consideration should be made for children and 'Rapid ART' as this presents an integral and potentially life-saving intervention in the AHD care package for children.

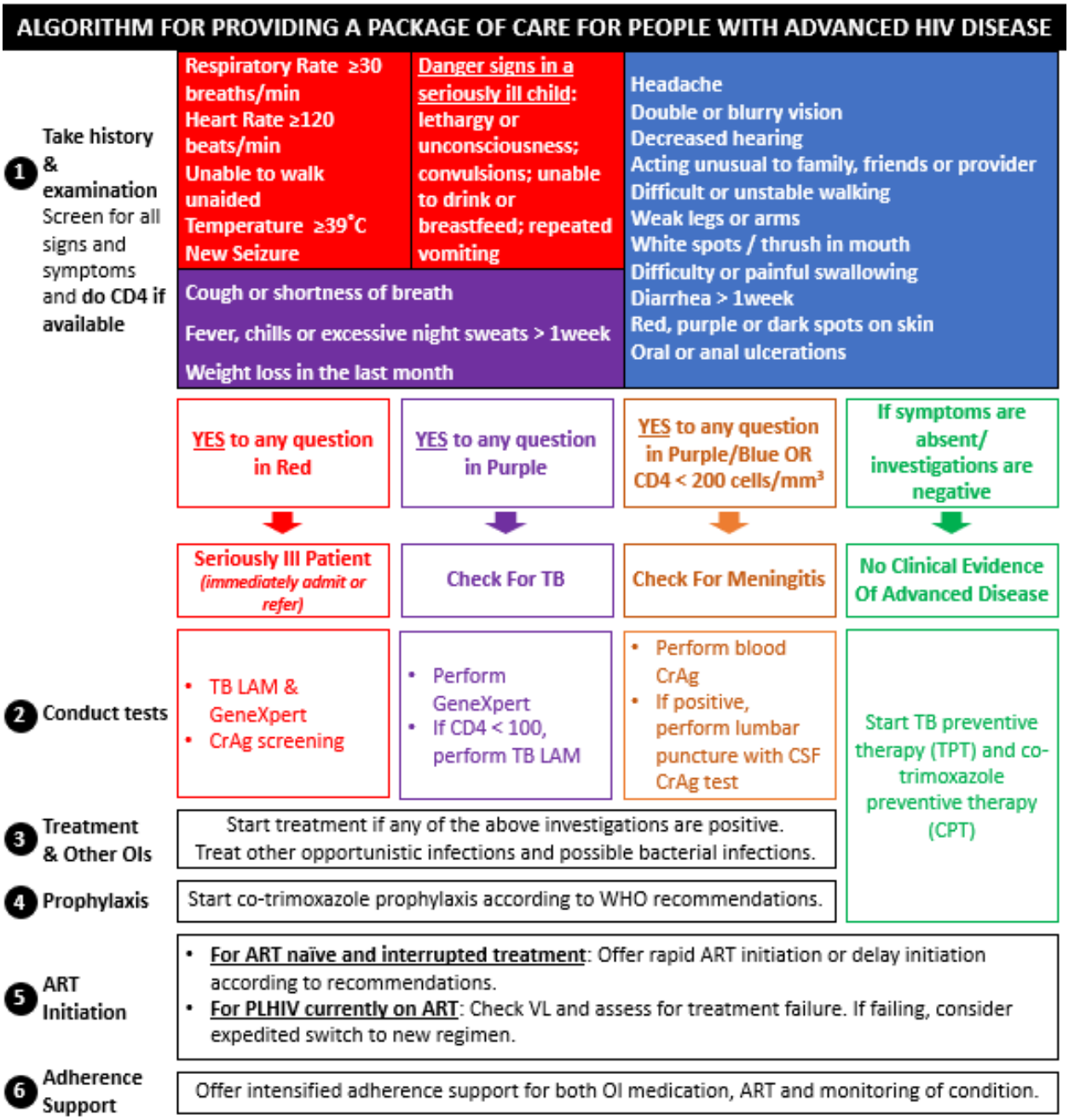
People presenting for the first time or those returning to care should undergo history and clinical examination to evaluate for significant opportunistic infections (such as signs and symptoms of TB and signs and symptoms suggesting meningitis) before rapid ART initiation is offered. Although not a requirement for ART initiation, baseline CD4 cell count testing should be performed to assist in determining whether the patient has AHD.

People who have no clinical signs and symptoms of TB or other opportunistic infections and whose cryptococcal antigen (CrAg) test is negative should initiate ART the same day in combination with their package of prophylaxis (summarized in greater detail in Section 4.6). For PLHIV with CD4 cell count <200 cells/mm^3 in facilities where CrAg testing result is not available on the same day, consideration could be given to starting fluconazole prophylaxis and discontinuing if the CrAg screening result is subsequently found to be negative.

Figure 1 below summarises the algorithm for providing a package of care for PLHIV with AHD.

[2] Njuguna IN, Cranmer LM, Otieno VO, et al. Urgent versus post-stabilisation antiretroviral treatment in hospitalised HIV-infected children in Kenya (PUSH): a randomised controlled trial. The Lancet HIV. 2018;5: e12-e22

Figure 1: Algorithm for providing a package of care for PLHIV with AHD



4.1 Baseline tests for ART initiation

Every patient with HIV entering care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection.

Conducting baseline assessment in AHD is particularly important to:

1. Rule out/diagnose existing co-morbidities, since it
    a. May impact timing of ART
    b. May require treatment that interacts with ART
2. Assist in the selection of ARV drug regimens
3. Determine need for screening and prophylaxis for opportunistic infections

As a minimum, the following tests should be conducted in all AHD clients:

1. CD4 T lymphocyte cell count (CD4 count)
2. Full blood count
3. ALT
4. Creatinine
5. Urinalysis
6. Hepatitis B and C screening
7. Pregnancy test for women of childbearing age
8. Fasting blood glucose and serum lipids if protease inhibitors are to be administered

In addition, other tests (including screening tests for sexually transmitted infections, cervical cancer, and tests for determining the risk of opportunistic infections and need for prophylaxis (CrAg and TB LAM)) should be performed as per this manual.

Patients living with HIV infection often must cope with many social, psychiatric, and medical issues that are best addressed through a patient-centred, multi-disciplinary approach to the disease. The baseline evaluation should include an evaluation of the patient's readiness for ART, including an assessment of high-risk behaviours, substance abuse, social support, mental illness, comorbidities, economic factors (e.g., unstable housing), and other factors that are known to impair adherence to ART and increase the risk of HIV transmission. Once evaluated, these factors should be managed accordingly.

The baseline evaluation should also include a discussion of risk reduction and disclosure of sexual and/or needle-sharing partners, especially with untreated patients who are still at high risk of HIV transmission. Education about HIV risk behaviours and effective strategies to prevent HIV transmission should be provided at each patient visit.

In the case of previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete antiretroviral (ARV) history, preferably through the review of

past medical records. Any outstanding tests should be conducted, and management reviewed, as needed.[3]

4.2 When to start ART in TB/HIV co-infected patients

TB/HIV co-infected patients have an increased risk of dying before TB treatment is completed and fatality occurs mainly in the first two months of TB treatment. There is a need to fast track these patients for both TB and HIV care and treatment alike. Delaying ART initiation increases the mortality due to HIV infection. Early initiation on ART treatment will reduce mortality and morbidity among HIV co-infected TB patients. Improved immune system functioning from ART helps to cure TB and decreases infectiousness and transmission of HIV.

All TB/HIV co-infected patients should be started on ART within 2-4 weeks of TB treatment initiation, irrespective of the CD4 cell count. Clinical assessment is the primary tool for evaluating patients both before TB treatment initiation and after ART treatment has been initiated. Laboratory investigations can help inform which regimen to choose but are not essential for ART initiation. Inability to perform laboratory investigations should not prevent patients from being initiated on ART.

Caution is needed for PLHIV with TB meningitis, since immediate ART in these patients is associated with more severe adverse events than initiating ART two months after the start of TB treatment.

Comprehensive patient preparation should be provided in view of the needed adherence to both TB and HIV treatments. Adherence counseling should be offered on an ongoing basis.

4.3 When to start ART in PLHIV with cryptococcal meningitis

Immediate ART initiation is contraindicated among PLHIV with cryptococcal meningitis because of the risk of life-threatening immune reconstitution inflammatory syndrome.

ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy and after four weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with flucytosine or fluconazole.

For people with signs and symptoms of meningitis, ART should be delayed pending results of lumbar puncture.

Guidelines from the Southern African HIV Clinicians' Society recommend starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis in people who test positive for serum cryptococcal antigen.

4.4 Timing of ART in other conditions

Table 2 below includes all conditions that require further investigation prior to initiating ART. Health care workers are encouraged to consult next level clinicians for further guidance when managing complicated cases.

[3] Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services.

Table 2: Medical Indications to Defer ART

Indication	Action
Tuberculosis	
TB symptoms (cough, night sweats, fever, recent weight loss)	Investigate for TB before initiating ART: • If TB is excluded, proceed with ART initiation and TB preventive therapy (after excluding contra-indications to TPT). • If TB is diagnosed, initiate TB treatment and defer ART. The timing of ART initiation will be determined by the site of TB infection and the client's CD4 cell count.
Diagnosis of drug-sensitive (DS) TB at a non-neurological site (e.g. pulmonary TB, abdominal TB, or TB lymphadenitis)	**When to start ART in TB/HIV co-infected patients:** All TB/HIV co-infected patients should be started on ART within 2-4 weeks of TB treatment initiation, irrespective of the CD4 cell count.
Diagnosis of drug-resistant (DR) TB at a non-neurological site (e.g. pulmonary TB, abdominal TB, or TB lymphadenitis)	Defer ART until 2-4 weeks after start of TB treatment.
Diagnosis of DS-TB or DR-TB at a neurological site (e.g. TB meningitis or tuberculoma)	Defer ART until 4-8 weeks after start of TB treatment.
Cryptococcal Disease/ Meningitis	
Signs and symptoms of meningitis e.g. neck stiffness, photophobia (intolerance of bright light), headache, confusion	• Investigate for meningitis before starting ART – complete history and examination by doctor/senior clinician. • Conduct serum CrAg and lumbar puncture for CSF MCS and biochemistry unless contraindicated.
CrAg positive in the absence of symptoms or signs of meningitis	Defer ART until the first 2 weeks of fluconazole prophylaxis have been completed.
Confirmed cryptococcal meningitis	Defer ART until 4-6 weeks of antifungal treatment has been completed
Other conditions	
Other acute illnesses e.g. *Pneumocystis s Jirovecii* pneumonia (PJP) or bacterial pneumonia	ART enrolment within 2 weeks of starting parallel PJP treatment is strongly recommended, or as soon as patient is clinically stable on PJP treatment and potential for any drug-drug interactions has been reduced.
Clinical symptoms or signs of liver disease	• Confirm liver injury using ALT and total bilirubin levels. ALT elevations > 120 IU/L with symptoms of hepatitis, and/or total serum bilirubin concentrations > 40 µmol/L are significant. • Investigate and manage possible causes including hepatitis B, drug induced liver injury (DILI), or alcohol abuse. • Initiate on liver friendly ART and TB medications as appropriate. Refer to ART guidelines and monitor liver function closely.
Note: Clients who are already on ART should NOT have their treatment interrupted upon diagnosis of the above conditions.	

4.5 Intensity of Follow-up and Adherence Measures for People Living with AHD

People with AHD require closer follow-up during the initial period of receiving ART to monitor the response to ART and to identify signs and symptoms of possible immune reconstitution inflammatory syndrome.[4] Facilities should use a differentiated service delivery approach—PLHIV who are stable on treatment would have a reduced frequency of clinical visits and medication prescribing (3-6 months), allowing health service resources to focus on care for patients who are ill and need intensive clinical follow-up[5].

Clients with the following danger signs and symptoms should be prioritized for in-patient care for further investigations, management, and close monitoring:

- Respiratory rate > 30 breaths/minute
- Temperature > 39°C
- Heart rate > 120 beats/minute
- Altered mental status: confusion, strange behavior, reduced level of consciousness (e.g., any component of GCS is abnormal; GCS ≤ 14/abnormal)
- Any other neurological problem: seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision
- Airway issues: new or worsening adenitis, with obstructive symptoms
- Unable to walk unaided

4.5.1 Referrals

Table 3 below shows recommendations regarding appropriate level of care for conditions/signs and symptoms AHD clients may present with. Standard guidance on referral procedures should be followed:

- Inform client/caregiver and obtain consent
- Communicate with referral facility and set up appointments etc. as appropriate
- Ensure complete documentation on referral forms/transfer letters and maintain appropriate records in facility e.g. documentation of referrals in registers etc.
- Feedback and confirmation of linkage to referral site – document confirmation that client reached referral site
- Share feedback with referral sites as appropriate e.g. through use of community workers responsible for linkage and tracking, telephonic communication, etc.

[4] Ford N, Meintjes G, Calmy A, et al. Managing advanced HIV disease in a public health approach. Clin Infect Dis. 2018; 66:106–110

[5] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.

Table 3: Recommendations regarding appropriate level of care

Condition	Level of care	Recommended care
Danger signs (as mentioned in Section 4.5)	Hospital	Should be admitted/referred with review by medical doctor or nurse clinician for further investigation and management and close monitoring
Cryptococcal Meningitis	• Hospital for induction phase • May be managed at health facility/home based care once stable in the consolidation/maintenance phases *Note:* Refer to hospital if condition deteriorates or signs of raised intracranial pressure appear (such as headache, nausea, vomiting, increased blood pressure, decreased mental abilities, confusion about time and then location and people as the pressure worsens, double vision, pupils that don't respond to changes in light, seizures, loss of consciousness, coma, and cranial nerve palsies such as eye movement problems, particularly cranial nerve VI)	Follow guidelines on monitoring of clients whilst on Amphotericin-B /Flucytosine
Tuberculosis	Community based care with reviews at health facility unless: • Danger signs • Co-morbidity requiring admission • Severe forms of TB requiring close monitoring e.g. TB meningitis with danger signs	

In case referrals are not feasible:

- Where referrals are not feasible because of cost or distance constraints, advice should be sought from an experienced clinician and, where indicated, presumptive treatment started at the peripheral site.
- Referral and assessment should not result in unwarranted delays in starting ART and prophylaxis.
- Health care workers should carefully assess the feasibility of more frequent visits and the client's ability to travel to the health facility.
- Consider all the conditions the client is being managed for and required follow up dates to align visits e.g. integrating TB review, ART refill etc. into a single appointment to maximize on services provided per visit.

4.5.2 Clinic Follow up schedule

Individualized assessment should be done to determine intervals between clinical assessment visits for AHD clients e.g. consider TB or chronic illness reviews and management. As indicated above, AHD clients require more intensive follow-up and monitoring so that new issues, such as IRIS events, can be promptly diagnosed and managed. The Lesotho AHD package of care recommends the following facility visit schedule for clients (see *Table 4*), and includes an additional 8 week visit during which standard

assessment including staging, OI screening, adherence assessment, clinical exam (including weight) etc. should be done.

Table 4: Facility visit schedule

ARV Regimen	Assessment / Investigations	Baseline or day of ART initiation	Week 2	Month 1	Month 2	Month 3	Month 6	Month 12	Every 12 months
All Regimens	Rule out active TB using TB screening tool	X	X	X	X	X	X	X	At every visit
	Adherence assessment		X	X	X	X	X	X	Children and Adolescents: 3 monthly Adults: 6-12 monthly
	Clinical exam (including weight)	X	X	X	X	X	X	X	
	Assessment for possible ARV side effects		X	X	X	X	X	X	
	Treatment Supporter	X	X					X	If adherence concerns

Additional interventions such as weekly clinical review phone calls for the first 4 weeks after enrollment into care can be considered.

4.5.2.1 *Missed appointments*

Adequate adherence counselling should be provided to clients and their treatment supporters prior to ART initiation to ensure clients understand the importance of adhering to clinic visit schedule. Facilities should ensure maximal use of existing resources to maximise ability to conduct and monitor adherence to clinic visits. This includes ensuring efficient patient flow, conducting integrated outreach and other differentiated delivery models, use of mobile health services (e.g. SMS reminders, integrated patient tracking standards) as well as ensuring clear complete documentation of all patient interaction as stipulated in the guidelines.

Flagging of clients with missed appointments should occur the day after the missed clinic visit and active tracking should be done through phone calls within 48 hours. Physical tracking should then follow if client does not return to facility within 5 days.

4.5.3 Differentiated service delivery for AHD clients

Patients who present with AHD may require a different level of care than those who present while still clinically well. In Lesotho, clinically stable clients are those who are (WHO stage 1 or 2) on ART for >6 months with good adherence, suppressed viral load (<1000 copies/ml) and CD4 ≥200 cell/mm^3. This category of patients should be given ARV refills to last 3-6 months to decongest health facilities so that more attention and resources can be focused on patients with AHD. Once patients improve and become stable, they should be encouraged to join a Community ART group to further decentralize care to the community level.

Clients should follow the recommended clinic visit schedule (community outreach if possible) and be assessed at 6 months i.e. viral load, CD4 and staging, to determine whether they are stable enough to qualify for differentiated ART refill models that suit their lifestyle.

4.5.4 Adherence measures

Intensified adherence support is recognized as benefiting people with AHD. Such support may be provided at the time of diagnosis and initiation of ART and during episodes of acute illness, both while hospitalized and during the immediate discharge period. Appropriate measures, contingent on the barriers to adherence identified for the PLHIV, can be taken[6].

Table 5: AHD specific adherence barriers and recommended measures

Barriers to adherence	Recommended measures
Increased pill burden due to OI treatment, prophylaxis etc.	• Use fixed dose combination pills
Physical challenges in attending clinic appointments	• Home-based follow-up • Integrated outreaches • Ensure clinic visits are aligned i.e. to minimise number of required visits
OIs affecting CNS, HIV encephalopathy leading to decreased understanding and remembering of adherence messages	• Treatment supporters including community health workers
Drug interactions and side effects	• Review possible drug interactions (as summarised in the consolidated ART guidelines) and ensure rational prescribing • Prevent and manage side effects including providing client education, monitoring, and providing symptomatic treatment as appropriate based on guidelines (refer to ART guidelines for management based on severity)

[6] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.

4.5.5 Post hospital-discharge care

Ensure clients are stable prior to discharge with defined treatment supporters and caregivers to whom post discharge care is explained. Where possible, link to community health workers to support care of the clients. Ensure next appointment dates are well documented and understood by clients and align these with monitoring requirements for all client conditions requiring post discharge review. Summary records of the client's care during admission should be documented including history, examination, laboratory investigations, final diagnosis, and in-hospital management.

Referral mechanisms and optimal communication (following discharge) back to the health center/lower level hospital must be implemented to ensure appropriate follow-up (such as continuation of fluconazole, TB treatment or the timing of the switch to second-line ART for those receiving an ART regimen that is failing). People discharged after hospitalization for AHD may also require more intensive follow-up as studies have shown high mortality in the first month of ART especially soon after ART initiation. For referrals, fill in the referral form to be sent back to the referring hospital for records. Refer to sections on post discharge care in this manual as well as standard treatment guidelines for further guidance.

4.6 Co-trimoxazole prophylaxis

Co-trimoxazole (CTX) prophylaxis is an inexpensive and cost-effective way to reduce morbidity and mortality among PLHIV. It protects against:

- Toxoplasmosis
- Pneumocystis Jirovecii pneumonia (PJP)
- Diarrhea caused by *Isospora belli* and *Cyclospora* species
- Certain bacterial infections, including bacterial pneumonia and urinary tract infections

4.6.1 Recommended groups

CTX prophylaxis is recommended for the following groups:

- Children (<5 years) under the following circumstances:
    - All HIV-exposed children starting at 4-6 weeks of age
    - All HIV-positive children < 5 years regardless of CD4 or HIV clinical stage
- HIV-positive adults, adolescents, and children ≥5 years under the following circumstances (summarized in *Table 6* below):
    - All patients with WHO clinical stage 3 or 4, including those with TB co-infection
    - All patients with WHO clinical stage 1 or 2 where the CD4 count is ≤ 350 cells/mm^3
    - All patients with clinical stages 2, 3 or 4 where CD4 count is not available

Table 6: Indications for Co-Trimoxazole Prophylaxis in Adults, Adolescents, And Children ≥5 Years

WHO Clinical Stage	CD4 is Available	CD4 is Not Available
4	Daily CTX	Daily CTX
3	Daily CTX	Daily CTX
2	Daily CTX if CD4 < 350	Daily CTX
1	Daily CTX if CD4 < 350	Do not give CTX

4.6.2 Co-trimoxazole dosing

Table 7: Co-Trimoxazole Prophylaxis Dosing

Age	Suspension (200/40 mg/5ml)	Single Strength Tablet (400/80 mg)	Double Strength Tablet (800/160 mg)
< 6 months	2.5 ml	¼ tablet	--
6 months – 5 years	5 ml	½ tablet	--
6-14 years	--	1 tablet	½ tablet
>14 years	--	2 tablets	1 tablet

4.6.3 Alternative to Co-trimoxazole

- Co-trimoxazole should be avoided in the following situations:
    - History of a severe rash with prior use of co-trimoxazole (or another 'sulfa' drug)
    - Severe renal disease
    - Severe hepatic disease
- Patients who are unable to take co-trimoxazole should be offered dapsone 100 mg daily (children: 2 mg/kg daily)

4.6.4 Adverse effects of Co-trimoxazole

Adverse effects of Co-trimoxazole are rare but include skin rash, Stevens-Johnson syndrome, anemia, neutropenia, jaundice, and renal failure.

- Patients with mild adverse effects can continue with the drug in a monitored setting until cessation of effects
- Desensitization should never be attempted in a patient who has developed Stevens-Johnson syndrome, anaphylaxis, or in children
- The MSF HIV/TB Clinical Guide has a desensitization regimen in the appendix and is free on the internet

4.6.5 When to Discontinue Co-trimoxazole Prophylaxis

- CTX should be continued in children (<5 years) until:
    - HIV infection has definitively been excluded in the child *and*
    - The infant is no longer at risk of acquiring HIV through breast-feeding
- CTX prophylaxis can be discontinued in adults, adolescents, and children > 5 years who:
    - Are on ART and have one CD4 count ≥ 350 cells/mm^3
    - TB co-infected patients after the completion of tuberculosis treatment if CD4 is ≥ 350 cells/mm^3 and the patient is restaged as WHO Stage 1 or 2
    - Patients with previous PJP infection if the conditions above are met

5. Management of Major AHD Conditions

Lesotho Ministry of Health has published robust sets of guidelines for the management of several focal AHD conditions. These are captured by documents such as the *2019 Edition of the National Guidelines for Drug Susceptible Tuberculosis*, *the 2019 Addendum to the National Guidelines on the Use of Antiretroviral Therapy for HIV Prevention and Treatment,* as well as the *May 2016 National Guidelines for the Use of Antiretroviral Therapy for HIV Prevention and Treatment*.

Considering these robust set of guiding documents, this AHD manual is intended to summarize the key considerations around screening, diagnosing, preventing, and treating AHD-related opportunistic infections and other AHD-related conditions. It does not reflect the full subset of Lesotho guidelines and should be used as a complementary resource to existing guideline documents.

5.1 Tuberculosis (TB)

5.1.1 Clinical Presentation and Screening

5.1.1.1 *Pulmonary Tuberculosis (PTB)*

Over 90% of patients with PTB develop a cough soon after disease onset.

- The most common symptoms of PTB are:
  - cough (persistent cough for 2 weeks or more)
  - fever
  - night sweats, and
  - weight loss
- Another feature to look for includes sputum production which may be blood stained (hemoptysis)
- General non-specific symptoms include shortness of breath, chest pain, a general feeling of illness (malaise), tiredness, and loss of appetite

Diagnosis: All persons (regardless of HIV status) with clinical features suggestive of PTB must submit sputum for bacteriological diagnosis (GeneXpert, culture).

Note: The physical signs in patients with PTB are often non-specific and in co-infected individuals may be caused by other HIV related illnesses. Possible findings include fever, wasting, enlarged lymph-nodes, pleural effusion, tachycardia, and dyspnea.

5.1.1.2 *Extra-Pulmonary Tuberculosis (EPTB)*

The clinical characteristics to assist in diagnosis of EPTB are summarized in *Table 8* below, along with recommended investigations in *Table 9*.

Table 8: Suggested clinical characteristics to assist in the diagnosis of EPTB

Suspect EPTB in patients with:	• Unintentional weight loss with night sweats and temperature > 37.5 °C or feels feverish • Breathlessness (effusion/pericarditis) • Enlarged glands in neck/armpit • Chest X-ray ○ Large heart (especially if symmetrical and rounded)

	○ Pleural effusion ○ Enlarged lymph nodes inside the chest • Chronic headache or altered mental state
Look and listen for:	• Swollen lymph nodes in the neck or armpits: ***Possible TB adenitis*** ○ If present with other types of EPTB, it may provide the only way to confirm the diagnosis • Signs of fluid in the chest: ***Possible TB pleural effusion*** ○ Absent breath sounds ○ Reduced chest wall movement ○ Dull to percussion • Signs of fluid around the heart: ***Possible TB pericarditis*** ○ Heart sounds distant ○ Swollen legs and/or abdomen ○ Neck and hand veins distended with arm held above the shoulder • Signs of meningitis: ***Possible TB meningitis*** ○ Neck stiffness ○ Confusion ○ Abnormal eye movements

Table 9: Recommended investigations for EPTB

Anatomical site	**Recommended investigations**
TB adenitis (especially from cervical region)	• Fine needle aspiration (FNA) for GeneXpert and cytology • Sputum if coughing for GeneXpert • Lymph node biopsy for histology and GeneXpert
Miliary TB	• Sputum if coughing for GeneXpert • CXR • TB Blood culture • Perform additional diagnostic tests as appropriate for associated symptoms and signs e.g. Lumbar puncture for GeneXpert if TB meningitis is suspected
TB meningitis	• Lumbar puncture (LP) for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Sputum for GeneXpert • CXR
Pleural effusion	• CXR • Pleural tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Sputum for GeneXpert • Pleural biopsy for histology
Abdominal TB	• Abdominal ultrasound for ascites, lymph nodes, hepatosplenomegaly • Ascitic tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Sputum for GeneXpert • CXR

TB of spine/bones/joints (osteoarticular TB)	• Spinal X-ray, • Joint tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Synovial biopsy for histology and GeneXpert • Sputum for GeneXpert
Pericardial TB	• CXR • ECHO (chest ultrasound) for pericardial thickening and effusion • Pericardial tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Sputum for GeneXpert
Neonatal TB	• Chest x-ray, • Lumbar puncture for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Gastric aspirates for GeneXpert • Histopathology examination of the placenta for AFB and granulomata. • Neonatal abdominal ultrasound for portal lymphadenopathy and primary liver focus • Evaluation of mother for tuberculosis.
Drug resistant TB – any anatomical site	• Culture and DST of relevant specimens
Renal TB	• Early morning urine for GeneXpert, culture and DST • Ultrasound • Urinalysis

5.1.2 TB Diagnosis

Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests for TB. LAM antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells and appears to be present only in people with active TB disease. Urine-based testing has advantages over sputum-based testing because urine is easy to collect and store and lacks the infection control risks associated with sputum collection. LF-LAM has sensitivity of 50 – 70% depending on CD4 count. LF-LAM will be used in the diagnosis of both pulmonary and EPTB in HIV positive adults and children with presumptive TB who:

- have a CD4 cell count < 100 cells/mm^3, or
- are seriously ill regardless of CD4 cell count (seriously ill is defined based on 4 danger signs; respiratory rate >30/min, temperature >39°C, heart rate >120/min, and unable to walk unaided), or
- have an unknown CD4 count

For pediatric patients, it is important to remember that diagnosis of TB in children can be challenging. Healthcare workers should screen for TB using the national algorithm for diagnosis in children. Further, a negative TB LAM, GeneXpert, or sputum microscopy does not rule out TB in children.

5.1.3 TB Preventive Therapy (TPT)

TPT prevents the progression of TB infection to active TB disease.

Given the high prevalence of HIV and TB in Lesotho, clinicians should always remember to provide information about TB, including TPT, to all HIV-infected patients who present for health services. Clinicians should also counsel patients about the benefits of taking TPT, side-effects associated with TPT, need for adherence to TPT, and should provide TPT to all persons who are eligible. Clinicians should also be aware of common drug-drug interactions between TPT regimens and different ARV classes. TPT is integrated within the HIV services provided by the HIV/ART clinics, MCH/ANC clinics, and pediatric clinics.

5.1.3.1 *Indications for TPT*

Eligible HIV-infected patients should be initiated on TPT irrespective of the CD4 count, WHO clinical stage, or ART status. Those who are already on ART and in whom active TB has been excluded should be initiated on TPT. There is an additional protective benefit of concomitant use of TPT and ART. Patients who are receiving TPT and who are eligible for ART should continue TPT while initiating ART. TPT should not delay ART initiation among eligible PLHIV. *Table 10* below summarizes the indications for TPT in Lesotho.

Table 10: Indications for TPT

Indications for TPT
PLHIV • All PLHIV ≥12 months in whom active TB diseases has been excluded as part of comprehensive HIV care • All HIV-positive infants < 12 months who have been exposed to TB through household contact, in whom active TB has been excluded • All PLHIV treated for TB immediately after completion of TB treatment or soon after **HIV-Negative** • All HIV-negative children <15 years, including infants <12 months, who have been exposed to TB through household contacts in whom active TB has been excluded • All patients with silicosis in whom active TB disease has been excluded • All health care workers in whom active TB disease has been excluded
Initiate TPT after: • Active TB has been excluded • Contraindications to TPT (i.e. active TB disease, active hepatitis, alcoholism, severe peripheral neuropathy, epilepsy, or kidney failure) have been excluded • Patients have been counselled on the benefits of TPT, the importance of adherence to TPT, importance of completion of TPT and on the need to return should possible side-effects or signs/symptoms of TB develop

5.1.3.2 *Screening*

During post-test counselling following diagnosis of HIV, patients should be screened for symptoms of active TB and be informed about the benefits of TPT. At every clinical encounter, PLHIV should be screened for signs and symptoms of TB using the Lesotho TB Screening Tool. Those who do not report any symptoms

of TB are highly unlikely to have active TB and should be offered TPT if they have no contraindications to TPT. Those with one or more signs or symptoms of active TB are considered to be Presumptive TB patients and must undergo further investigations for active TB disease. Presumptive TB patients are not eligible for TPT until active TB has been excluded. Once TB has been excluded, TPT should be initiated and the patient should be followed up closely.

5.1.3.3 *Contraindications to TPT*

HIV-infected patients with signs and/or symptoms of TB, or with signs and/or symptoms of active liver disease should not be offered TPT.

Patients should not be offered TPT if they report:

- Acute or chronic liver disease; signs and symptoms suggestive of active hepatitis are nausea, vomiting, right upper quadrant pain, jaundice, dark urine
- Regular and heavy alcohol consumption (e.g. self- reported alcohol intake of units per week: >28 (men), >21 (women))
- Symptoms of severe peripheral neuropathy
- History of epilepsy or convulsions
- Kidney failure
- Known hypersensitivity to any TPT drug
- Presumed infection with an Isoniazid (or Rifampin) resistant strain of TB.

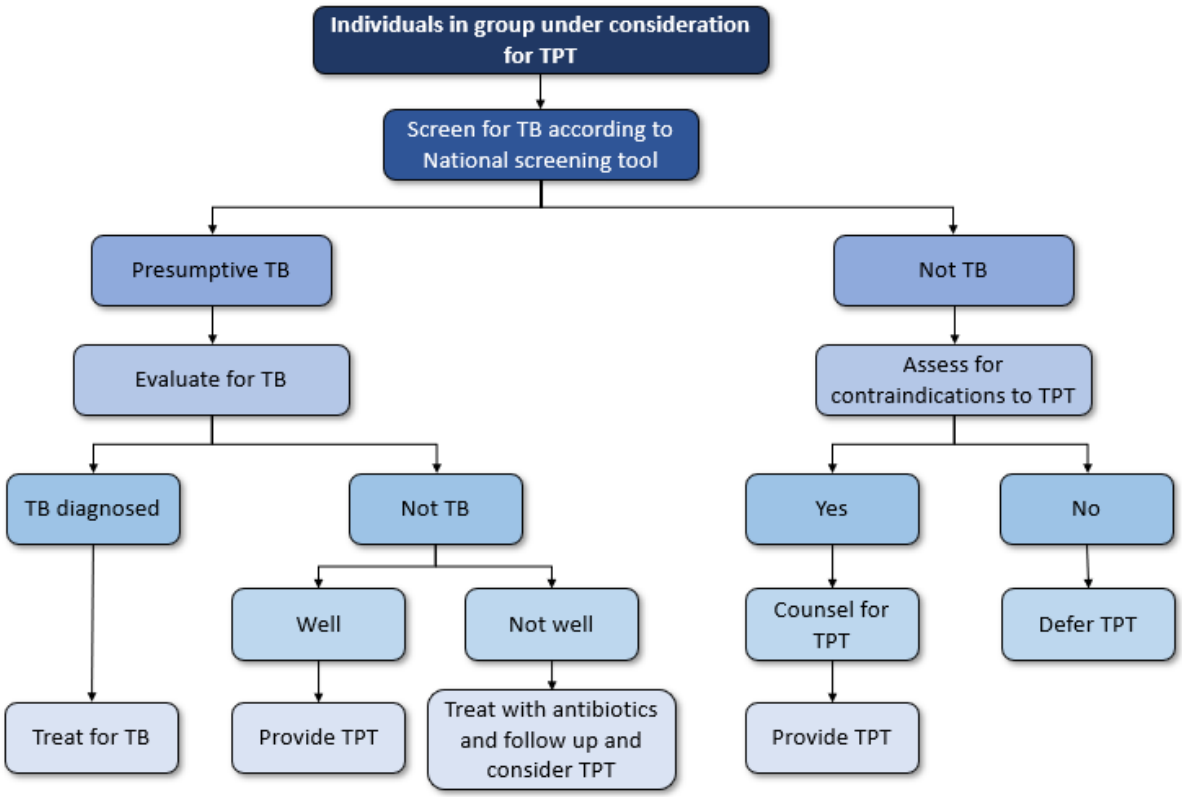
The absence of baseline liver function tests should not preclude the initiation of TPT. However, all HIV-infected patients should have a baseline lab assessment, the most recent ALT result should be reviewed if available.

Table 11: Interpretation of ALT levels in the context of initiating TPT

Baseline Liver Function Tests	Course of action
Normal up to 2x the upper limit of normal (ULN) in the absence of symptoms of hepatitis	Initiate TPT, no further testing required
2-5x the ULN in the absence of symptoms of hepatitis	Initiate TPT; Check ALT monthly
Greater than 5x the ULN and/or symptoms of hepatitis	Do not initiate TPT

5.1.3.4 *Algorithm for Tuberculosis Preventive Therapy (TPT)*

Figure 2: Algorithm for TPT



5.1.3.5 *Regimens*

Lesotho is transitioning to combination prevention using Rifapentine and Isoniazid (HP). However, use of Isoniazid alone (IPT) will continue as indicated below until a formal transition to HP is made.

5.1.3.5.1 Isoniazid Preventive Therapy (IPT)

For patients still on IPT, Pyridoxine should be given concomitantly with isoniazid to prevent the occurrence of peripheral neuropathy. However, patients should not be denied IPT due to non-availability of pyridoxine. IPT should be given once daily for 6 months. Strict adherence to IPT is essential. If a patient has an interruption in IPT for no more than three months, he/she can be restarted if still asymptomatic. Thus, in case of interruption of less than 3 months, the treatment can be completed over 9 months.

5.1.3.5.2 Rifampicin and Isoniazid (RH)

RH is also a short-course TPT regimen that combines INH and RIF, two antibiotics active against TB. Rifampicin and isoniazid combination are taken once daily, for 12 weeks (90 doses in 3 months). The WHO LTBI guidance document released in early 2018 describes the 3RH regimen as an alternative option to 6H, for treatment of Latent TB Infection (LTBI) in children and adolescents <15 years of age, in countries with high TB incidence. However, the shorter 3RH regimen for children offers benefits for patients and health systems. Several studies have demonstrated that 3RH is better tolerated, with fewer side effects and better adherence than 6 months of isoniazid alone.

5.1.3.5.2.1 Drug-drug interactions of RH in patients on ART

- No dose adjustments are required for efavirenz containing regimens.
- For individuals taking lopinavir/ritonavir, dolutegravir or nevirapine, dose adjustment of the antiretroviral drug is necessary as rifampicin is a cytochrome system enzyme inducer.

5.1.3.5.3 Weekly rifapentine and isoniazid (3HP) for 3 months (12 doses)

Studies have shown that there is no significant difference in the incidence of TB between those on 3-month weekly regimen of rifapentine plus isoniazid and 6 months of isoniazid monotherapy. However, risk of hepatotoxicity is significantly lower in HP compared to IPT. Weekly HP regimen can be safely given with DTG although caution must always be taken. The regimen is also associated with higher completion rates

5.1.3.5.3.1 Drug-drug interactions of HP in patients on ART

- Use cautiously in patients on DTG containing regimens. Double the dose of DTG by increasing frequency from once a day to twice a day.
- Maintain EFV dose at 400mg daily.
- Do not use rifapentine in PLHIV on protease inhibitors or nevirapine.

5.1.3.6 *TPT in pregnant and breastfeeding women*

- Although HP regimen is associated with higher risk of adverse pregnancy outcomes, isoniazid (INH) is safe in pregnancy and during breastfeeding.
- TPT should be offered to all eligible HIV-infected pregnant and breastfeeding women after TB screening and exclusion of active TB.
- TPT can be started at any time during pregnancy.
- In the event that a woman on IPT becomes pregnant, TPT should be continued.
- Following delivery, TPT should be continued during breastfeeding to complete the six-month course of therapy.

5.1.3.7 *Monitoring patients on TPT*

Patients on TPT should be monitored through monthly clinical assessments that include:

- Screening for symptoms and signs of active TB (i.e. cough of any duration, fever, night sweats or weight loss).
- Screening for possible side-effects of isoniazid or rifapentine (e.g. rash, peripheral neuropathy, convulsions, or any signs/symptoms of hepatitis including nausea and vomiting, jaundice, right upper quadrant pain and dark urine).
- Adherence to TPT.

If a patient on TPT develops symptoms of active TB or possible side-effects due to isoniazid or rifapentine:

- Discontinue TPT immediately.
- Investigate for active TB disease:
    - Send sputum specimen (morning) for GeneXpert Ultra.
    - Refer if needed, to ensure that investigations are completed.

- If active TB is confirmed, a full TB treatment regimen should be started.
- Perform other laboratory investigations as clinically indicated (e.g. LFTs for those with symptoms of hepatotoxicity).

Note:

- Routine laboratory monitoring of liver function tests (e.g. ALT) is not required during TPT.
    - However, if a patient is known to have an elevated ALT at baseline (2-5x ULN), then monthly monitoring of the ALT is indicated.
    - An ALT should also be ordered if symptomatic hepatitis develops while on TPT.
    - If the ALT is greater than 5x the ULN, then TPT should not be restarted and the patient should be referred for further investigations.
- All other laboratory tests should be ordered as clinically indicated.
- TPT provides protective benefit to patients who have successfully completed TB treatment.
- All HIV-infected patients should take TPT for three months immediately after completion of TB treatment, based on regimen.

5.1.4 Management of Active TB

For detailed information on the management of PLHIV with active TB, refer to the latest National TB management guidelines.

5.1.4.1 *Treatment of New Tuberculosis Cases*

Lesotho has adopted the use of RHE in the continuation phase in line with the WHO recommendation for settings with high INH mono-resistance. All new TB cases will be treated according to the treatment regimen for a New TB Case which involves administration of HRZE in the first 2 months of the initial phase and RHE in the 4 months of continuation phase. The recommended treatment regimen for new cases is represented as 2HRZE/4HR. Patients should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy. *Table 12* below shows the recommended Lesotho regimen and doses that all treating clinicians are to adhere to.

Table 12: Recommended treatment regimen and dosages for new adult TB cases

Phase of treatment	**Drugs**	**Weight in kg**			
		30-39	**40-54**	**55-70**	**>70**
Intensive phase of 2 months	**(RHZE)*** (150mg/75mg/400mg/275mg)	2 tabs daily	3 tabs daily	4 tabs daily	5 tabs daily
Continuation phase of 4 months	**(RHE)** (150mg/75mg/275mg)	2 tabs daily	3 tabs daily	4 tabs daily	5 tabs daily

***Fixed-dose combination (FDC) drug

5.1.4.2 *Previously treated patients*

Previously treated TB patients require further investigations to determine optimal course of therapy. Previous TB treatment is a strong determinant of drug resistance, and this should be investigated since drug resistance hinders the effectiveness of first-line TB medications and amplifies resistance.

- All previously treated TB patients should provide specimen for culture and drug susceptibility testing (DST) at or before start of treatment.
- Rapid molecular testing (GeneXpert, LPA) should also be performed in all previously treated cases.
    - If rapid testing reveals rifampicin resistance, the patient should receive empiric DR treatment while awaiting phenotypic DST results.
    - Those patients with results showing rifampicin sensitivity, should be treated with first line regimen.

Note: Retreatment regimen is no longer recommended for patients who require retreatment for TB.

5.1.4.3 *Treatment for pregnant women*

The benefit of treating active TB disease in a pregnant woman far outweighs the risks that the medications may pose to both the mother and the fetus. No changes to the regimen are necessary.

5.1.4.4 *Treatment for breastfeeding women*

A woman who is breastfeeding and has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. All first-line TB medications are compatible with breastfeeding and a woman can safely continue to breastfeed her baby during treatment. The child should continue to breastfeed normally but be given prophylactic isoniazid and rifampicin (RH) for 3 months. BCG vaccination of the newborn should be postponed until the end of RH prophylaxis.

5.1.4.5 *Treatment for women taking the oral contraceptive pill*

Rifampicin interacts with the contraceptive pill with a risk of decreased protective efficacy against pregnancy. A woman on oral contraceptives may choose between the following two options, after consultation with a physician, while receiving treatment with rifampicin:

i. take an oral contraceptive pill containing a higher dose of estrogen (50 mcg) or
ii. switch to another form of contraception

5.1.4.6 *Treatment for patients with liver disorders*

Isoniazid, rifampicin, and pyrazinamide are all associated with hepatitis. Of the three medications, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice; pyrazinamide is the most hepatotoxic.

Patients with hepatitis virus carriage, a past history of acute hepatitis, and excessive alcohol consumption can receive the usual short-course chemotherapy regimen provided that there is no clinical evidence of chronic liver disease. However, hepatotoxic reactions to TB medications may be more common in these patients and should be anticipated.

Patients with liver disease should not receive pyrazinamide. Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total duration of 8 months. Alternative regimens are 9 RE or 9 SHE in the initial phase followed by HE in the continuation phase, with a total treatment duration of 12 months. Therefore, recommended regimens are 2 SHRE/ 6HR or 9RE or 2 SHE/ 10HE.

In case of acute hepatitis, which may or may not be related to TB or TB treatment, the medical officer's clinical judgment is required. In some cases, TB treatment may be deferred until acute hepatitis has resolved. When the clinician decides to treat TB during acute hepatitis, the combination of SE for 3 months is the safest option. If the hepatitis has resolved, the patient can receive a continuation phase of 6 months of RH. If the hepatitis fails to resolve, SE should be continued for a total of 12 months.

Expert consultation is advised in treating patients with advanced or unstable liver disease in conjunction with clinical and laboratory monitoring.

5.1.4.7 *Treatment of patients with renal failure*

Isoniazid, rifampicin, and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. Patients with renal failure can take normal dosages. Ethambutol is excreted by the kidney. Because of increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. Where facilities can monitor renal function closely, it may be possible to give ethambutol in reduced doses or for it to be given intermittently. The safest regimen to administer to patients with renal failure is 2HRZE/ 4HRE.

All patients that fall under the category "special circumstances" should be referred to and managed by an experienced Medical Officer.

5.2 Cryptococcal Disease and Meningitis

5.2.1 Clinical Presentation

Cryptococcal meningitis (CM) is a major cause of mortality in PLHIV with AHD. Patients with CM may present with symptoms and signs related to inflamed meninges (including neck stiffness), raised intracranial pressure (including headache, confusion, altered level of consciousness and mental status, nausea, vomiting, sixth cranial nerve palsies with diplopia, photophobia, neck stiffness, altered mental status, visual impairment and papilledema) and encephalitis (including memory loss and new-onset psychiatric symptoms).

Note: The absence of symptoms of meningitis does not exclude CM: approximately one in three patients with asymptomatic cryptococcal antigenemia has concurrent CM.

5.2.1.1 *Screening*

WHO recommends rapid Cryptococcal antigen test (CrAg) testing on serum, plasma or whole blood on all adults and adolescents (>10 years) living with HIV who have a CD4 cell count <200 cells/mm^3 at any point during their management. This is especially critical before initiating ART, reinitiating ART (after ART interruption > 3 months) or switching to 2nd line ART treatment. When CD4 testing is not available, Serum CrAg should also be performed on all critically ill patients or WHO stage 3 and 4. Routine screening is not

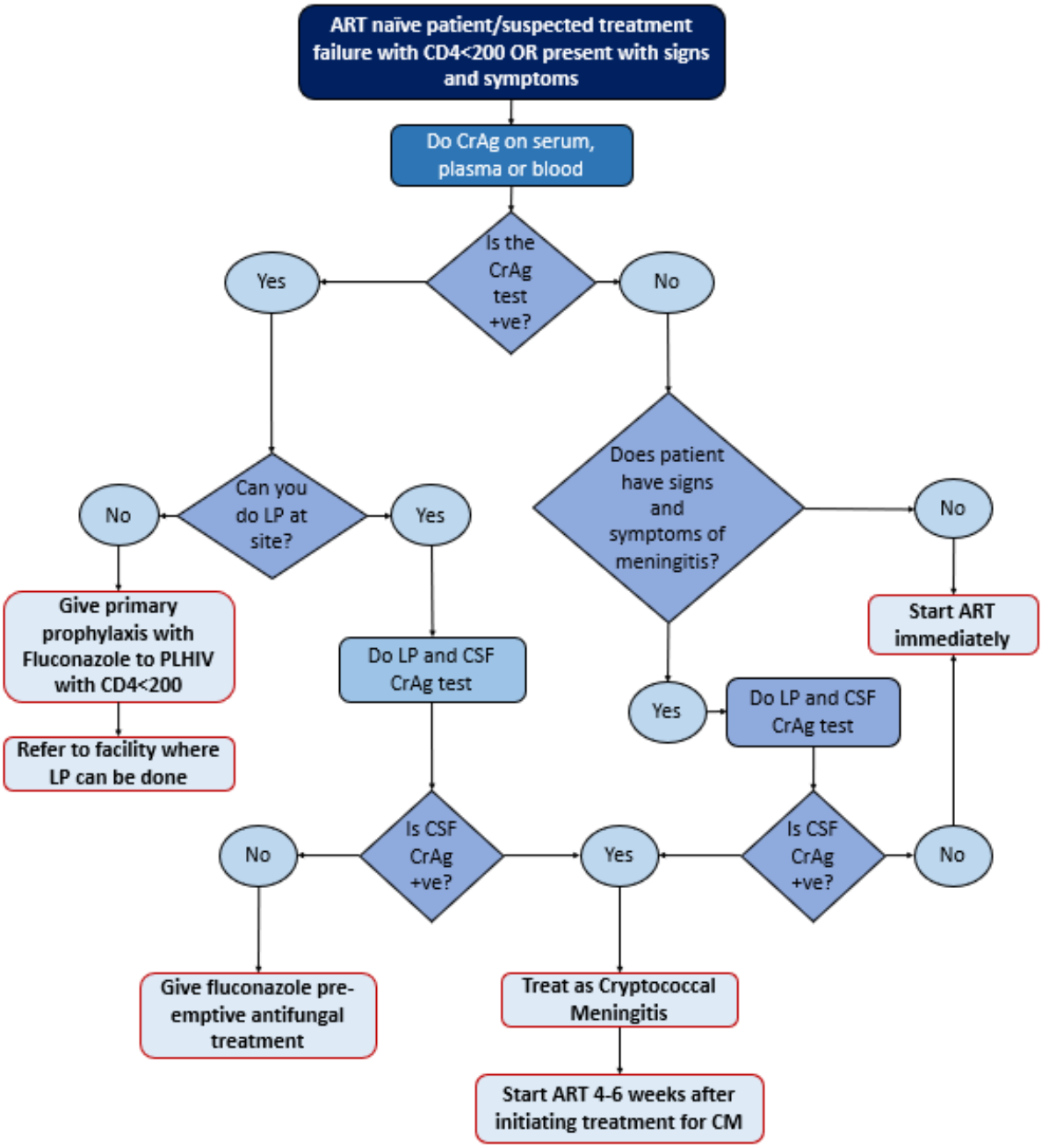
recommended in HIV infected children, adults or adolescents with a CD4 count <200 cells/mm^3 who are virally suppressed on ART.

5.2.1.2 *Diagnosis*

All HIV-seropositive adults and adolescents with clinically suspected meningitis or a positive blood CrAg test should be investigated for CM. Lumbar puncture (LP) with rapid cerebral spinal fluid (CSF) Cryptococcal antigen assay (CrAg) is the preferred diagnostic approach. However, where CrAg is not available, lumbar puncture with CSF India ink test examination is the alternative diagnostic approach. If LP is not available immediately or if focal neurological signs are present, serum/plasma/finger prick whole blood may be tested for CrAg to determine if the patient has disseminated cryptococcal disease.

If CSF is positive for either CrAg or India ink, immediately initiate antifungal treatment. Patients with a positive blood CrAg test and symptoms/signs of meningitis should be empirically started on antifungal treatment as per treatment outlined in Section 5.2.4. As part of evaluation, clinicians should remember the differential diagnosis for meningitis in PLHIV e.g. TB meningitis, CNS toxoplasmosis etc. especially where screening for cryptococcus is negative.

Figure 3: Management of CM



5.2.2 Prophylaxis

When CrAg screening is not available, primary prophylaxis with Fluconazole should be given to adults and adolescents living with HIV who have a CD4 cell count <200 cells/mm^3.

Table 13: Fluconazole Prophylaxis

Recommended regimen for prophylaxis
Fluconazole 200 mg daily for adults and 6 mg/kg/day for adolescents and children

Criteria to stop prophylaxis:

- When the client is stable and adherent to ART, has had antifungal prophylaxis for at least one year, has a CD4 cell count ≥ 100 cells/mm^3, and a fully suppressed viral load OR
- When the person is stable on and adherent to ART, has had antifungal prophylaxis for at least one year and has a CD4 cell count ≥ 200 cells/mm^3

5.2.3 Pre-Emptive Treatment

All individuals without any signs or symptoms of CM and who screen positive on rapid test on serum, plasma or whole blood CrAg but have a negative CSF CrAg, should be given fluconazole pre-emptive antifungal treatment.

Pre-emptive treatment is an alternative strategy to prophylaxis that aims to prevent progression to disease after infection has occurred. Fluconazole preemptive treatment involves giving the exact same consolidation and maintenance phases as treatment. The same discontinuation recommendations for treatment apply.

5.2.4 Drug treatment of CM in adults, adolescents, and children

Once definitive diagnosis of cryptococcal meningitis has been made based on positive CSF CrAg, India ink or culture, treatment should be initiated promptly. Presumptive/empiric treatment should be considered when access to these diagnostic tests is limited and clients present with typical signs and symptoms especially when accompanied by clinical signs indicating severe illness.

There are three phases in the treatment of Cryptococcal Meningitis: the induction phase, consolidation phase, and maintenance phase. The drugs for the different phases and duration of treatment are summarized in *Table 14*.

Table 14: Recommended treatment regimen and dosages for CM cases

Phase	Drug	Comments
Induction Phase (2 weeks)	**Recommended:** Amphotericin B deoxycholate (1mg/kg/day) + Flucytosine (100mg/kg/day in four divided doses) for 1 week, followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents (up to a maximum of 800mg daily))	**Note:** Liposomal amphotericin-B (L-AmB) is preferred over amphotericin-B deoxycholate, since L-AmB has demonstrated equivalent efficacy and better safety compared with the conventional form of AmB deoxycholate. When available, L-AmB should be dosed 3-5 mg/kg/day.
	Alternative*: Fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + Flucytosine (100 mg/kg/day, divided into four doses per day) **Or** Amphotericin B deoxycholate (1mg/kg/day) + high-dose Fluconazole (1200mg/day for adults, 12mg/kg/day for adolescents and children, up to a maximum of 800mg daily)	
Consolidation phase (8 weeks)	Fluconazole 800mg/day for adults (or 6-12mg/kg/day in children and adolescents)	Initiate ART **4–6 weeks** after starting CM treatment and there is clinical response to antifungal therapy
Maintenance Phase	Fluconazole 200mg/day for adults (or 6 mg/kg/day in children and adolescents)	**Criteria to stop maintenance therapy:** **If viral load monitoring is available:** Patient must be stable and adherent to ART and antifungal treatment for at least 1 year and have a CD4 ≥200 cells/mm^3 and a fully suppressed viral load **If viral load monitoring is not available:** Patient must be stable on ART and antifungal medicines for at least 1 year and have a CD4 ≥200 cells/mm^3
*Fluconazole monotherapy is no longer recommended.		

5.2.5 Management of patients with CM

Patients with CM are often extremely ill and need to be managed in a prompt manner in a health care facility. Once diagnosis has been confirmed as above or decision made to start pre-emptive treatment, the good clinical practice principles in *Table 15* should be applied.

Table 15: Good clinical practice principles for management of patients with CM

Pre-emptive hydration and electrolyte supplementation	
Adults and Adolescents	One liter of normal saline solution with 20 mEq of potassium chloride (KCl) over a minimum of two hours (preferably first thing in the morning) before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCl tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided 12 mmols/day (3 tablets). Magnesium glycerophosphate or chloride twice daily, or magnesium chloride 4 mEq twice daily.
AmB Treatment Monitoring (adults, adolescents, and children)	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly
Management (adults, adolescents, and children)	
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous infusion and/or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.
Elevated creatinine	If creatinine increases by ≥2 fold from the baseline value, increase pre-hydration to 1L every eight hours and consider temporarily omitting a dose of amphotericin B. Once creatinine improves, restart amphotericin B (AmB-Deoxycholate) at 0.7 mg/kg/day and consider alternate-day amphotericin B. If creatinine continues to rise, consider discontinuing amphotericin B and continuing with fluconazole at 1200 mg/day, especially if seven doses of amphotericin have been received. Consider fluconazole dose adjustment if significant renal impairment. Monitor creatinine daily.
Severe anaemia	Transfusion should be undertaken if possible, for severe amphotericin B–related anaemia (anaemia may also be a reason to discontinue amphotericin B prematurely in the second week of a planned two-week induction course of amphotericin B with fluconazole)
Additional notes: • Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia. • Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children. • Flucytosine – because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered to monitor for 5FC associated anemia, Neutropenia and Thrombocytopenia. • The incidence of renal dysfunction and electrolyte disturbance is much less with liposomal amphotericin preparations, but renal function and electrolytes still need to be monitored.	

In addition to the above, apply the following principles:

1) *Monitor response to treatment* through daily monitoring of resolution of symptoms and signs during induction phase.
2) *Manage persistent or recurrent symptoms:* Patients with CM can experience persistent or recurrent symptoms. In such cases, apply the following:
    a) Review history for possible treatment failure
    b) Perform LP with measurement of opening CSF pressure
    c) Consider paradoxical IRIS in patients who have initiated ART
    d) CSF culture where possible
3) *Manage relapse by applying the following:*
    a) Restart induction treatment accounting to treatment section above
    b) Manage raised intracranial pressure with LP
    c) Reinforce adherence
4) *Defer ART initiation for 4-6 weeks from initiation of antifungal treatment in ART naïve patients.* Also, defer ART switches due to treatment failure for 4-6 weeks.

5.3 Toxoplasmosis

5.3.1 Clinical Presentation, Screening, and Diagnosis

Major presenting symptoms of toxoplasmosis include:

- headache
- fever
- seizure
- focal neurologic signs (facial palsy, hemiparesis), and
- confusion

Toxoplasmosis can be diagnosed via clinical head CT scan for features of ring-enhancing lesions with edema.

5.3.2 Prophylaxis

Co-trimoxazole (summarized in Section 4.6 above) is the preferred recommended prophylaxis. Alternatively, dapsone can be used.

5.3.3 Treatment and Management

Confirmed toxoplasmosis can be treatment with 1920 mg BD (60mg/kg/day) of CTX for 6 weeks plus folic acid 5mg daily. Steroids can be considered to reduce edema.

5.4 Pneumocystis Jirovecii Pneumonia (PJP)

5.4.1 Clinical Presentation and Diagnosis

Diagnosis of PJP is mainly clinical, and patients commonly present with sub-acute onset and progression of shortness of breath, non-productive cough, and chest pain. Fever is not always present but can be high. PJP is common in HIV-infected children and may be the presenting condition. The peak age for PJP in children is six months, and any exposed infant with presumptive PJP disease needs an immediate DNA

PCR to confirm HIV infection status. Patients commonly have severe immunosuppression, CD4 <200 cells/mm^3, or CD4% <15% in infants and young children. Physical examination shows tachycardia, increased respiratory rate ± rales. Hypoxia is common, and cyanosis may be present. Auscultation may be normal in many cases and in the presence of hypoxia should raise the suspicion of PJP.

Chest X-ray findings: often bilateral symmetrical interstitial infiltrates ("ground-glass" appearance) but may be normal in up to 30% of cases.

Table 16: Management of PJP

Signs and symptoms	**Symptoms:** Progressive exertional dyspnea (95%), fever and chills (>80%), non-productive cough (95%), chest discomfort, difficulty breathing, fast breathing, and weight loss. **Signs:** Pulmonary symptoms: tachypnea, pulmonary examination may reveal mild crackles and rhonchi but may yield normal findings in up to half of the patients. Children may have cyanosis, nasal flaring, and intercostal retractions.
Diagnosis	Chest X-Ray is the main diagnostic tool • Diffuse interstitial infiltrates extending from the peri-hilar region. • Pneumatoceles and pneumothorax are possible but not common. • Pleural effusions and intrathoracic adenopathy are rare. ***However, the chest X-Ray may also be normal***
Management and treatment	**Preferred therapy:** 120mg/kg/day in 3 divided doses for 21 days (typical adult dose is 2 double-strength tablets thrice a day). **Alternative:** Dapsone 100mg once daily + Trimethoprim 5mg/kg/day TID for 21 days OR Primaquine 15-30mg once daily + clindamycin 600mg IV 6 hourly for 21 days. **Patients with severe disease (PaO2 < 70 mmHg at room air):** Corticosteroids (prednisolone 40mg twice daily for 5 days, then 40 mg once daily for 5 days, then 20 mg once daily for the remaining 11 days of antibiotic therapy). **Secondary prophylaxis with cotrimoxazole 960mg once daily** should be given until the patient is stable on ART with immune recovery - CD4 > 350 cells/mm^3 for six months.
Prophylaxis	Initiate all HIV-infected people on Cotrimoxazole preventive therapy.

5.4.2 Prophylaxis

Co-trimoxazole (summarized in Section 4.6 above) is the preferred recommended prophylaxis.

5.4.3 Treatment and Management

Table 17: Treatment and Management of PJP

Preferred regimen: High dose cotrimoxazole: 120mg/kg/day in 3 divided doses for 21 days (typical adult dose is 2 double –strength tablets three times a day). **Alternatives:** Dapsone 100mg once daily + Trimethoprim 5mg/kg/day TID for 21 days OR Primaquine 15-30mg once daily + clindamycin 600mg IV 6 hourly for 21 days.
Patients with severe disease (PaO2 < 70 mmHg at room air): Corticosteroids (prednisolone 40mg twice daily for 5 days, then 40 mg once daily for 5 days, then 20 mg once daily for the remaining 11 days of antibiotic therapy). **Secondary prophylaxis with cotrimoxazole 960mg once daily** should be given until the patient is stable on ART with immune recovery - CD4 > 350 cells/mm^3 for six months.

5.5 Severe Bacterial Infections

Although the original opportunistic pathogens described in AIDS were protozoal and fungal organisms, bacterial infections are now recognized with increased prevalence and altered expression in patients with HIV infection. Bacterial infections have been shown to cause substantially increased morbidity and mortality both early and late in the course of HIV infection. Just as strategies have been developed for primary and secondary prophylaxis of classical HIV-related opportunistic infections, prevention of bacterial complications should be a high priority. The signs of serious bacterial infection in HIV-positive patients are subtle. Diagnostic evaluation should include cultures of blood and other relevant clinical specimens. Empiric antimicrobial therapy based on the clinical presentation may be lifesaving in patients with invasive bacterial disease complicating HIV infection.

5.5.1 Enteric Bacterial Infections

5.5.1.1 *Epidemiology*

Rates of Gram-negative bacterial enteric infections are at least 10 times higher among HIV-infected adults than in the general population, but these rates decline when patients are treated with ART. The risk of bacterial diarrhea varies according to CD4 count and is greatest in individuals with clinical AIDS or CD4 <200 cells/mm^3.

The bacteria most frequently isolated by culture from HIV-infected adults are Salmonella, Shigella, and Campylobacter. Escherichia coli may contribute to the burden of diarrheal disease, but their role is poorly understood. Clostridium difficile-associated infection (CDI) is common in HIV-infected patients; recent data suggest that low CD4 count (<50 cells/mm^3) is an independent disease risk factor in addition to the traditional risk factors such as exposure to a health care facility or to antibiotics.

Incidence of community-onset CDI is increasing, and health care providers should also consider CDI in the evaluation of outpatient diarrheal illnesses in HIV-infected individuals. As with bacterial enteric infections in HIV-uninfected persons, the probable source for most enteric infections in HIV-infected patients is ingestion of contaminated food or water. HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase risk of enteric bacterial infections.

5.5.1.2 *Clinical Manifestations*

The three major clinical syndromes of infection with Gram-negative enteric bacteria among PLHIV are:

1. Self-limiting gastroenteritis
2. More severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss
3. Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal (GI) illness

Severe community-associated diarrhea is often defined as ≥6 loose stools per day with or without other signs of disease such as fecal blood, orthostatic hypotension, or fever. Loose stool is defined as defecated material that takes the shape of a container. In HIV-infected patients, the risk of more profound illness increases with the degree of immunosuppression. Relapses in infection with Salmonella and other Gram-negative bacterial enteric pathogens after appropriate treatment are common in PLHIV.

5.5.1.3 *Diagnosis*

Assessment of patients with diarrhea should include:

- a complete history,
- a medication review because diarrhea is a common side effect of some ART and antibiotics,
- quantification of the diarrheal illness by stool frequency, volume, duration, and presence of blood,
- associated signs and symptoms, such as presence and duration of fever

Physical examination should include measurement of temperature and assessment of volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood:

- Stool cultures are required to obtain antibiotic sensitivity testing for isolated enteric pathogens.
- Because incidence of bacteremia associated with Salmonella gastroenteritis is high in advanced HIV disease, blood cultures should be obtained from PLHIV with diarrhea and fever. For suspected shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.

Other infections for which PLHIV are at risk, albeit at a lower rate, are non-jejuni non-coli Campylobacter species, such as *Campylobacter fetus*, *Campylobacter upsaliensis*, and *Campylobacter lari*, and the enterohepatic Helicobacter spp. (*Helicobacter cineadi* and *Helicobacter fennelliae*), which were originally described as Campylobacter spp. Blood culture systems will typically grow these bacteria, but they are unlikely to be identified on routine stool cultures performed by most laboratories because growing these fastidious organisms requires special stool culture conditions.

A stool sample for C. difficile toxin or polymerase chain reaction (PCR) assay should be routinely performed for patients with diarrhea who have recently received or are currently receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy, those who have been hospitalized in the past 4 to 6 weeks (or are currently hospitalized), those who reside in a long-term care facility, those with CD4 counts <200 cells/mm^3, those taking acid-suppressive medications, and those with moderate-to-severe community acquired diarrhea.

Endoscopy, when available, should be reserved only for patients in whom stool culture, microscopy, C. difficile toxin assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails.

5.5.1.4 *Preventing Exposure*

The most common exposures are through ingestion of contaminated food or water and fecal-oral exposures. Providing advice and education about such exposures is the responsibility of the health care provider. A patient's clinical condition and CD4 count can help the provider determine what prevention recommendations are most appropriate. Patients with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness are at the greatest risk of enteric illnesses; however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Patients should be advised to regularly wash their hands with soap and water or alcohol-based cleansers to reduce the risk of enteric infection. With regard to preventing enteric infection, soap and water are preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are only partially active against norovirus and *Cryptosporidium*. PLHIV should be advised to wash their hands after potential contact with human feces (e.g., as through defecation, cleaning feces from infants, or contact with a person who has diarrhea), after handling pets or other animals, after gardening or other contact with soil, before preparing food and eating, and before and after sex. Antimicrobial prophylaxis to prevent bacterial enteric illness is not recommended.

5.5.1.5 *Empiric Treatment*

In most situations, treatment of diarrheal disease in PLHIV does not differ significantly from that in immunocompetent individuals. Decisions on therapy are based on an assessment of diarrhea severity and hydration status.

Patients should be informed of the importance of maintaining hydration and be given oral or intravenous (IV) rehydration, if indicated. Because diarrheal disease can produce temporary malabsorption or lactose intolerance, consuming a bland diet and avoiding fat, dairy, and complex carbohydrates also are likely to be useful. The effectiveness and safety of probiotics or antimotility agents have not been adequately studied in PLHIV with diarrheal illnesses. Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI.

After obtaining stool samples for diagnostic evaluation, initiation and duration of empiric antimicrobial therapy depends upon the patient's CD4 count and clinical appearance. If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice. No further work-up may be necessary and no treatment other than oral rehydration may be required, for example, in patients with CD4 counts >500 cells/mm^3 who have had 1 to 2 days of loose stools without fever or blood. However, a short course of antibiotics may be indicated in PLHIV with CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with AHD (i.e., CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness) and clinically severe diarrhea (i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease) should undergo diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment. The mainstay of care and treatment includes severity-adjusted oral/intravenous fluids and antibiotics as determined by dehydration status and stool exam/culture, respectively.

Empiric therapy with ciprofloxacin is reasonable. IV ceftriaxone is a reasonable alternative. Therapy should be adjusted subsequently based on the results of the diagnostic work-up. Diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity, such as bloody stool or dehydration, should be evaluated and directed therapy should be started once a diagnosis is confirmed.

5.5.1.6 *Pathogen Specific Therapy*

5.5.1.6.1 Salmonella spp

Immunocompetent hosts who are not HIV-infected often do not require treatment for Salmonella gastroenteritis, as the condition is usually self-limited, and treatment may prolong the carrier state. In

contrast, all PLHIV with salmonellosis should be treated, although no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of Salmonella bacteremia 20- to 100-fold and mortality as much as 7 times higher than that in HIV-negative patients.

Table 18: Treatment for Salmonella Infection

Treatment for Salmonella infection	Duration
• Fluoroquinolone: Ciprofloxacin is the preferred agent* • Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded-spectrum cephalosporins such as ceftriaxone	The optimal duration of therapy for HIV-related Salmonella infection has not been defined. • For patients with CD4 counts ≥200 cells/mm^3 who have mild gastroenteritis: ○ without bacteraemia: 7 to 14 days of treatment ○ with bacteraemia: 14 days, provided clearance of bacteraemia is documented [Longer treatment is suggested if bacteraemia persists or if the infection is complicated, that is, if metastatic foci are present] • For patients with AHD (CD4 <200 cells/mm^3): 2 to 6 weeks of antibiotics
*Other fluoroquinolones, such as levofloxacin would likely be effective in treating salmonellosis in PLHIV, but they have not been well evaluated in clinical studies	

5.5.1.6.2 Shigella spp

Therapy for Shigella infections is recommended both to shorten the duration of illness and to possibly prevent spread of the infection to others.

Table 19: Treatment for Shigella Infection

Treatment for Shigella infection	Duration
Fluoroquinolone: Ciprofloxacin is the preferred agent	• 7–10 days
Depending on antibiotic susceptibilities, alternative agents include: • TMP-SMX • Azithromycin	 • 7–10 days • 5 days

5.5.1.6.3 Campylobacter spp

The optimal treatment of Campylobacteriosis in PLHIV is poorly defined. Culture and testing for the antibiotic susceptibility of Campylobacter isolates is recommended. For mild-to-moderate Campylobacteriosis, initiating therapy with a fluoroquinolone such as ciprofloxacin for 7 to 10 days (if the organism is sensitive) or azithromycin for 5 days is a reasonable approach.

5.5.1.6.4 Clostridium difficile

Available data suggest that PLHIV respond to treatment of CDI similarly to HIV-uninfected patients. Vancomycin and Metronidazole are recommended.

5.5.2 Community Acquired Pneumonia (CAP)

5.5.2.1 *Epidemiology*

Bacterial respiratory diseases, including sinusitis, bronchitis, otitis, and pneumonia, are among the most common infectious complications in PLHIV, occurring with increased frequency at all CD4 counts. This section focuses on the diagnosis, prevention, and management of bacterial CAP in PLHIV.

Bacterial pneumonia is a common cause of HIV-associated morbidity. Recurrent pneumonia, considered two or more episodes within a 1-year period, is an AIDS-defining condition. The incidence of bacterial pneumonia in PLHIV has decreased progressively with the advent of combination ART but continues to be prevalent in CLHIV. Despite ART, bacterial pneumonia remains more common in individuals with HIV than in those who do not have HIV. Bacterial pneumonia may be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4. Bacterial pneumonia in individuals with HIV results from multiple risk factors, particularly immune defects. A CD4 count decrease, especially when below 100 cells/mm^3 continues to be a major risk factor for pneumonia due to routine bacterial pathogens. Other immune defects include quantitative and qualitative B-cell abnormalities that result in impaired pathogen specific antibody production, abnormalities in neutrophil function or numbers, and abnormalities in alveolar macrophage function. Lack of ART or intermittent use of ART increases the risk for pneumonia, likely due to uncontrolled HIV viremia. Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include tobacco, alcohol, and/or injection drug use, and chronic viral hepatitis. Chronic obstructive pulmonary disease (COPD), malignancy, renal insufficiency, and congestive heart failure are emerging as risk factors for pneumonia, particularly in the population of older adults with HIV. Risk for CAP can also increase with obesity, an emerging health problem in PLHIV.

5.5.2.2 *Microbiology*

In PLHIV, *Streptococcus pneumoniae* and *Haemophilus species* are the most frequently identified causes of community-acquired bacterial pneumonia, the same as in individuals without HIV. Staphylococcus aureus (S. aureus) and S. pneumoniae are among the most common etiologies of pneumonia in association with influenza infection. Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila species* have been reported as infrequent causes of CAP in PLHIV. The frequency of *P. aeruginosa* and *S. aureus* as community-acquired pathogens is higher in individuals with poorly controlled HIV than in those without HIV.

5.5.2.3 *Clinical Manifestations*

The clinical and radiographic presentation of bacterial pneumonia in individuals with HIV, particularly in those with higher CD4 count and HIV viral suppression, is similar to those in individuals without HIV.

Patients with pneumonia caused by bacteria such as *S. pneumoniae* or *Haemophilus spp* characteristically have acute onset (3–5 days) of symptoms, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum, and dyspnea. The presence of fever, tachycardia, and/or hypotension can be indicators of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia, and in such cases, clinicians should strongly consider hospitalizing the patient.

Patients with bacterial pneumonia typically have signs of focal consolidation and/or pleural effusion on lung examination. Individuals with bacterial pneumonia characteristically exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. The frequency of these typical radiographic findings, however, may depend on the underlying bacterial pathogen. Those with pneumonia due to *S. pneumoniae* or *Haemophilus spp* typically present with consolidation, whereas cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*. The white blood cell (WBC) count is usually elevated. The elevation may be relative to baseline WBC count in those with AHD. Neutrophilia may also be present. In PLHIV, the incidence of bacteremia accompanying pneumonia is greater than in individuals without HIV, especially when infection is due to *S. pneumoniae*.

5.5.2.4 *Diagnosis*

Patients with clinical symptoms and signs suggestive of pneumonia should have antero-posterior and lateral chest radiographs. Given the increased incidence of Mycobacterium tuberculosis (M. tuberculosis) in PLHIV, a TB diagnosis should always be considered in PLHIV who have pneumonia. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB and sputum samples should be collected and examined. A Gram stain of expectorated sputum and two blood cultures are recommended for patients with severe pneumonia, in those who are not on ART; or in those who are known to have a CD4 count <350/ml. Microbiologic diagnostic testing is indicated whenever epidemiologic, clinical, or radiologic clues prompt suspicion of specific pathogens that could alter standard empirical management decision. Blood cultures are more likely to be positive in PLHIV than in those without HIV. PLHIV, particularly those with lower CD4 counts, are at increased risk of invasive infection with *S. pneumoniae.*

Diagnostic thoracentesis should be performed in all patients with pleural effusion if concern exists for accompanying empyema, and pleural fluid should be sent for microbiologic studies. Therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion. Given the increased risk of invasive pneumococcal disease in patients with HIV, clinicians should be vigilant for evidence of extra-pulmonary complications of infection.

5.5.2.5 *Prevention*

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community. General precautions to maintain health, such as adhering to hand hygiene and cough etiquette and refraining from close contact with individuals who have respiratory infections, should be emphasized for patients with HIV as for other patient populations.

ART is associated with a decreased risk of bacterial pneumonia among HIV infected patients. Similarly, in many studies, daily administration of TMP-SMX for PJP prophylaxis reduced the frequency of bacterial respiratory infections.

5.5.2.6 *Treatment*

The basic principles of antibiotic treatment of pneumonia are the same for PLHIV as for those who do not have HIV. As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should preferably be collected before antibiotic therapy is initiated or within 12 hours to 18 hours of antibiotic initiation. However, antibiotic therapy should be administered promptly, without waiting for the results

of diagnostic testing. In PLHIV, providers must also consider the risk of opportunistic lung infections, such as PJP, that would alter empiric treatment.

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. In addition to considerations regarding ability to take oral medications, adherence, and other confounding factors (e.g., housing, comorbid diseases), severity of illness is a key factor that helps to guide decisions regarding treatment location.

5.5.2.6.1 Outpatient Treatment

Table 20: Summary of Outpatient Treatment

Outpatient Treatment	Notes

• **Oral beta-lactam plus an oral macrolide**
  ○ Preferred beta-lactams are amoxicillin or amoxicillin-clavulanate; alternatively, cefuroxime can be given
  ○ Preferred macrolides are azithromycin or clarithromycin
  OR
• **Oral respiratory fluoroquinolone**
  ○ Preferred: levofloxacin or moxifloxacin
	• An oral respiratory fluoroquinolone (levofloxacin or moxifloxacin) should be used as an alternative to a beta lactam in patients who are allergic to penicillin
	• If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative in addition to a beta-lactam

Note: Empirical monotherapy with a macrolide for outpatient pneumonia treatment is not routinely recommended in patients with HIV due to concerns of growing pneumococcal resistance.	

5.5.2.6.2 Inpatient Treatment

5.5.2.6.2.1 Non-Severe Pneumonia

Table 21: Summary of Inpatient Treatment with non-severe pneumonia

Inpatient Treatment (non-severe pneumonia)	Notes

• **Intravenous (IV) beta-lactam plus a macrolide**
  ○ Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam
  ○ Preferred macrolides are azithromycin or clarithromycin
  OR
• **Respiratory fluoroquinolone (IV)**
  ○ Preferred: levofloxacin or moxifloxacin
	• IV penicillin is an acceptable option for treatment of pneumococcal disease in PLHIV. In patients who are allergic to penicillin, an IV respiratory fluoroquinolone (levofloxacin or moxifloxacin [750 mg/day]) alone should be used.
	• If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative in addition to a beta-lactam

Note 1: Monotherapy with a macrolide is not recommended. **Note 2:** Fluoroquinolone monotherapy should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy.	

5.5.2.6.2.2 Severe Pneumonia

Table 22: Summary of Inpatient Treatment with severe pneumonia

Inpatient Treatment (severe pneumonia)
IV beta-lactam plus either IV azithromycin or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) (AI) • Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam
Note 1: When the aetiology of the pneumonia has been identified based on reliable microbiological methods, antimicrobial therapy should be modified and directed at the identified pathogen.

Most pathogens can be treated adequately with recommended empiric regimens. *P. aeruginosa* and S. aureus (including community-acquired MRSA) as causes of pneumonia are exceptions. Both pathogens occur in specific epidemiologic patterns with distinct clinical presentations for which empiric antibiotic coverage may be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empiric treatment if results are negative.

The duration of therapy for most patients is 5-7 days. The patient should be afebrile for 48–72 hours and should be clinically stable before discontinuation of treatment. A switch to oral therapy should be considered in patients with CAP on IV antibiotic therapy who have improved clinically, can swallow, and tolerate oral medications, and have intact gastrointestinal function.

Suggested criteria for clinical stability include oral temperature <37.8°C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure ≥90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood >60 mm Hg. A longer duration of IV and overall antibiotic therapy is often necessary in patients who have severe pneumonia or who have bacteremia, particularly if due to *S. pneumoniae* or *S. aureus* and complicated infection is present.

5.5.3 Bacterial Meningitis

5.5.3.1 *Introduction*

Meningitis is an acute bacterial infection of the meninges, which may affect the brain and lead to irreversible neurological damage and auditory impairment. Bacterial meningitis is a medical emergency and treatment is based on early parenteral administration of antibiotics that penetrate into the cerebrospinal fluid (CSF). Empiric antibiotic therapy is administered if the pathogen cannot be identified or while waiting for laboratory results. The main bacteria responsible vary depending on age and/or context.

5.5.3.2 *Causes by age and risk factor*

- Children ≤7 days: Gram-negative bacilli (*Klebsiella spp*, *E. coli*, *S. marcescens*, *Pseudomonas spp*, *Salmonella spp*) and group B streptococcus
- Children > 7 days—3 months: *S. pneumoniae* accounts for 50% of all bacterial meningitis; *L. monocytogenes* is occasionally responsible for meningitis during this period
- Children 3 months—5 years: *S. pneumoniae*, *H. influenza B* and *N. meningitides*
- Children > 5 years and adults: *S. pneumoniae* and *N. meningitides*
- Immunosuppressed patients (HIV, malnourished): high percentage of Gram- negative bacilli (specially *Salmonella spp*) and *M. tuberculosis*
- Meningitis may be related to *S. aureus* when associated with skin infection or skull fracture

5.5.3.3 *Clinical features*

The clinical presentation depends on the patient's age:

- **Children under 1 year**:
  - The classic signs of meningitis are usually absent.
  - The child is irritable, appears sick with fever or hypothermia, poor feeding, or vomiting.
  - Other features include seizures, apnoea, altered consciousness, bulging fontanelle (when not crying); occasionally, neck stiffness and purpuric rash
- **Children over 1 year and adults:**
  - Fever, severe headache, photophobia, neck stiffness
  - Brudzinski's sign (neck flexion in a supine patient results in involuntary flexion of the knees) and Kernig's sign (attempts to extend the knee from the flexed-thigh position are met with strong passive resistance)
  - Petechial or ecchymotic purpura (usually in meningococcal infections)
  - In severe forms: coma, seizures, focal signs, purpura fulminans

5.5.3.4 *Investigations*

Lumbar puncture (LP):

- Macroscopic examination of CSF: antibiotic therapy should be initiated immediately if the LP yields a turbid CSF.
- Microscopic examination: Gram stain (but a negative examination does not exclude the diagnosis) and white blood cell count (WBC).
- In an epidemic context, once the meningococcal etiology has been confirmed, there is no need for routine LP for new cases.

Table 23: Summary of investigations for bacterial meningitis

	Pressure	Aspect	WBC (leucocytes/mm^3)	Protein	Other tests
Normal CSF		Clear	< 5	Pandy– < 40 mg/dl	–
Bacterial meningitis	++++	Cloudy, turbid	100-20 000 mainly neutrophils In neonates: > 20 In immunocompromised, the WBC may be < 100	Pandy+ 100-500 mg/dl	Gram stain +
Viral meningitis	Normal to +	Clear	10-700 mainly lymphocytes	Pandy–	–
TB meningitis	+++	Clear or yellowish	< 500 mainly lymphocytes	Pandy+	AFB
Cryptococcal meningitis	++++	Clear	< 800 mainly lymphocytes	Pandy–	India ink

5.5.3.5 *Antibiotic Treatment*

Table 24: Summary of treatment for bacterial meningitis

	No associated skin infection		Associated skin infection (including umbilical cord infection)	
	First line	**Alternative**	**First line**	**Alternative**
0 to 7 days < 2 kg	**ampicillin** IV 100 mg/kg every 12 hours + **cefotaxime** IV 50 mg/kg every 12 hours	**ampicillin** IV 100 mg/kg every 12 hours + **gentamicin** IV 3 mg/kg once daily	**cloxacillin** IV 50 mg/kg every 12 hours + **cefotaxime** IV 50 mg/kg every 12 hours	**cloxacillin** IV 50 mg/kg every 12 hours + **gentamicin** IV 3 mg/kg once daily
0 to 7 days ≥ 2 kg	**ampicillin** IV 100 mg/kg every 8 hours + **cefotaxime** IV 50 mg/kg every 8 hours	**ampicillin** IV 100 mg/kg every 8 hours + **gentamicin** IV 5 mg/kg once daily	**cloxacillin** IV 50 mg/kg every 8 hours + **cefotaxime** IV 50 mg/kg every 8 hours	**cloxacillin** IV 50 mg/kg every 8 hours + **gentamicin** IV 5 mg/kg once daily
8 days to < 1 month ≥ 2 kg	**ampicillin** IV 100 mg/kg every 8 hours + **cefotaxime** IV 50 mg/kg every 8 hours	**ampicillin** IV 100 mg/kg every 8 hours + **gentamicin** IV 5 mg/kg once daily	**cloxacillin** IV 50 mg/kg every 6 hours + **cefotaxime** IV 50 mg/kg every 8 hours	**cloxacillin** IV 50 mg/kg every 6 hours + **gentamicin** IV 5 mg/kg once daily
1 to 3 months	**ampicillin** IV 100 mg/kg every 8 hours + **ceftriaxone** IV 100 mg/kg on D1 then starting on D2: 100 mg/kg once daily or 50 mg/kg every 12 hours	**ampicillin** IV 100 mg/kg every 8 hours + **gentamicin** IV 2.5 mg/kg every 8 hours	**cloxacillin** IV 50 mg/kg every 6 hours + **ceftriaxone** IV 100 mg/kg on D1 then starting on D2: 100 mg/kg once daily or 50 mg/kg every 12 hours	**cloxacillin** IV 50 mg/kg every 6 hours + **gentamicin** IV 2.5 mg/kg every 8 hours
> 3 months	**ceftriaxone** IV Children: 100 mg/kg on D1 then starting on D2: 100 mg/kg once daily or 50 mg/kg every 12 hours (max. 4 g daily)		**cloxacillin** IV Children < 40 kg: 50 mg/kg every 6 hours Children ≥ 40 kg: 2 g every 6 hours + **ceftriaxone** IV Children: 100 mg/kg on D1 then starting on D2: 100 mg/kg once daily or 50 mg/kg every 12 hours (max. 4 g daily)	
Adults	**ceftriaxone** IV: 4 g once daily or 2 g every 12 hours		cloxacillin IV: 2 g every 6 hours + ceftriaxone IV: 4 g once daily or 2 g every 12 hours	

5.5.3.5.1 Duration of antibiotic therapy

Duration depends on the pathogen:

- *Haemophilus influenzae*: 7 - 10 days
- *Streptococcus pneumonia*: 10-14 days
- *Group B streptococcus* and *Listeria spp*: 14-21 days
- Gram-negative bacilli: 21 days

If the pathogen is unknown:

- Children < 3 months: 2 weeks beyond the first sterile CSF culture or 21 days
- Children > 3 months and adults: 10 days
  Consider extending treatment or alternative diagnoses if fever persists beyond 10 days. On the other hand, a 7-day course of ceftriaxone is sufficient in patients who are making an uncomplicated recovery.

5.5.4 Sepsis

5.5.4.1 *Introduction*

Sepsis is widespread inflammation resulting from the immune system trying to fight an infection, usually bacterial. Disseminated intravascular coagulation during sepsis reduces blood flow to limbs and internal organs, depriving them of nutrients and oxygen and resulting in organ failure. It is difficult to predict the aetiology without laboratory support. In clinical practice, nearly all patients with this type of presentation are empirically put on IV ceftriaxone. Although enteric fever and non-typhoid salmonellosis can be common among AIDS patients, incidence of gram-negative sepsis is not different from HIV negative individuals.

5.5.4.2 *Clinical features*

A diagnosis of sepsis is made when a patient presents with high grade fever, tachycardia, tachypnea, and low blood pressure. Symptoms suggesting onset of sepsis include fever, headache, sweating, chills and/or rigors, dyspnea, nausea, and vomiting. Obviously, these symptoms are non-specific although cough, dysuria or neck stiffness can suggest underlying the pathology. Fever can be absent, and hypothermia can be seen in severe sepsis. A detailed history and examination are necessary.

5.5.4.3 *Investigations*

Consider the following before empirical treatment:

1. FBC
2. Blood culture
3. Chest X-ray

5.5.4.4 *Treatment*

The goals of treating a patient with sepsis and HIV infection are:

1. Treat the underlying infection by IV antibiotics

2. Preserve vital organ perfusion through adequate IV Fluids
3. Maintain tissue oxygenation

5.5.4.4.1 Supportive therapy

1. Maintain mean arterial pressure at 50-60mmHg using IV fluids
2. Monitor daily fluid input and output and calculate fluid balance
3. Give oxygen per required need
4. Correct anaemia by blood transfusion if hemoglobin is below 10mg
5. Monitor liver and kidney functions
6. Ensure adequate nutritional support
7. Prevent bedsores by frequently changing patient's position
8. Treat fever and pain as required
9. Do not give steroids

6. Other Considerations for the Management of AHD

Beyond the major conditions as summarized by the package of care above, there are a number of additional clinical considerations that are pertinent to the management of AHD. Related entities include but are not limited to immune reconstitution inflammatory syndrome (IRIS), HIV drug resistance, cervical cancer, cytomegalovirus infection, severe malnutrition, and depression. As guidance for managing these conditions is contained in a number of national guideline documents, this guideline only covers high-level considerations for the management of each condition. For further information, refer to the robust clinical guidance documents.

6.1 Immune Reconstitution Inflammatory Syndrome (IRIS)

6.1.1 Background

Following the initiation of ART, the immune system is reconstituting and begins to respond to antigens more vigorously, which may result in a paradoxical reaction with worsening symptoms and signs of an opportunistic infection despite appropriate treatment. This situation is referred to as immune reconstitution inflammatory syndrome (IRIS). IRIS most commonly occurs in TB/HIV co-infected patients after the initiation of TB and HIV treatment.

6.1.2 Screening and Identification

IRIS can present in two ways:

- **Paradoxical IRIS** – a patient is diagnosed with an opportunistic infection, most commonly TB, starts appropriating OI treatment followed by ART, and then develops worsening or new signs and symptoms of their opportunistic infection.
- **Unmasking IRIS** – a patient is screened for opportunistic infections before initiation of ART and no signs or symptoms of OI are found. The patient then starts ART, followed by onset of new symptoms and signs of an opportunistic infection (most commonly TB).

Occurrence: IRIS usually occurs within the first 2-12 weeks of initiating ART but can occur up to 6 months after ART initiation.

The key risk factors for IRIS include the following:

- Severe immune suppression (CD4 count <50 cells/mm^3)
- High viral load (>100,000 copies/mL)
- Early initiation of ART
- Marked rise of CD4 count and fall of viral load following ART initiation
- Presence of subclinical opportunistic infections

IRIS is a diagnosis of exclusion and particular attention should be paid to assess/exclude the following:

- TB treatment failure or drug resistant TB
- ART treatment failure, especially due to poor adherence
- Other opportunistic infections
- Side effects of TB treatment and/or ART
- Drug fever
- Other HIV-related diseases (lymphoma, Kaposi's sarcoma)

6.1.3 Management

The management of IRIS is to continue treatment for the opportunistic infection as well as HIV and provide supportive management with non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroids may be used in cases with severe signs. Admit all patients with danger signs. Neither the OI treatment nor ART should be stopped unless a patient has severe, life-threatening symptoms despite proper IRIS management. Clinicians should explain the possibility of IRIS to HIV patients when initiating them on ART, even if they do not have any signs or symptoms of opportunistic infection (i.e., if symptomatic already, developing brief worsening of symptoms before becoming better, or if asymptomatic, developing new symptoms). The presence of IRIS does not mean a patient is failing ART.

Danger signs include, but are not limited to:

- Respiratory distress (RR > 30)
- Fever (T >39°C)
- Tachycardia (HR > 120)
- New or worsening adenitis, with obstructive symptoms

6.2 Treatment Failure and Drug Resistance

HIV drug resistance (HIVDR) occurs when the virus starts to make changes (mutations) to its genetic make-up (RNA) that are resistant to certain HIV drugs, or classes of HIV drugs. HIV drug resistance poses a significant threat to the lives of PLHIV and threatens progress made in the HIV response. HIVDR results in more rapid virologic failure among people receiving ART and increases the need for second and third-line regimens, which may be associated with greater toxicity, adverse events, poorer adherence, and higher costs.

HIVDR may also negatively affect the ability to prevent HIV transmission using ARV-based pre- or post-exposure prophylaxis or topical microbicides. Surveillance data should inform the selection of first- and

second-line regimens for ART, as well as ARV drugs for prevention of mother-to-child transmission (PMTCT), to optimize treatment outcomes using a public health approach.

The WHO has identified three types of HIV drug resistance:

1) **Transmitted HIVDR (TDR)** – occurs when an uninfected, treatment-naïve person is infected with a drug-resistant strain of HIV from someone with HIVDR mutations.
2) **Acquired HIVDR (ADR)** – occurs when a treatment-experienced PLHIV develops drug mutations in the presence of ART as a result of sub-optimal treatment adherence, treatment interruptions, inadequate drug concentrations in the body, or the use of suboptimal drugs and combinations.
3) **Pre-treatment HIVDR (PDR)** – HIVDR that is detected at the time of first-line ART initiation or re-initiation, that could be due to transmitted drug resistance, or HIVDR acquired as a result of previous ARV exposure, such as mothers and children in PMTCT programs.

According to LePHIA (2017), the prevalence of transmitted drug resistance was 11.4%, with the most common mutations conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and this has informed the shift to adaptation of DTG as the preferred ART regimen base as opposed to EFV. In addition, the 2018/19 Adult HIV drug resistance survey revealed a pretreatment drug resistance of 17.6% for all ARV classes and 17% for NNRTIs, with acquired drug resistance prevalence of 3.23% and 6.9% amongst people on ART for 12 and 48+ months, respectively.

HIVDR is one of the well-recognized causes of treatment failure due to:

- Poor adherence
- Treatment interruption
- Problems of medicine administration and availability
- Pharmacokinetic reasons (medicine-medicine interactions, food-ARVs interaction)
- Tolerability (taste, vomiting, food interaction)
- Resistance

Up to 25% of people presenting with AHD have temporarily interrupted ART. At presentation, they may have developed clinical symptoms[7][8][9] typical of an underlying opportunistic infection which may include any combination of tuberculosis, severe bacterial infections, cryptococcal meningitis, and PJP. Once a patient re-engages with care, a set of steps must be taken by the clinician to ensure they identify the underlying cause and address it accordingly. A comprehensive clinical assessment of the patient must be done.

[7] Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. Trop Med Int health.2011; 16: 1297-1313

[8] McMahon JH, Spelman T, Ford N, Greg J, Mesic A, Ssonko C et al. Risk factors for unstructured treatment interruptions and association with survival in low to middle income countries. AIDS Res Ther. 2016; 13:25

[9] Meintjes G, Kerkhoff AD, Burton R, Schutz C, Boulle A, Van Wyk G et al. HIV-related medical admissions to a South African district hospital remain frequent despite effective antiretroviral therapy scale-up Medicine (Baltimore). 2015; 94:e2269

6.2.1 Recognition of Treatment Failure

- Virological deterioration
    - Unsuppressed HIV viral load
        - Two consecutive viral load tests ≥1000 RNA copies/ml after six months on effective therapy and 2-3 months of enhanced adherence support
    - Virological conditions indicating a need to change to 2nd or 3rd line therapy include:
        - Virological failure (viral load criteria): persistent viral load ≥ 1000 RNA copies/ml after at least 6 months on ART, OR
        - Log drop <0.7 for children less than 2yrs or < 0.5 for more than 2yrs based on two consecutive viral load measurements 3 months apart for an individual who has been on ARVs for at least 6 months, with adherence support

    Note: Even though it is not recommended to change to a second or third-line ART regimen for low level viremia (viral loads between 100 – 1000 copies/ml), patients with low level viremia should be thoroughly evaluated in a similar fashion to patients with viral loads ≥ 1000 copies/ml. This is because persistent low-level viremia may be an independent predictor of virologic failure and needs further investigation.

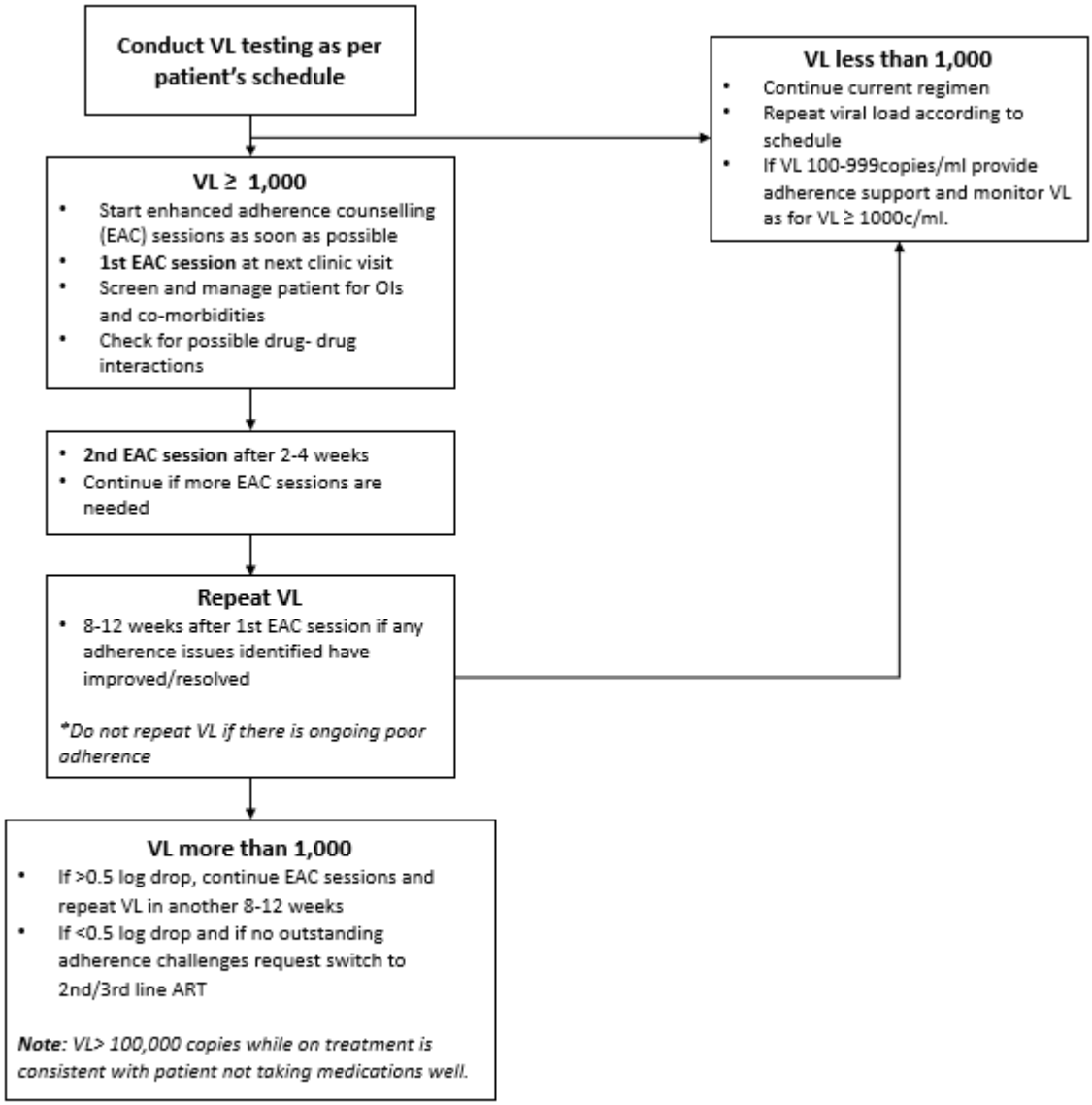
- Immunological deterioration
    - Steady decline in CD4+ count
- Clinical deterioration
    - Weight loss/ poor growth/ failure to thrive (FTT)
    - Delay in neurodevelopmental milestones in children and adolescents
    - Recurrent infections, such as oral candidiasis, persistent diarrhea, recurrent severe bacteria pneumonia
    - Development of opportunistic infections (new WHO 3 or 4)

6.2.2 Managing Treatment Failure

Each patient on ART must have a VL test as per schedule (6-months after starting ART then annually, or 6-monthly in adolescents and pregnant and breastfeeding women (PBFW) or according to updated guidelines). Management depends on the VL test result. Patients with an undetectable VL result should continue on their current regimen (see *figure 4*). Those with low level viraemia (VL 100 – 999 copies/ml) require close monitoring adherence support as for clients with VL ≥ 1000c/ml.

Individuals presenting with signs of clinical deterioration, as outlined above, should immediately receive viral load and CD4 testing to evaluate for virologic and immunologic deterioration. Those with a suppressed viral load need thorough evaluation for other causes of disease.

Figure 4: Algorithm for assessing and managing a patient based on VL test results



*Patients with high viral load ≥ 1000 cps/ml should undergo at least 2 EAC's sessions within 1 month to rule out non-adherence issues. If viral load persistently remains elevated ≥ 1000 cps/ml, after 3 months of ongoing EACs, switch to an appropriate second- or third-line ART regimen in consultation with hospital ART Advisory Committee. Third line cases require approval from National ART advisory committee and the Hospital ART advisory committee should facilitate timely submission.

6.2.3 Changing Therapy due to Treatment Failure

In the setting of treatment failure, resistance should be suspected once complete non-adherence ("drug holiday") is excluded. Drug resistance testing is used to determine whether a patient with HIV has a mutated form of the virus that does not respond to ART. Resistance testing is indicated among patients failing PI-based or DTG-based regimen in order to guide the choice of ART. Genotypic resistance testing (GRT) is the method used in Lesotho to identify HIV drug resistance. Once results are available on drug

resistance mutations, information on more efficacious treatment options can be obtained from the Stanford HIV Database website[10].

6.2.3.1 *Indications for Genotypic Resistance Test (GRT)*

If available, GRT should be carried out in the following cases to guide regimen selection:

- Treatment failure on a PI or DTG based regimen
- 2nd line treatment failure
- Client with a complicated ART history

The Hospital and National ART advisory committees can be consulted to guide decisions on eligibility for GRT as needed.

6.2.3.2 *ART regimen selection*

A completely new regimen that includes a new class of agents with at least two fully active ARVs is ideal. Where resistance testing is not possible, empiric decision making is indicated based on clinical history, VL result, local resistance patterns, and national guidelines[11]. All regimen decisions should be made in consultation with hospital ART Advisory Committees.

6.3 Cervical Cancer

Cervical cancer is a type of cancer that occurs in the cells of the cervix — the lower part of the uterus that connects to the vagina. Various strains of the human papilloma virus (HPV), a sexually transmitted infection, play a role in causing most cervical cancer. Cervical cancer is the most common cancer among Basotho women and causes the most cancer-related deaths in this group. HIV-positive women are at a higher risk of precancerous lesions and invasive cervical cancers. Refer to standard Lesotho cervical cancer guidelines for further guidance.

6.3.1 HIV and cervical cancer

Women living with HIV (WLHIV) have a higher prevalence of HPV (the risk of infection increases with the degree of immunosuppression) and a higher prevalence of persistent HPV infection and infection with multiple high-risk HPV types. This increased susceptibility to HPV infection leads to:

- A greater risk of pre-cancer and cancer at younger ages, which increases with the degree of immunosuppression
- An increased risk of developing invasive disease up to 10 years earlier than in women not infected with HIV, and
- More frequent presentation of advanced HIV disease with smaller chance of survival of five years

[10] https://stanfordhealthcare.org/medical-conditions/sexual-and-reproductive-health/hiv-aids/treatments/hiv-drug-resistance-testing.html

[11] Addendum to the national guidelines on the use of antiretroviral therapy for HIV prevention and treatment. 2019 pp 22-27

Cervical cancer is an AIDS-defining illness, since WLHIV who become infected with HPV are more likely to develop pre-invasive lesions, which, if left untreated, quickly progress to invasive cancer. Invasive cervical cancer is classified as WHO stage 4 condition, therefore a sign of advanced HIV disease.

WLHIV are four to five times more likely to develop invasive cervical cancer than HIV-negative women and generally present with more advanced lesions and have a poorer prognosis. Compared with the general population, PLHIV are at considerably increased risk for all types of anal and genital HPV-associated cancers and their precursor lesions.

6.3.2 HPV vaccination

Currently three HPV vaccines providing protection against high-risk HPV types 16 and 18 have been licensed; they are:

- The bivalent vaccine (protection against types 16 and 18 only)
- The quadrivalent vaccine (contains additional protection against types 6 and 11, which are responsible for 90% of benign anogenital warts or condyloma)
- Nonavalent (offers protection against 6, 11, 16, 18, 31, 33, 45, 52, and 58)

The recommended target population for HPV vaccination are girls aged 9–14 years, prior to initiation of sexual activity. The vaccines should be given **before** a girl becomes infected with HPV. A girl can become infected with HPV soon after she becomes sexually active, so, as an important primary prevention intervention against cervical cancer, HPV vaccination of girls should occur prior to onset of sexual activity.

6.3.2.1 *Dosing*

Table 25: Dosing for HPV vaccination

Age for girls	Dosage
9-14 years	• Two doses: ○ Second dose 6 months after the first dose **Note**: this may still be given within 15 months from the first dose
15 years or older, HIV infected or immunocompromised	• Three doses: ○ Second dose to be given 1-2 months from first dose ○ Third dose to be given at 5-6 months

Note: The three-dose schedule (0, 1–2, and 6 months) remains recommended for girls aged 15 years and older and for immunocompromised individuals, including those known to be HIV-positive (regardless of whether they are receiving ART). It is not necessary to screen for HPV or HIV infection prior to HPV vaccination.

6.3.2.2 *Contraindications to HPV vaccines*

HPV vaccines should not be given to the following:

- Anyone who has experienced severe allergic reactions after a previous dose of the vaccine or after exposure to one of its components (e.g., yeast)
    - Symptoms of an allergic reaction may include itching, rash, urticaria, or blisters

- If any of these symptoms occurs post-HPV vaccination, no more doses should be given, and other vaccines that may have these same components included in them should be avoided

- Girls with severe febrile illness
- Girls or women who are pregnant:
  - If a girl becomes pregnant after initiating the vaccination series, the remainder of the regime should be delayed until after the pregnancy.
  - If the HPV vaccine is inadvertently administered to a girl or woman who is pregnant, no intervention is necessary. She should be reassured that the vaccine does NOT contain live virus, and that no health problems in mother or child have been observed to date after accidental HPV vaccination during pregnancy. The remaining vaccine dose(s) should be postponed until after the pregnancy, at which time the HPV vaccine series can be completed. It is not necessary to restart the vaccine series after the pregnancy.
  - In case of the HPV vaccine being given to someone who is breastfeeding, available data does not indicate any safety concerns.

6.3.3 Integrating cervical cancer screening and treatment with HIV services

All contacts between a patient and a health worker should be used as an opportunity for provision of HIV testing services and provision of appropriate HIV education, prevention, and care. The integration of cervical cancer and HIV services can occur in two ways:

- Women attending HIV testing services (HTS) should be encouraged to seek cervical cancer screening if they are aged 25 years and above.
- Women attending clinics for cervical cancer screening should be offered HTS and linked to appropriate HIV prevention, care, and treatment services.

6.3.4 Approach for HIV-positive and HIV-negative women

HIV-positive women are often presented with cervical cancer almost 10 years earlier than HIV-negative women (mean age 44 years versus 53 years), an important finding for screening programmes. In addition, severely immune-compromised women (e.g. CD4+ counts <200 cells/µL) are significantly more likely to have advanced stage disease at initial diagnosis than HIV-negative women.

Table 26: Summary of approaches for HIV-positive and HIV-negative women

	HIV-negative	HIV-positive
Vaccination	• 9-14 years: 2 doses, 6 months apart • 15 years or older: 3 doses	3 doses: • Second dose to be given 1-2 months from first dose • Third dose to be given at 5-6 months
Screening	• Ages 25 years and above	• Ages 25 years and above
Frequency of screening	• 25-49 years: every 3 years • 50 years and above: every 5 years	• Every 2 years from when client is sexually active or from 25 years, whichever is earlier.

Exit from screening	• 65 years if previous two consecutive screenings were negative	• No exit • Continue every 2 years
Management of precancerous lesion	• Available suitable method	
Management of cervical cancer	• Based on staging and classification	

6.3.5 Screening and Diagnosis

The national target group for screening is women between the ages of 25 and 49 years. All HIV-positive women should be offered cervical cancer screening at diagnosis, if eligible, by meeting the following criteria:

- Aged 25 years and above
- Have not been screened in the past two years and are due for next test

This means that HIV-positive women should have more frequent screening for cervical cancer than HIV-negative women, with screening every two years from the age of 25. Unlike for HIV-negative clients, cervical cancer screening among WLHIV should continue beyond the age of 65.

See Cervical cancer screening guidelines for guidance on pregnant and postnatal women.

6.3.5.1 *Screening methods*

The following screening methods will be offered in Lesotho, however newer screening techniques will be adopted as they become available:

- Visual inspection using 5% acetic acid (VIA) and/or Lugol's iodine (VILI)
    - To note there are high false positives results with VIA in teenage girls
- HPV DNA Nucleic acid test
- Pap smear/cytology

Women who are found to have abnormalities on screening should be offered treatment and follow up in order to prevent the development of cancer or to treat cancer at an early stage.

6.3.6 Treatment Methods

Various treatment options that will be available for the treatment of pre-cancerous lesions are described below:

- **Ablative Methods:** These methods involve destroying abnormal cervical tissue. Cells are destroyed by thermo-coagulation, cryotherapy, electrosurgical cauterization, or vaporization with a laser beam.
- **Excision methods:** These methods involve the removal of the abnormal area of the cervix and the transformation zone. Excision methods have the advantage of providing tissue for histopathological diagnosis. The excision methods which will be offered in Lesotho are LLETZ and cold knife biopsy.

6.3.7 Post-treatment follow-up

Follow up after treatment will be at one year irrespective of the treatment methods. Clients should be counselled on the importance and need of follow-up.

During the healing process after any procedure (e.g. biopsy or treatment), WLHIV might have increased viral shedding. During counselling, it is especially important for the provider to stress that the patient should discuss this with her partner(s) and abstain from intercourse until healing has occurred (two weeks after ablative treatment and 4-6 weeks after a LEEP). In situations where this may not be possible, condoms should be used consistently and correctly.

6.3.8 Invasive cervical cancer

Cervical cancer is curable if detected and treated in its early stages. It is important that providers have a basic understanding of the signs and symptoms of cervical cancer so that clients can be appropriately managed in a timely manner.

The clinical presentation of invasive cervical cancer depends on the location and spread of the cancer. The clinical presentation is mainly determined by the patterns of growth and spread. All clients with symptoms of invasive cancer should be referred.

Table 27: Symptoms of invasive cervical cancer

Type	Symptoms
Micro-invasive cancer	• May be asymptomatic • May be detected on investigation of an abnormal Pap smear, colposcopy or conization (cone biopsy)
Early Cancer	• Vaginal discharge, sometimes foul smelling • Irregular vaginal bleeding (of any pattern) in women of reproductive age • Post-coital spotting or bleeding in women of any age, even young women • Post-menopausal spotting or bleeding
Late Cancer	• Urinary frequency and urgency • Backache • Lower abdominal pain
Very Late	• Severe back pain • Weight loss • Blood in the urine • Decreased urine output (from obstruction of the ureters or renal failure) • Leakage of urine or faeces through the vagina • Symptoms of bowel obstruction • Leg swelling (oedema), usually unilateral
Note: In cases of abnormal peri-menopausal bleeding, cervical cancer should always be considered	

Table 28: Signs on Examination

Signs on Clinical Examination	
Early signs	• Contact bleeding • Enlarged cervix (often barrel-shaped) • Dirty water looking offensive vaginal discharge

Late signs	• General:
	  ○ Severe anaemia
	  ○ Weight loss
	• Pelvic:
	  ○ Growth or ulcerative lesion on the cervix on pelvic examination
	  ○ Fistulae between the vagina and bladder or rectum if the cancer has spread to these organs (this can result in the incontinence of urine and/or faeces through the vagina)

6.3.8.1 *Referral of cases*

Patients identified at the health centre level as having a suspected case of cervical cancer must be referred immediately to a hospital for further management, including biopsy and staging (examination under anesthesia). In order to fast track management of the client, referring center can initiate management of the client including the following:

1. Consult/refer for review by medical officer
2. Stabilise client – resuscitation, control bleeding, iron and folate supplementation, pain control, treat infections and comorbidities
3. Investigations:
   i. Take biopsy if resources are available at district hospital
   ii. Perform FBC, Urinalysis, U and E, LFT, Chest X ray, Ultrasound scan of the pelvis and abdomen
   iii. An experienced clinician should perform examination under anaesthesia as part of staging
   iv. Perform other tests based on clinical presentation
   v. HIV test /STI screening including Syphilis serology

Note: Definitive diagnosis of cancer (by histopathology) is mandatory before any extensive investigation and/or therapy.

6.3.8.2 *Invasive cervical cancer treatment*

Invasive cervical cancer may be treated by:

- Surgery (for early stage), and/or
- Radiotherapy with or without chemotherapy (for advanced stages)

6.4 Palliative care (PC)

Palliative care is an approach that improves the quality of life of patients and their families facing problems associated with life-threatening and life-limiting illnesses. It consists of the prevention and relief of suffering by means of early identification and assessment and treatment of pain and other forms of physical, psychosocial, and spiritual suffering.

The five key domains of PC are:

1. Pain and symptom relief
2. Access to drugs
3. Emotional and spiritual support
4. Grief counselling
5. Support for family caregivers and family-based advanced care planning

As the illness advances further, palliative care gradually takes precedence over curative care. It can help people with advanced disease to have dignity and peace during difficult and final phases of life. Bereavement care with the extended family is part of the continuum of care after the patient dies.

Strategies are developed to allow existing community structures to link patients and their families with staff at primary, secondary, and tertiary level facilities. Communication within and by multidisciplinary teams, cultural sensitivity, and resources are needed to manage differing aspects of pain and symptom relief that are key elements of the provision of PC.

Table 29: Conditions and suggested care

Condition	Suggested Care
Weight loss, fatigue, and weakness	• Provide nutritional support, plenty of oral fluids, fruits, and vegetables
Bleeding, shortness of breath	• Do vaginal packing for emergency situation and refer to the secondary level of care • Supplement with haematinics
Foul smelling vaginal discharge	• Maintain good personal hygiene, use of charcoal on sanitary pad to control the odour • Change sanitary pads at reasonable intervals
Single swollen leg	• Elevation of affected leg when at rest
Other problems of Advanced Disease	
Nausea and vomiting	• Give anti-emetics
Pressure sores	• Frequent position change
Bowel or bladder incontinence	• Use of diapers; catheterize and do bladder control by clamping the catheter at intervals
Fistulae	• Promote good personal hygiene

6.5 Cytomegalovirus (CMV) Infection

Cytomegalovirus infection is a systemic viral infection that usually manifests as cytomegalovirus retinitis among severely immunocompromised people. The reported prevalence of cytomegalovirus retinitis is highest in Asia and appears to be low in Africa. Among children, cytomegalovirus is responsible for cytomegalovirus pneumonitis, and HIV-exposed infants have a higher incidence of congenital cytomegalovirus. Since cytomegalovirus is a systemic infection, improving access to early diagnosis and affordable, oral systemic treatment with valganciclovir is a priority.

6.5.1 Clinical Presentation and Diagnosis

Major presenting symptoms of Cytomegalovirus Infection are:

- Variable malaise
- Visual loss
- Bloody diarrhea
- Vision loss

There is currently no lab test used to make a definitive diagnosis of CMV.

6.5.2 Treatment and Management

Oral valganciclovir is used for the management of cytomegalovirus retinitis which is the commonest manifestation in AIDS.

6.6 Severe Malnutrition

The 2013 Mid-Term Review of the Lesotho National HIV and AIDS strategy revealed that food insecurity was increasingly becoming an important drive of the HIV epidemic. Poverty and food insecurity in Lesotho are further fueled by high HIV prevalence. The link between HIV and nutrition is often described as a vicious cycle: both malnutrition and HIV weaken the immune system. HIV infection increases nutrient requirements and at the same time impairs nutrient intake and absorption. On the other hand, poor nutrition increases the risk of opportunistic infections and accelerates the progression of HIV and AIDS.

Good nutrition is an important component in the comprehensive care of PLHIV. Additional energy and nutrient intake enhance immune rehabilitation and adherence to ART. PLHIV will therefore benefit from referral to supplementary food programs. Refer to nutrition guidelines for additional information.

6.6.1 Nutrition priorities

It is critical that patients receive nutrition services as a component of care and treatment package. This can be achieved through integration of nutrition assessment counselling and support (NACS).

- Nutrition assessment
- Nutrition counselling and support
- Micronutrient supplementation and food supplementation
- Management of severe wasting
- Management of nutrition complications of ART and TB drugs

Nutrition assessment, counselling, micronutrients, and food supplementation are well documented in the national Integrated Management of Acute Malnutrition (IMAM) protocol. In addition, the NACS manual serves as a quick guide to health professionals to implement NACS. Therefore, this manual only highlights key aspects in nutritional assessment, counselling, and support.

6.6.2 Types of malnutrition

There two types of malnutrition:

1. Undernutrition
2. Overnutrition

This manual focuses on undernutrition and specifically severe undernutrition/malnutrition which could worsen prognosis for AHD.

6.6.3 Malnutrition in children

Nutritional needs of children should be considered within the context of the national Infant and Young Child Feeding (IYCF) guidelines, which emphasizes on breastfeeding and introduction of complementary food for children. Management of illnesses is also well articulated in the national Integrated Management of Childhood Illnesses (IMCI) manual. Refer to Section 8.5 for more information on malnutrition in children.

6.6.4 Nutrition in pregnant and lactating women

Nutritional needs of women are increased during pregnancy and lactation period. Presence of disease puts more strain on the nutrients and energy requirements of women. More focus should be on women in both, the prenatal and postnatal periods. Addressing nutrients requirements of women during these periods is also covered in the IMAM guidelines and NACS manual.

6.6.5 Malnutrition in Adults

Severe malnutrition in adults presents in the form of:

- Micronutrient deficiencies (Iron, Folate, Vitamin A, Iodine, etc.)
- Acute weight loss due to short-term food scarcity or illness; high risk of mortality in immune compromised people
- Chronic “thinness” due to chronic inadequate intake, leading to compromised metabolic function

Consequences of severe malnutrition are:

- Increased morbidity
- Reduced survival
- Growth faltering and developmental delays in children
- Poor food absorption
- Metabolic complications (problems in the body’s ability to make use of energy)
- Increased risk of infections
- Lost productivity and expenses for treating illness
- Faster disease progression in HIV and TB-infected people
- Increased risk of chronic disease

6.6.6 Screening

Continuous nutrition monitoring is critical at every health facility visit. Options for monitoring are based on the setting and capacity. Screening for severe malnutrition is conducted in the following ways:

- Anthropometric (body measurements)
- Clinical and biochemical assessments are most commonly used together to classify a person’s nutritional status:
    - Clinical—signs and symptoms, appetite test

    - Biochemical—laboratory investigations
- Dietary assessments can be used to help determine why a patient might be malnourished and how he/she could improve nutritional status through dietary changes
    - Dietary Intake—24-hour recall, usual intake

6.6.7 Diagnosis

Diagnosis of malnutrition using Anthropometric Assessment is dependent on the classification of the nutritional status. Classification is in different forms:

- Severely Malnourished with medical complications
- Severely Malnourished without medical complications
- Moderately malnourished
- Normal
- Overweight
- Obese

6.6.7.1 *Diagnosis of nutritional status of children 0-59 months using Standard deviations /Z-scores and MUAC*

Table 30: SD/ Z-Scores and MUAC cut-offs for children 0-59 months

Nutritional status	Weight-for-height (SD/Z-score)	MUAC	COLOUR CODE
Severe malnutrition	<-3	< 11.5cm	
Moderate malnutrition	< -2 to ≥ -3	≥ 11.5 to < 12.5cm	
Normal	≥ -2 to < +2	≥ 12.5cm	
Overweight	≥ +2 to < +3	≥	
Obese	≥ +3	≥	

6.6.7.2 *Diagnosis of nutritional status of children and adolescents 5 to 18 years*

BMI-for-age is a recommended indicator of undernutrition for children and adolescents 5-18 years of age.

- It should replace Z-scores (standard deviations) for children under-5 years and BMI for children above 5 years
- It is based on the fact that BMI varies with age and gender during childhood and adolescence (i.e. BMI is age and sex specific)

Table 31: BMI-for-age cut-offs for children and adolescents (5-18 years)

Nutritional status	SD (Z-score)	Colour code
Severe malnutrition	< -3	
Moderate malnutrition	< -2	
Overweight	> +1	
Obesity	> + 2	

6.6.7.3 *Diagnosis of nutritional status of pregnant and lactating women (until child is 6 months of age)*

As BMI cut-offs are not accurate in pregnant women or adults with oedema since their weight again is not linked to nutritional status, MUAC should be used for these groups.

Table 32: MUAC cut-offs for pregnant women

Nutritional status	Adults MUAC	Nutritional status	Adolescents MUAC
Severe malnutrition	< 21cm	Severe malnutrition	< 17.5cm
Moderate malnutrition	≥ 21 to < 23.0 cm	Moderate malnutrition	≥ 17.5 to < 19.5cm
Normal	≥ 23cm	Normal	≥ 19.5cm

6.6.7.4 *Diagnosis of nutritional status of Adults ≥ 19 years*

Body Mass Index (BMI) is the best indicator of nutritional status of adults over 18 years of age.

- BMI is also an indicator of advanced disease and mortality risk
- It is calculated with a formula that includes the client's weight and height
    - Weight in kg/ (height in m) ^{2}
- BMI below or above established WHO cut-offs indicates a need for nutrition interventions

Table 33: BMI cut-offs for adults

Nutritional Status	BMI
Severe malnutrition	< 16.0
Moderate malnutrition	≥ 16.0 to < 18.5
Normal nutritional status	≥ 18.5 to < 25.0
Overweight	≥ 25.0 to < 30.0
Obese	≥ 30.0

6.6.8 Treatment and Management

Nutritional assessment and management are a central component to the comprehensive care of PLHIV. Numerous studies have shown the association between indices of nutritional states such as BMI and mortality.

Nutrition treatment of patients on ART and TB-DOTs (Directly Observed Therapy) programmes is implemented following NACS approach which is in line with the national Integrated Management of Acute Malnutrition (IMAM). Nutrition rehabilitation of undernourished patients on care and treatment programmes contribute to the national targets of 90 – 90 – 90, adopted from the UNAIDS fast track strategy.

Table 34: Treatment and Management of Severe Malnutrition

Category	Indices	Criteria for nutrition support	Food supplementation	Targeted nutritional status
Children (6 to 59 months)	Weight for height z-scores	If the z-score is < - 3SD	Plumpy nut based on the weight of child: 3.5 – 5.4kg = 2.0 pkts/day 5.5 – 8.4kg = 3.0 pkts/day 8.5 – 10.4kg = 4.0 pkts/day 10.5 –11.9kg = 4.5 pkt/day	z-scores is < - 2SD
	MUAC in (cm)	<11.5 cm *No bilateral pitting oedema*		MUAC above 12.5cm
Adolescents (5 to 18 years)	BMI for age	If the z-score for BMI-for-age is < - 3SD	Plumpy nut ≥ 12kg = 5pkts/day	BMI z-score is above -2SD for 2 consecutive months
	MUAC in (cm)	Children 5-9yrs = <12.9 cm Children 10-14yrs = < 16. cm Adolescent 15-17yrs= < 17.5cm *No bilateral pitting oedema*		MUAC above 14.5cm MUAC above 18.5cm MUAC above 19.5cm
Adults (≥ 19 years)	BMI	If the BMI is < 16.0	Plumpy nut ≥ 12kg = 5pkts/day	BMI is ≥ 18.5
	MUAC	Non-pregnant women = < 21.5cm Adult men = < 22.5cm *No bilateral pitting oedema*		MUAC above 22.5cm MUAC above 23.5cm
Pregnant and postpartum women with infants < 6 months of age	MUAC	Adolescent mothers = < 17.5cm Adult mothers= <21.0cm *No bilateral pitting oedema*	Super cereal	MUAC above 19.5cm MUAC above 23.0cm

6.7 Depression

PLHIV are at high risk of mental, neurological, and substance-use disorders. Systematic reviews from both low- and high-income countries showed that depression is one of the most prevalent mental health comorbidities in people with HIV. A systematic review conducted in 2015 reported depression prevalence rates as high as 80% among PLHIV, but with wide variation across studies, which is attributed to the screening and diagnostic criteria used. Depressive symptoms have been reported as common in many studies in sub-Saharan Africa, where the HIV burden is also high.

PLHIV who have depression are less likely to achieve optimal treatment adherence. Although chronic HIV care settings provide an opportunity to detect and manage depression among PLHIV, it is often overlooked and unrecognized by health-care providers. Treatment, or lack of it, for mental health disorders can affect general health, adherence to ARV drugs and retention in care, and may lead to potential side-effects and drug interactions being overlooked.

6.7.1 Description of depression

The term "depression" is often explained as feelings of being sad, discouraged, hopeless, irritable, unmotivated, as well as a general lack of interest or pleasure in life. When these feelings last for a short period of time, it may be referred to as an episode of 'stress'. But it is likely to be a depressive disorder when these feelings last for more than two weeks and interfere with regular daily activities. Depressive disorders, also known as mood disorders, include three main types: major depressive disorder (MDD), persistent depressive disorder, and bipolar disorder. Depressive disorders can affect people of any age, including children, teenagers, adults, and older adults.

6.7.2 Clinical Presentation of Major Depressive Disorder (MDD)

The diagnostic criteria for MDD are:

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure. *[Note: Do not include symptoms that are clearly attributable to another medical condition]*
    i. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, and hopeless) or observation made by others (e.g., appears tearful) (Note: In children and adolescents, can be irritable mood)
    ii. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
    iii. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day
    (Note: In children, consider failure to make expected weight gain)
    iv. Insomnia or hypersomnia nearly every day
    v. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
    vi. Fatigue or loss of energy nearly every day
    vii. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
    viii. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
    ix. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The episode is not attributable to the physiological effects of a substance or to another medical condition
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders
E. There has never been a manic episode or a hypomanic episode
[Note: This exclusion does not apply if all manic-like or hypomanic-like episodes are substance induced or are attributable to the physiological effects of another medical condition]

Note 1: Criteria A–C represent a major depressive episode

Note 2: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

6.7.3 Screening

Regarding screening tools, the general consensus is that the PHQ (Patient Health Questionnaire), with both, the two item (PHQ-2) and nine item (PHQ-9) questionnaires, meets the criteria for a good screening tool in its validity, reliability, and brevity. Additionally, the PHQ is free and accessible in the public domain. Since the establishment of its validity, about two decades ago, the diagnostic validity of the PHQ-9 remains reputable.

6.7.4 Treatment and Management

People with a depressive illness seldom seek treatment. Evidence has shown that even the most severe depression can get better with some form of treatment. The types of treatment shown to be effective include pharmacological treatment (antidepressants) and forms of psychotherapy. Early diagnosis and intervention with appropriate treatment are the best ways to deal with depression. All PLHIV suspected or diagnosed with depression or any other mental health illness should be referred for appropriate psychological management. For more information, please see: https://www.researchgate.net/publication/293569074_Major_Depressive_Disorder.

7. Vaccinations

Providing vaccinations to PLHIV does not appear to accelerate HIV disease progression and is recommended as an important part of the HIV care package. However, people with severe immunosuppression may be at higher risk of complications from some live attenuated vaccines, and the response to other inactivated vaccines may be less effective because of their degree of immunosuppression. Additional doses or revaccination after immune reconstitution on ART may therefore be required.

7.1.1 Bacille Calmette-Guérin (BCG) vaccine

Children who are HIV positive or of unknown HIV status with symptoms consistent with HIV should not receive BCG vaccine. This policy is currently being reviewed by WHO and is potentially subject to change.

7.1.2 Human Papillomavirus (HPV)

Due to increased risk of cervical cancer, vaccine schedule for HPV as recommended by WHO below is key for HIV infected women:

- A three-dose schedule (0, 1–2 and 6 months) should be used if HPV vaccination is initiated after 15 years of age and for those younger than 15 years known to be immunocompromised and/or living with HIV (regardless of whether they are receiving ART). It is not necessary to screen for human papillomavirus infection or HIV infection before HPV vaccination.

For more details, refer to Section 6.3.2.

7.1.3 Measles

Children and adults with HIV infection are at increased risk of measles. Therefore, live vaccine should not be used for children and adults with severe immunosuppression as recommended by WHO. WHO defines severe immunosuppression with respect to measles vaccine eligibility as CD4 cell count <50 cells/mm^3.

Chronological vaccination should be routinely administered to potentially susceptible, asymptomatic children and adults living with HIV and should be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to WHO definitions.

7.1.4 Meningococcal vaccination

Meningococcal vaccination should be offered to everyone with immunodeficiency, including those patients with AHD.

7.1.5 Polio vaccine

Polio vaccine is life attenuated and its use in patients with AHD should be in line with WHO recommendation as indicated below:

- Inactivated polio vaccine or bivalent oral polio vaccine may be administered safely to asymptomatic infants living with HIV. HIV testing is not a prerequisite for vaccination.
- Bivalent oral polio vaccine is contraindicated among severely immunocompromised people with known underlying conditions such as primary immunodeficiencies, disorders of the thymus, symptomatic HIV infection or low CD4 cell count; these populations can safely receive inactivated polio vaccine.

7.1.6 Yellow Fever

Yellow fever vaccine may be offered to asymptomatic PLHIV with CD4 cell counts ≥200 cells/mm^3; it is therefore contra-indicated in people with AHD until they achieve a CD4 cell count ≥200 cells/mm^3. Although the data on the safety and immunogenicity of yellow fever vaccine when used among CLHIV are limited, yellow fever vaccine may be administered to all clinically well children. HIV testing is not a prerequisite for vaccination.

8. AHD in Children

8.1 HIV Encephalopathy

HIV is known to invade the central nervous system at the time of infection and cause widespread damage. In children, especially in younger perinatally affected children, this leads to a condition known as HIV encephalopathy, which affects all areas of neurodevelopment. HIV encephalopathy risk factors include viral load (high plasma/CSF viral load) in a child, route of HIV transmission (vertical), and timing of ART (i.e., late initiation).

8.1.1 Clinical presentation

Neurological and developmental abnormalities are frequent complications of HIV infection in children, especially in younger perinatally affected children.

- Gross discrepancy between the actual and developmental age; failure to attain or loss of developmental milestones; loss of intellectual ability
- Progressive impaired brain growth demonstrated by stagnation of head circumference
- Acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances

8.1.2 Diagnosis

A complete history and physical examination should be done as HIV Encephalopathy is mainly a clinical diagnosis and is made after exclusion of several other conditions that might have similar clinical picture such as:

- CNS infections e.g. toxoplasmosis, herpes simplex, varicella zoster etc.
- Acute intoxication
- Drug effects
- Malignancies

8.1.3 Treatment

The mainstay of prevention and treatment of HIV Encephalopathy is ART. Supportive treatment should also be offered for complications caused by the infection, such as physiotherapy and speech therapy where indicated.

8.2 Esophageal Candidiasis

The most common fungal infections in children with HIV infection are caused by Candida spp. Esophageal candidiasis continues to be one of the most frequent opportunistic infections in children with HIV

infection. Risk factors for esophageal candidiasis include low CD4 cell count, high viral load, and neutropenia.

8.2.1 Clinical presentation

Esophageal candidiasis often presents with odynophagia, dysphagia, or retrosternal pain, and children, unlike adults, often experience nausea and vomiting. Therefore, children with esophageal candidiasis may present with dehydration and weight loss.

8.2.2 Diagnosis

One should have a high index of suspicion of esophageal candidiasis for a child who presents with the above-mentioned signs and symptoms and who also has oral candidiasis. Treatment with systemic antifungals should be started as soon as possible.

Esophageal candidiasis has a classic cobblestone appearance on barium swallow. Findings on endoscopy may range from a few, small, raised, white plaques to elevated confluent plaques with hyperemia and extensive ulceration.

8.2.3 Treatment

Oral fluconazole for 14 to 21 days.

8.3 Tuberculosis

(Only additional information that is more specific for children is included here; for other information on TB, refer to Section 5.1 under Management of Major AHD Conditions)

In children, TB may not present the same way as in adults. It is primarily the result of primary infection not reactivation disease, and extra pulmonary TB (EPTB) is the most common.

8.3.1 Signs and symptoms

Signs and symptoms of TB disease in children include**:**

- Cough
- Feelings of sickness or weakness, lethargy, and/or reduced playfulness
- Weight loss or failure to thrive
- Fever
- Night sweats
- Regressed milestones

8.3.2 Diagnosis

As children are normally unable to provide sputum for diagnostic purposes (they usually swallow it), sputum induction must be done for all children with presumptive TB so as to get sputum for bacteriological diagnosis.

8.4 PJP

For PJP in children, refer to Section 5.4 under Management of Major AHD Conditions.

8.5 Malnutrition

Children living with HIV/AIDS are at increased risk of malnutrition. Chronic infection including HIV/AIDS can lead to poor growth and may reduce appetite, food intake, and nutrient absorption at a time when the body needs good nutrition the most to fight the infection. The result is a further weakened immune system that is ill equipped to fight the virus and infections like tuberculosis.

In children aged 6–60 months, WHO defines severe acute malnutrition (SAM) as a weight-for-height of less than -3 standard deviations of the WHO standards, or a mid-upper arm circumference (MUAC) of less than 115 mm, and/or the presence of bilateral oedema (swelling of both feet).

There are two specific clinical forms that children with severe malnutrition present with.

Table 35: Malnutrition in children

Kwashiorkor	Marasmus
Bilateral pitting oedema, starting in feet and legs	Extremely emaciated
Reduced fat muscle tissue, which may be masked by oedema	Fat and muscle tissue extremely reduced
Skin lesions cracked and peeling; patchy and fragile	Thin, flaccid skin hanging in loose folds
Hair changes colour (yellow/reddish and becomes sparse, dry, and brittle	Normal
Frequent infections due to skin lesions	Frequent infections but showing no clinical signs (no fever)
Frequent association with dehydration which may be masked by oedema	Frequently associated with dehydration
Apathetic and lethargic: irritable when handled	Alert and irritable

8.5.1 Signs and symptoms

Signs and symptoms include:

- Lack of appetite or interest in food or drink
- Tiredness and irritability
- Inability to concentrate
- Always feeling cold
- Loss of fat, muscle mass, and body tissue
- Regressed or delayed milestones

8.5.2 Diagnosis

The main diagnostic features are:

- Weight for height less than -3 SD
- Mid-upper arm circumference less than 115mm
- Oedema of both feet

8.5.3 Treatment

Children with uncomplicated severe malnutrition (those with appetite, and who are clinically well and alert) can be managed in the community or as outpatients using ready-to-use therapeutic food (RUTF)**.**

Children with complicated severe malnutrition (those with poor appetite, fever, pneumonia, dehydration, severe oedema or infants aged less than six months) are managed in inpatient facilities until complications are resolved, using the WHO's 10 steps to management of severe acute malnutrition.

9. Appendix

9.1 Roles and Responsibilities

Table 36: Roles and Responsibilities by stakeholder levels

LEVEL	STAKEHOLDERS AND KEY RESPONSIBILITIES
National	• HIV and TB programs: Joint coordination, mentoring/ coaching, collaboration, monitoring and evaluation, and support supervision; Oversee quality assurance for TB LAM and CrAg; contribute to development and revision of guidelines, algorithms and SOPs; Joint training and mentorship; monitor stock status for TB and CM commodities; recording and reporting; provide further testing e.g. culture and Drug Susceptibility Testing • Budget and plan for procurement of TB LAM kits • Budget and plan for procurement of CrAg kits • Supply Chain Directorate/NDSO: Procurement and distribution of commodities; Forecasting, quantification, and procurement of commodities • PEPFAR/Global Fund/WHO/CHAI and other development partners: Provide funding and work with MOH to monitor the phased implementation
District	• Reporting with support from the DHMT focal person • Provide oversight and support to health facilities to implement roll out of the AHD package of care including coaching and training • Support supervision and mentorship to health facilities to support implementation • Strengthen referral linkages from HIV testing centers
Implementing Partners	• Jointly work with district teams and mentors to train and mentor health workers on triaging and AHD management • Support reporting, data use and performance reviews at the health facility level through the district • Strengthen referral linkages from HIV testing centers
Health Facility	• Implementation of AHD package of interventions • Routinely collect patient data and ensure accurate and complete documentation in the registers • Quantification and ordering supplies • Implementing CQI projects • Client education
PLHIV and Civil Society	• Advocate for funding • Implement prevention initiatives, treatment literacy, adherence support and contact tracing; referral of PLHIV and presumptive TB cases