GUIDELINES
FOR
MANAGEMENT OF
OPPORTUNISTIC INFECTIONS
AND
ANTI RETROVIRAL TREATMENT
IN ADOLESCENTS AND ADULTS
IN ETHIOPIA

Federal HIV/AIDS Prevention and Control Office
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PART I

GUIDELINES
FOR
MANAGEMENT OF OPPORTUNISTIC INFECTIONS IN ADULTS AND ADOLESCENTS

Table of Contents

Tables

Foreword

Antiretroviral treatment began in 2003 and *free* ART was launched in Ethiopia in 2005. An estimated 977,394 Ethiopians are currently living with HIV, out of whom 258,264 require antiretroviral treatment (ART).

Recognizing the urgent need for antiretroviral treatment, the Government of Ethiopia (GOE) issued the first antiretroviral (ARV) guidelines in 2003, which were revised in 2005 to facilitate a rapid scale up of ART. Within two years, patients on treatment at 117 hospitals and 108 health centres increased from 900 to 62,221.

Opportunistic infections (OIs) and malignancies resulting from depletion of the immune system are major causes of morbidities and mortalities among AIDS patients. Prophylaxis and early treatment of OIs have been clearly shown to prolong and improve the quality of life for people living with HIV, even before the advent of ART.

In order to realise universal access to free ART by 2009/2010, the Federal Ministry of Health (MOH) is committed to decentralize further the expansion and integration of HIV/AIDS prevention and control activities with primary health care services at grass roots where the majority of the population lives.

Expansion and strengthening ART care and treatment activities at regional, zonal, woreda and kebele levels through targeted social mobilization and active community participation are planned to create an environment to prevent and control spread of the epidemic. The process of task shifting: training of nurses and community health agents in prevention, treatment, care and support activities will further strengthen community linkages and ensure availability of standard minimum packages of HIV/AIDS services at primary health care level.

This revised 3rd edition of guidelines for use of OI and ARV drugs in adult and adolescent care is based on recent national and worldwide evidence and experience and is intended as a clear guide for rational and safe use of OI and antiretroviral drugs. The Federal Ministry of Health believes that these guidelines, along with other national implementation guidelines, will be instrumental in accelerating and scaling up ART uptake and treatment and prevention of other opportunistic infections to meet the millennium development goals (MDG).

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Acronyms and Abbreviations

AED	Antiepileptic Drug
AFB	Acid Fast Bacilli
ART	Antiretroviral Therapy
BF	Blood Film
BID	Twice per day
BP	Blood Pressure
CBC	Complete Blood Count
CHF	Congestive Heart failure
CHAI	Clinton Foundation HIV/AIDS Initiative
CMV	Cytomegalovirus
CNS	Central Nervous System
CPK	Creatinine phospho Kinase
CSF	Cerebro Spinal Fluid
CT	Computerized Tomography
CTM	Cotrimoxazole
CX-ray	Chest X-ray
D4T/DDI	Stavudin/Didanosin
DOT	Directly Observed Treatment
EMG	Electromyography
EMB	Ethambutol
FHI	Family Health International
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GOE	Government of Ethiopia
HAART	Highly Active AntiRetroviral Treatment
HAPCO	HIV/AIDS Prevention and Control Office
HCT	HIV Counselling and Testing
HEENT	Head, Eyes, Ears, Nose and Throat
HSV	Herpes Simplex Virus
Hx	History
ICP	Isoniazid Chemoprophylaxis
IgG	Immunoglobulin
IM	Intramuscular
INH	Isoniazid
IRIS	Immuno Reconstitution Inflammatory Syndrome
IPT	Isoniazid Preventive Treatment
IV	Intravenous
KS	Kaposi Sarcoma
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LP	Lumbar Puncture
LIP	Lymphocytic Interstitial Pneumonia
MAC	Mycobacterium avium complex
MDR	Multidrug-resistant TB

MRI	Magnetic Resonance Imaging
MTB	Miliary Tuberculosis
NCS	Nerve conduction studies
NNRTI	None-Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic Infection
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PLWHA	People Living With HIV/AIDS
PML	Progressive Multifocal Leuckoencephalopathy
PMN:	Polymorphonuclear leukocyte
PO	By Mouth
PPV	Positive Predictive Value
Px	Physical examination
PZA	Pyrazinamide
QID	Four times per day
RBS	Random Blood Sugar
RDT	Rapid Diagnostic Test
RFT	Renal Function Test
Rx	Treatment
STM	Streptomycin
TB	Tuberculosis
TBC	Tuberculosis
TMP-SMX	Trimethoprim Sulphamethoxazole
UTI	Urinary Tract Infection
URTI	Upper Respiratory Tract Infection
VL	Viceral Leishmaniasis
VZV	Varicela Zoster Virus
WHO	World Health Organisation
XDR-TB	Extensively Drug-Resistant Tuberculosis
2RHZE/6HE	Rifampicin, Isoniazid, Pyrizinamide, Ethambutol /Isoniazid, Ethambutol

1. Introduction

The HIV pandemic created unprecedented burden on the economies and health care systems of affected countries, particularly in sub-Saharan Africa, where prevalence is highest. In Ethiopia, the total number of people who have died due to HIV/AIDS in 2006 alone was 88,997; and in 2007, it is estimated that, 71,902 people will die. In 2007, there are an estimated 898, 350 children have lost one or both parents to the epidemic (AIDS orphans). According to the calibrated single point estimate (from 2005 sentinel surveillance and EDHS data), prevalence of adult infection is 2.1% (urban 7.7%, rural 0.9%). In 2007, the estimated number of people living with HIV is 977,394, including 64,813 children. The current estimate of people requiring antiretroviral therapy is 258,264 and of these 6% (15,716).are children.

HIV causes progressive depletion of the CD4 T cells, resulting in conditions known as opportunistic infections or malignancies. More than 90% of these are responsible for AIDS morbidities and mortalities. A study of 230 hospital patients with HIV infection, identified oro-pharyngeal candidiasis and TB as the commonest OIs, followed by OIs in the central nervous system, sepsis, Pneumocystis pneumonia (PCP) and bacterial pneumonia in that order. Kaposi's sarcoma and lymphoma were reported in 8.4% and 3% respectively.[1]

Prophylaxis and early treatment of other infections were clearly shown to improve the quality and length of life of people living with HIV, even before the advent of HAART. However, opportunistic infections continue to cause morbidity and mortality in HIV/AIDS patients even after ART. Some patients do not have a sustained response to antiretroviral agents for multiple reasons, including poor adherence, drug toxicities, drug interactions, or initial acquisition of a drug-resistant strain of HIV-1. Therefore OIs continue to cause substantial morbidity and mortality in patients with HIV-1 infection despite use of ART.

This document updates the 2002 guidelines for clinical management of HIV in adults. However, the approach differs in terms of arrangement and content. Key features of these guidelines are:

- They are developed by a panel of clinicians with wide experience in treating opportunistic infections, as well as in training health professionals in clinical management of such complications related to HIV/AIDS.
- Attempts have been made to ensure recommendations are complete and in agreement with other national guidelines and current medical recommendations.

- Recommendations are more user-friendly, mainly targeting low level health professionals

[1] Daniel et al EMJ

- They are intended to complement more comprehensive textbooks, journals, and other relevant informational materials
- They will require periodic updates based on local data and clinical experiences

2. Objectives and Targets

2.1. Objectives

- To provide standardized simplified preventive (prophylaxis) and management approaches to opportunistic infections common in Ethiopia
- To promote evidence-based, safe and rational use of OI drugs
- To demonstrate management of OI in the context of ART
- To prepare a reference manual for health service providers, program managers, and people living with HIV

2.2. Targets

- Health care workers caring for people infected with HIV
- HIV/AIDS program managers, health planners, and researchers
- Institutions involved in OI drug procurement and supply chain management

3. Management of Common Opportunistic Infections

Opportunistic infections are the predominant causes of morbidity and mortality among HIV-infected patients. Main areas affected are the nervous, gastro-intestinal and respiratory systems, and the skin. The level of immunity determines the occurrence and type of opportunistic infections. In general milder infections, such as herpes zoster and other skin infections, occur early whereas serious life- threatening infections such as CNS toxoplasmosis and cryptococcal meningitis occur later with severe immunity. Some life-threatening infections, such as pneumonia and TB, may occur early as well as later. When TB occurs later it is atypical, more disseminated and more extra pulmonary.

Although these guidelines are organised by systems, patients must be assessed and managed holistically since HIV disease is a multi-systemic condition. Concurrent infectious and non-infectious conditions, such as diabetes, hypertension and bronchial asthma, sometimes occur with OIs, and require appropriate management. Non-opportunistic pathogens such as M. Tuberculosis, Entamoeba histolytica or Strongyloids stercoralis, etc are frequent, severe and recurrent among patients with HIV disease. All patients with OI must be followed up after initiation of treatment; if there is no improvement, patients may be referred for better care or more thorough investigation if facilities permit. All patients must be enrolled in chronic HIV care services, including ART, after standard clinical and immunological assessments of eligibility are conducted.

Treatment of OIs entails administration of different drugs, therefore drug interactions, toxicities, and overlap toxicities should always be addressed, especially in patients already on ART and/or TB DOTS.

Unit 1: Management of OI of the Respiratory System.

Patients with HIV infection are vulnerable to respiratory diseases from early to advanced stages of AIDS. These can be infectious, neoplastic or related to problems outside the lungs, with concurrent or pre-existing lung conditions like hypersensitivity or chronic obstructive lung disease. The approach to respiratory dysfunction in HIV patients should be based on the same clinical considerations as for patients with normal immunity and conditions that occur during immune deficiency state.

The common respiratory diseases among people living with HIV are opportunistic infections, which occur across the spectrum of clinical HIV infection: infection by Streptococcus pneumoniae, Mycobacterium tuberculosis and Pneumocystis. jiroveci. Upper respiratory tract and lower respiratory tract infections are common but lower respiratory tract infections are life-threatening. This unit presents basic principles in diagnosis and treatment of the HIV-infected patient with respiratory disease. Emphasis is given to common aetiologies, clinical presentations, recommended investigations and treatment in resource-limited settings.

Management of patients with respiratory disease starts with taking a good history and meticulous physical examination of the upper and lower respiratory tracts, complemented by laboratory investigations, like sputum for gram stain and AFB, with chest X-ray in selected patients.

Upper respiratory tract diseases include pharyngitis, tonsillitis, rhinitis, sinusitis and otitis media. They occur relatively early, before advanced immune deficiency develops and thus constitute WHO stage II clinical conditions. The common organisms are Streptococcus pneumoniae, Staph aureus or H. influenza. Candida albicans is also a recognized cause of pharyngitis indicative of clinical stage III.

Diagnosis in Ethiopia is usually based on clinical examination only. In pharyngitis, the throat looks inflamed with hypertrophy and exudates formation on the pharynx. Otitis media presents with earache and headache associated with discharge from the external ear. This condition is common in children but also often seen in adult patients with HIV infection and hence PIHCT should be offered routinely. On examination there may be tragus tenderness with visible ear discharge and/or evidence of inflamed tympanic membranes on otoscope examination. Sinusitis produces facial pain and headache that is associated with post nasal drip. Usually the maxillary sinus is involved and patients will have tenderness over the cheeks and tender regional lymphadenopathy can be also detected. Oral candidiasis presents with oral sores, change in the sense of taste, and when it involves the throat and oesophagus, pain on swallowing; however it can be asymptomatic in some patients. Diagnosis is established clinically when a curd-like membrane is visible on the surface of the tongue and buccal mucosa. Typically the base of the membrane bleeds upon scraping it.

Treatment: the preferred regimen for bacterial URI is amoxicillin/clavulanic acid 625mg BID for seven to ten days. An alterative regimen is ampicillin or amoxicillin preferably extending the course of treatment to fourteen days. If penicillin allergy is a problem, CTM 960mg bid can be given for the same period. Give paracetamol for pain. It is necessary to document resolution of clinical findings after treatment and if not resolved refer to the next health facility. Oral and pharyngeal thrush are treated with oral miconazole gel 2% applied twice daily; patients should not eat/drink for two hours after applying the gel. If this does not work or is unavailable, use fluconazole 100mg daily for 14 days. This regimen is also effective for oro-pharyngeal candidiasis.

Common diseases of lower respiratory tract infections: include TB, bacterial pneumonia and PCP. The principal symptoms of respiratory diseases include cough, sputum production, chest pain, dyspnea, wheezing and haemoptysis but it is difficult to differentiate these by history and physical examination alone. In any case, the history should indicate whether onset of illness is acute or chronic and also record symptoms related to upper respiratory tract diseases like nasal discharge, sneezing, facial pain, stridor and tracheal pain. Some of these symptoms may be primarily due to illnesses outside the lungs, like congestive heart failure resulting from valve, myocardial and pericardial diseases.

Physical Examination:

- Assess vital signs, recording blood pressure, respiratory rate and temperature.
- Observe for evidence of distress, such as inability to talk, facial sweating, nasal flaring, use of accessory muscles, presence of central cyanosis and altered mental function. Presence of these signs indicates a need for consultation with experienced doctors for possible inpatient management or referral to next health facility.

By the end of the physical examination you should be able to formulate a differential diagnosis to explain the anatomic abnormality.

It is useful to consider the following during patient assessment

- ***Evidence of advanced immune deficiency state e.g. oral thrush etc.***
- ***Evidence for extra pulmonary involvement like meningitis, arthritis, hepatitis and pericarditis. Presence of these conditions usually warrants inpatient management.***
- ***Evidence for poor prognosis, like age over 60, severe distress manifested by tachypnea (RR>30/minute), cyanosis, grunting, retractions, multiple lobe involvement and systolic blood pressure below 80mmHg. These conditions necessitate inpatient management.***
- ***If the CD4 count is available, it is useful to consider the aetiological differential diagnosis (refer to Table 1)***

Table 1: Summary for CD4 correlates with respiratory diseases

CD4 count/µL.	Respiratory disease
Any CD4 count	• URI • Bacterial pneumonia • TB • Lymphoma • Non-specific interstitial pneumonias.
CD4 count <200	• PCP • TB but often disseminated • Cryptococcus pneumonia • Bacterial pneumonia often with bacteraemia or sepsis.
CD4 count <100	• Bacterial pneumonia due to *Pseudomonas aeruginosa* • *Toxoplasmosis* • *Kaposi*
CD4 <50	• MAC • CMV • Fungal infections

Bacterial pneumonia.

This can occur in immune-competent individuals but the risk increases six-fold among HIV-infected individuals. Bacterial pneumonia occurs during the whole spectrum of HIV disease, but tends to be more severe and recurrent as the CD4 counts drops significantly; in addition pneumonia can concomitantly present with sinusitis and/or bacteraemia. If not treated promptly, extra pulmonary complications like empyema, meningitis, pericarditis, hepatitis and arthritis can follow. *Streptococcus pneumoniae* and *Haemophylus influenzae* are the most common aetiologies of community acquired pneumonia. Typically the patient presents with sudden onset of cough, sputum production, chest pain, fever and/or shortness of breath.

Diagnosis: The clinical suspicion is based on a history of acute symptoms presented over days to a few weeks and/or abnormal physical signs of systemic infection and consolidation in the affected lung/s. Gram stain of sputum is useful to confirm diagnosis of pneumonia and possibly to predict the organism causing it. Chest X-ray can be useful in diagnosis of bacterial pneumonia but can be non- specific in advanced immune deficiency stage. Refer to algorithm.

Treatment: Amoxicillin is the drug of choice for community-acquired bacterial pneumonia. Start with 500mg tid for ten days. In patients with penicillin allergy use erythromycin 500mg qid for the same duration. Follow up is necessary to document resolution of initial symptoms or to monitor complications. Moreover, the patient has to be staged to determine eligibility for ART. When the patient has presented with clinical evidence of severe pneumonia, which includes tachypnea (RR>30/minute), old age (>70 years), cyanosis, hypotension, systolic blood pressure <80mm Hg, multilobar involvement and altered mental status, admit for parentral antibiotic treatment and supportive therapy or refer the patient if admission is impossible.

1.2. Pneumonia due to *Pneumocystis jiroveci*

The cause of pneumocystosis (*P jiroveci)* is a fungal agent. Frequently PCP occurs when the CD4 count drops below 200cells/μL, indicating primary prophylaxis with cotrimoxazole. This disease was common in North America before the advent of ART but is less apparent in Africa, including Ethiopia; however this could be due to underreporting or failure to diagnose it correctly. Nevertheless a good number of patients in Ethiopia are diagnosed empirically for treatment of PCP**.** Typical clinical presentations are characterized by insidious onset of low grade fever, dry cough, and dyspnea exacerbated by exertion. Physical examination often reveals fever, tachypnea, tachycardia and scattered rales in the lungs but examination of the lungs can appear normal in some patients.

Diagnosis: Presumptive diagnosis of PCP is based on clinical judgement and typical chest X-ray findings revealing a perihilar interstitial infiltration with tendency to spread outwards. Note that the chest X-ray can be normal in 20% of patients. Definitive

diagnosis of PCP is based on demonstration of the organism from an induced sputum sample using special stains like Giemsa or methylamine silver stains, but these tests are not routinely done in Ethiopia.

Treatment: use Trimethoprim 15-25 mg/Kg, which amounts to cotrimoxazole 3- 4 single-strength tablets three or four times daily for 21 days. Close monitoring is necessary during the initial five days of treatment and if patient grows sicker, administration of oxygen is useful. In severely ill patients with marked respiratory distress and extensive chest X-ray findings, prednisolone has to be given simultaneously; 80mg for the first five days, 40 mg until 11 days and 20 mg until completion of cotrimoxazole. Toxicity of cotrimoxazole, like skin rash, bone marrow suppression, hepatitis and renal failure can be troublesome in some patients with advanced HIV disease and requires close monitoring. Alternative regimens for mild to moderate cases of PCP include:

1. clindamycin 600 mg qid plus primaquine 15 mg bid

or

2. clindamycin 600 mg qid plus dapsone 100 mg daily.

- Secondary prophylaxis after completion of the course of treatment with cotrimoxazole should be started (refer to national ART guideline). In addition, the patient has to be prepared for ART as s/he is automatically eligible for ART regardless of the CD4 count.

1.3. Pulmonary Tuberculosis.

M. tuberculosis is the leading cause of morbidity and mortality among PLWHA worldwide. In Ethiopia the co-infection rate is 20-50% creating a dual epidemic of symptomatic HIV infection and tuberculosis. Tuberculosis enhances progression of HIV infection by inducing immune activation, and HIV increases the risk of infection as well as reactivation of latent tuberculosis. Hence it is conceivable that tuberculosis can occur across the clinical spectrum of HIV infection.

Tuberculosis can cause pulmonary and/or extra-pulmonary symptoms depending on the degree of immune suppression. In patients with good immunity, tuberculosis typically involves the apical lung fields and causes either cavitations or fibrosis visible in a chest X-ray. However, in patients with CD4 count below 200 cells/µL, tuberculosis is often atypical, with lower zone infiltration on chest X-ray and tends to be extra-pulmonary; e.g. pleural effusion, scrofula, meningitis and other form of tuberculosis.

A TB suspect is a patient with persistent cough and/or sputum production of longer than two weeks with constitutional symptoms including fever, weight loss and anorexia. This mode of presentation indicates pulmonary tuberculosis, which is the major form in both HIV positive and negative patients. Symptoms of extra pulmonary disease are more common in patients with HIV co-infection particularly when the CD4 count is low. Systemic symptoms like fever, sweating, weight loss and cough

are non-specific manifestations of many complications of HIV, but the health worker should consider tuberculosis as a first possibility. Offer HCT for all TB suspects and refer co-infected individuals to HIV care and treatment.

Diagnosis: tuberculosis is likely when any of the following is detected singly or in combination:

1. Specific radiological findings on chest CX-ray, which include apical fibrosis or cavity lesion.
2. Typical findings of epitheloid cells with caseous formation on cytological or histological examination of tissue sample or bacteriologic tests, such as smear and culture, from infected sample

Definitive diagnosis of tuberculosis is however based on isolation of *Micobacterium tuberculosis* on culture media. This test is not widely available in Ethiopia and therefore is seldom done. In most health facilities in Ethiopia pulmonary tuberculosis is diagnosed when two sputum samples are positive for acid fast bacilli or one sample is positive for AFB and the chest X-ray shows typical radiological features.

Tuberculosis can present as immune reconstitution syndrome following commencement of HAART. These patients need to be treated for tuberculosis and continue taking ART, but drug toxicity and interactions should be monitored strictly; refer to ART guideline.

Treatment: TB treatment has two phases: an intensive phase of 8 weeks followed by a continuation phase of 4-6 months, depending on the regimen used. Selection of the regimen depends on the treatment category of the patient (refer to TB-leprosy manual for details). A new TB patient co-infected with HIV belongs to category I and accordingly the following drugs are used (refer to national TB manual for treatment details for the remaining categories);

1. Intensive phase: rifampicin, isoniazid, ethambutol and pyrazinamide for 8 weeks. Follow patients for clinical evidence of hepatitis. Bear in mind that drug interactions of nevirapine with rifampin can occur and potential additive toxicity to the liver when ARVs are used with anti-TB drugs during this phase.
2. Continuation phase: INH with ethambutol* for six months.

Atypical mycobacterium infections among HIV infected individuals are uncommon in Ethiopia. In one study only two cases of MAC were reported among patients with pulmonary TB and HIV infection in Ethiopia♥.

* This regimen is associated with high recurrence rate of active tuberculosis after completion of treatment.
♥ Getachew etal.

Table 2: Summary of main respiratory infections

Aetiology	Clinical findings	Lab investigations	Characteristic Radiological` changes	1st line drug/s
Bacterial pneumonia	Fever, productive cough, dyspnea and tachypnea < 2 weeks. Abnormal findings on auscultation common.	Leukocytosis; Positive blood culture; Suggestive Gram stain	Lobar consolidation	amoxicillin
PCP	Dyspnea, dry cough, retrosternal pain; on inspiration and normal to few scattered rales on auscultation.	Identification of organism on sputum stain; De-saturation of arterial blood.	Peri hilar and interstitial infiltration	Cotrimoxazole for 3 weeks.
Tuberculosis	Chronic fever, cough, sputum production, night sweating, hemoptysis, adenopathy.	Sputum examination for AFB; AFB on aspirate from lymph node; Culture for MTB from sputum, blood or tissue aspirate when ever possible.	Upper lobe consolidation, cavitations or fibrosis.	2RHZE/6HE.

1.4. Correlation of pulmonary diseases and CD4 count in HIV infected patients.

Differential diagnosis of respiratory disease can be narrowed if the CD4 count is determined; when it is above 200cells/µL, diagnosis is either bacterial pneumonia or tuberculosis. If available, a chest X-ray is useful to influence diagnosis because these illnesses have specific or characteristic radiological features when the CD4 count is above 200. However, the differential diagnosis accuracy decreases as the CD4 count declines below 200cells/µL, although a chest X-ray can still be helpful to suggest the probable diagnosis. It is sensible not to delay treatment, but empirical treatment without establishing the cause is seldom justifiable, refer to Table 3.

Table 3: Diagnostic approach when a patient presents with respiratory symptoms and a CD4 count >200 cells/µL or <200 cells/µL

Chest X-ray abnormality	Clinical presentation	CD4 >200 and possibility	CD4 <200 and possibility	Action	Remarks
Normal	Patient appears well or Patient is ill	Consider URI or early/ incubating infection	Consider URI, PCP, TB or cryptococcal infection	Follow up With symptomatic therapy	PCP is common below 200 CD4 count and can present as normal in 20% of cases. Rarely TB in advanced immune suppression. *Ideally broncho alveolar lavage will be useful.* *Empirical therapy for PCP is justified in the Ethiopian setting if patient appears dyspnic and sputum is not yielding AFB.*
Alveolar /reticular	Acute onset 5-7 day	Consider bacterial pneumonia	Consider bacterial pneumonia	Sputum gram stain Empiric treatment	Avoid using CTM for treatment of BP
	Sub acute onset >2 weeks	Consider TB	Consider TB, PCP, lymphoma KS	Sputum AFB.	Often difficult to differentiate TB and PCP radio logically. Decision has to be based on clinical presentation and sputum result for AFB. Kaposi usually present with concomitant mucosal dermal lesions.
Cavitory	Sputum production , hemoptysis	TB Lung abscess Nocardia	TB, lung abscess Nocardia	Sputum AFB. Consider anti-TB treatment.	TB is the common cause of cavitations.
Miliary	Patient is usually ill	TB	TB and rarely fungal infections.	Sputum AFB Empirical treatment	In most patients CD4 is very low and watch for IRIS.
Nodular	< 1 CM	TB Bacterial pneumonia	TB Bacterial pneumonia	Sputum for Gram stain or AFB	Decide treatment based on the clinical course.
	>1cm	TB	TB, lymphoma	Sputum AFB	Tissue diagnosis is preferable; decision to treat needs expert opinion.
Diffuse/bilateral	Acute onset in one week	Consider bacterial pneumonia	Consider bacterial pneumonia	Sputum Gram stain Empiric treatment for BP	Do not use cotrimoxazole to treat bacterial pneumonia.
	Sub acute onset >2weeks	TB	TB, PCP	Sputum AFB Treat for TB or PCP based on sputum result.	Concomitant infection with TB and PCP is possible if CD4 is below 200/µL.

Unit 2: Management of Gastrointestinal Opportunistic Diseases

The GI OI diseases commonly manifest with diarrhoea, nausea and vomiting, dysphagia and odynophagia among others. There are a number of opportunistic and pathogenic organisms causing GI disease in patients infected with HIV.

A scenario of multiple concurrent GI infections is fairly common. The general principle of managing GI opportunistic infections is identifying and treating the specific offending agent providing supportive care to monitor situations such as fluid loss. A number of drugs can cause adverse effects that present with clinical manifestations referable to GIS. The clinical presentations may be similar to manifestations of OIs of the GI, posing challenges to successful differential diagnosis.

2.1. Dysphagia and odynophagia

Dysphagia (difficulty in swallowing) and odynophagia (painful swallowing) are symptoms of oesphagitis occurring at advanced stages of AIDS. They are usually caused by candida, HSV, CMV, and aphthous ulcers. As well as a sign of severe immunodeficiency, esophagitis also seriously impairs the patient's nutritional status. Therefore prompt diagnosis and treatment are mandatory to avert nutritional complications among other things.

Diagnosis: is frequently made on clinical grounds, but when facilities are available upper GI endoscopy with or without biopsy may be done.

Treatment: Dysphagia and/or odynophagia are treated as oesophageal candida on clinical grounds, in particular when oropharyngeal candida is present. Thrush or oropharyngeal candida is characterized by white, painless, plaque-like lesions on the buccal surface and/or tongue. Patients are empirically treated with Fluconazole in presumptive oesophageal candida. If the response is unsatisfactory they are referred or investigated if facilities are available, to rule out other causes. Patients with dysphagia and/or odynophagia appear to be in stage IV of HIV disease; therefore, the necessary baseline assessment and counselling must be done in order to put them on ART.

Drug of choice: Fluconazole 200 mg PO daily for 14 days

Alternatively, ketoconazole 200 mg twice daily for 4 weeks.

Risk of recurrence after completing treatment may be high. Patients should be re-treated and ART initiated after the appropriate workup, if patient is not already on ART. If the patient is on ART, s/he should be investigated for treatment failure. Take necessary precautions regarding drug interactions especially with ketoconazole. Patients may need hospital admission for supportive care till the oesophageal symptoms improve and necessary long term treatments are started.

Diarrhoea

Diarrhoea is defined as passing more than four loose or watery stools/day for >3 days. It may be acute or chronic, persistent or intermittent. Diarrhoea is among the most frequent symptoms of HIV disease. Delay in treatment can result in fluid loss and hemodynamic instability. Chronic diarrhoea may also lead to nutritional deficiencies and wasting. Diarrhoea is caused by opportunistic or pathogenic organisms, such as viruses (including HIV), bacteria, protozoa, fungi, helminthic, non-infectious causes and drugs. (Diarrhoea occurs as an adverse reaction to a number of drugs).

Diagnosis: Investigate the duration, volume, frequency, consistency of stools as well as any history of abdominal pain, tenesmus, nausea, vomiting, and presence of constitutional symptoms such as fever. Thorough physical examination is necessary to find out the state of hydration and the status of HIV disease among other things.

Laboratory evaluation: Stool microscopy including modified acid fast stain
Stool culture when indicated (optional)

Management: The most important first step is correction of fluid loss. Depending on the severity of dehydration, ORS or IV fluid therapy can be given. Patients with severe dehydration are admitted for intravenous fluid administration.

Table 4: Management of dehydration

Two of the following signs: • Lethargy or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin when pinched goes back very slowly • Systolic blood pressure (SBP)<90	Severe Dehydration	• Start intravenous fluid immediately. If the patient can drink, give ORS while the drip is set up. Give 100ml/kg Ringer's lactate solution or normal saline(30ml/kg in 30 minutes and the rest 70ml/kg in 2.5 hours) • Reassess the patient every 1-2 hours. If hydration status is not improving apply intravenous drip more rapidly. • Also give ORS as soon as the patient can drink.
Two of the following signs: • Sunken eyes • Drinks eagerly, thirsty • Skin when pinched goes back slowly	Some Dehydration	• Give in clinic at least 2200-4000ml ORS over 4 hours • Give frequent small sips • Reassess after 4 hours and classify for dehydration
Not enough signs to classify as some or severe dehydration	No Dehydration	• Advise on Drinking extra fluid Continue eating When/if to return immediately

If specific enteric pathogen is identified or strongly suspected on clinical grounds, it should be treated accordingly.

Table 5: Treatment of specific enteric pathogens

Agent	CD4	Symptom	Diagnosis	Rx
E. hystolytica	any	bloody stool, colitis	Stool microscopy	Metronidazole
Giardia	any	Watery diarrhoea	Stool microscopy	Metronidazole
Cryptosporidium	<150	Watery diarrhoea	Modified AFB	ART
Isospora belli	<100	Watery diarrhoea	Modified AFB	TMP-SMX
Microsporidium	< 50	Watery diarrhoea	Giemsa stain	Albendazole
CMV	<50	Watery/bloody diarrhoea, colitis	Tissue biopsy	Ganciclovir

Patients with bloody diarrhoea but repeatedly negative stool results: empirical treatment with ciprofloxacin or norfloxacin can be given, especially when patient has constitutional symptoms such as fever.

Symptomatic treatment: Use anti-diarrhoeal agents Loperamide 4mg stat then 2mg after each bowel motion or Diphenoxylate 5mg QID. Necessary caution should be taken to avoid anti-diarrhoeal agents in bacterial or parasitic infectious colitis or enteritis, since toxic mega colon may occur.

Patients with chronic diarrhoea develop nutritional deficiencies of variable severity; therefore proper nutritional assessment and support are helpful.

2.3 Peri-anal problems

A number of chronic or acute peri-anal problems commonly occur in patients with HIV disease, particularly in advanced stages of immunodeficiency. These include recurrent peri-anal abscesses, chronic peri-anal fistula, peri-anal herpes (severe, persistent and extensive), and peri-anal warts (sometimes largewith obstructive problems). Patients with peri-anal problems frequently go to local healers and receive different kinds of local therapy that usually complicate the situation. All patients with such problems deserve PIHCT. Then the necessary assessment and preparations are done to to enroll patients in chronic HIV care including ART.

Treatment of peri-anal abscess: It is not difficult to make the clinical diagnosis of peri-anal abscess. All patients with acute or chronic peri-anal condition must be thoroughly evaluated and per rectum done routinely. Peri-anal abscess may extend depending on the immunological status of the patient; therefore early treatment is mandatory to avoid this and more serious morbidity. If patients require surgical incision, it should be done promptly on first visit, or referral made if the surgery is unavailable. Otherwise, broadspectrum antibiotics such as amoxacillin-clavulanic acid (augmentin) alternatively amoxacillin or ampicillin must be administered in sufficient dose for at least 10 days. Palliative care including Sithz baths and analgesics are also important. Ultimately these patients are enrolled in chronic HIV care.

2.4. Peri-anal and/or genital herpes:

Latent or active infection with HSV I and II are common in the general population, and is usually mild in immunocompetent persons. Severe cutaneous disease or visceral involvment is usually restricted to patients with advanced immunosuppression with a CD4 count <100 cell/mm^3

The lesions become extensive, persistent, severe and sometimes bleeding. Unless thorough evaluation with regular inspection of genital and peri-anal areas is done, patients very often don't complain about genital lesions. The response to Acycovir is gratifying if it is done in sufficient dose (400mg 4 to 5 X/d) and sufficient duration (10 days to 2 weeks in moderately severe or severe cases). IV Acyclovir may be administered for severe mucocutaneous disease or visceral involvement (5mg/Kg IV 8 hourly for 2 weeks, switched to oral with evidence of clinical improvement). There is risk of recurrence with severe immunodeficiency. In such cases repeat treatment and put patient on chronic HIV care including ART. Herpetic oro-labial infection is treated the same way as ano-genital herpes.

The treatment of anal and genital warts is particularly frustrating when they are large. Unlike other opportunistic infections the response to ART is not satisfactory. Patients who have very well responded immunologically with ART continue to suffer from the warts. Depending on the size,cauterization, podophyllin treatment and surgical debuking, etc may be tried. Patients are referred to where these services are available.

Unit 3: Management of Opportunistic Diseases of the Nervous System

Neurological manifestations of HIV can occur at any time from viral acquisition to the late stages of AIDS; they are varied and may affect any part of the nervous system including the brain, spinal cord, autonomous nervous system and the peripheral nerves. HIV affects the nervous system in 70-80% of infected patients. The effect may be due to direct effect of the virus, opportunistic infections and/or malignancies. For certain neurological manifestations a single aetiology is responsible while in others it is due to multiple causes.

Most life-threatening neurological complications of HIV occur during the severe immunodeficiency state and specific aetiological diagnosis in the Ethiopian setting is often a major challenge. Thus, this unit attempts to guide the management of common opportunistic infections and other treatable conditions in the nervous system

Diagnosis of neurological disorders in HIV in our setting depends on the history and standard neurological examinations. In view of this, health care providers must be able to perform a physical examination to detect neurological abnormalities. There can be single or multiple abnormal neurological findings in the same patient necessitating holistic neurological evaluation. Thus the examination should include assessment of:

- Mental status comprising cognitive function, orientation and memory.
- Cranial nerves
- Motor function including DTR
- Sensation

Table 6: Summary of common HIV-associated neurological and related syndromes

Syndrome	Possibilities	Diagnosis
Painful legs (extremities)	Peripheral neuropathy, metabolic disorders or vascular insufficiency.	Hx, Px, NCT
Difficulty walking	Musculoskeletal disorders, Spinal cord lesions, Myopathies, peripheral neuropathies, or some brain lesions.	Spinal X-ray,, CT, MRI, CK, LDH LP when indicated
Severe headache +/- focal neurological deficit +/- seizure	Meningo encephalitis, Meningitis, CNS Toxoplasmosis, brain abscess, Tuberculoma, CNS lymphoma.	Imaging (CT, MRI) LP when indicated
Acute confusion	1. Meningo-encephalitis 1- Systemic infections like malaria, or septicaemia, 2- Metabolic disorders: – electrolyte abnormalities, hypoglycemia, renal or liver failure	Blood film, CBC, blood culture, LP (CSF analysis) RFT, LFT, RBS electrolytes if diarrhoea or dehydration present
Chronic behavioral change	PML* AIDS dementia, Chronic meningitis.	Clinical CSF analysis

Always exclude local causes.
*Has associated neurological deficits.

3.1. Peripheral Neuropathies

Peripheral neuropathies are among the most common causes of painful legs in HIV infection; they arise as a complication of HIV infection itself, of drug therapy, or of other metabolic or organ dysfunction or nutritional deficiencies.
Distal symmetrical sensory polyneuropathy is the most common presentation but mono-neuropathies can also occur. The neuropathies associated with HIV can be classified as:

- Primary, HIV-associated
- Secondary causes related to medications, OIs or organ dysfunctions

Diagnosis: Peripheral neuropathy diagnosis in HIV-infected patients is based on the clinical picture presenting with pain, tingling sensations, paresthesia or numbness. Physical examination can reveal depressed or absent ankle reflex, decreased sensitivity to different modalities of sensation and in severe cases, difficulty in walking. The feet and sometimes the hands are involved in symmetrical distribution. The diagnosis can be supported by electro diagnostic studies including electromyography (EMG) and nerve conduction studies (NCS) when available. Blood tests are frequently obtained to exclude other causes of neuropathy. In most instances, however, diagnosis is almost always clinical.

Treatment

- Avoid the offending agent if identified
- Substitute or switch drugs such as d4T/DDI when the neuropathy is severe
- Remove other drugs associated with peripheral neuropathy
- Supplement vitamin intake for all patients including concomitant administration of pyridoxine with INH.
- Adjuvants for pain management indicated for patients with pain and paresthesias only.

Monitoring of events

- Recognize presence of peripheral neuropathy
- Asses severity at each clinical visit
- Avoid drugs causing neuropathy

3.2. Persistent headache with (+/-) neurological manifestations +/- seizure

Headache is a very common symptom, found in diverse clinical conditions; when persistent and not improving with analgesics, it might indicate a serious underlying condition particularly if accompanied by neurological abnormalities.

Approaches to management of persistent headache in HIV infection include:

- exclude local causes e.g. sinusitis, dental abscess
- perform clinical assessment for presence of neurological signs or symptoms
- look for evidence of meningismus or space occupying lesion
- *if there is a sign of space occupying lesion* look for papilloedema or focal neurological deficit
- consider toxoplasmosis, brain abscess, tuberculoma, CNS lymphoma
- Perform lumbar puncture, *if there are signs of meningitis;* however deep coma, recurrent seizure and hemiparesis with or without papilloedema are contraindications to lumbar puncture.

3.3. Management of common CNS infections presenting with headache and/or seizure

3.3.1 Toxoplasmosis

CNS toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. In immuno-suppressed individuals the disease occurs almost exclusively due to reactivation of latent infection. Seroprevalence varies substantially in different communities; in Ethiopia, general prevalence is about 80% in the adult population. Clinical disease is rare among patients with $CD4^+$ T lymphocyte counts >200 cells/μL. The greatest risk is among patients with a $CD4^+$ T lymphocyte count <50 cells/μL.

Clinical manifestations: The most common clinical manifestations of toxoplasmosis among patients with HIV infection are headache, confusion, and/or motor weakness and fever. Physical examination might demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Other unusual and relatively rare presentations may include retinitis, pneumonia, and evidence of other multifocal organ involvement due to dissemination of infection. CT scan or brain MRI will typically show multiple contrast-enhancing lesions, often with associated oedema.

Diagnosis: HIV infected patients with CNS toxoplasmosis are mostly seropositive for anti-toxoplasma IgG antibodies. A positive result does not support the diagnosis. However, absence of the IgG antibody makes a diagnosis of toxoplasmosis unlikely. Anti-toxo plasma IgM antibodies are usually absent and if present show a more recent infection.

Definitive diagnosis of CNS toxoplasmosis requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample. *In the absence of imaging support, empirical treatment is justified when patients present with focal neurological findings and the CD4 count is < 200 cells μL. Failure to respond to conventional therapy, based on presumptive clinical diagnosis within a week or two of initiation of therapy, suggests the diagnosis is unlikely*.

With empirical treatment for toxoplasmosis, nearly 90% of patients will demonstrate clinical improvement within days of starting therapy. Radiological evidence of improvement is usual after 14 days of treatment.

Treatment: Initial therapy of choice consists of a combination of pyrimethamine,sulfadiazine and leucovorin. Pyrimethamine penetrates the brain parenchymal efficiently even in the absence of inflammation.

First-line regimen in ideal circumstances:

Sulfadiazine, 1-2 gm p.o.q 6h for six weeks or 3 weeks after resolution of lesion

S/E: crystal urea, rash

C/I: severe liver, renal and hematological disorders; known hypersensitivity to Sulfonamides

Dosage/form: 500 mg tablets,

PLUS

Pyrimethamine

Loading dose of 200 mg once, followed by:

Pyrimethamine 50-75 mg/day

S/E: rash, fever and bone marrow depression (neutropenia and thrombocytopenia)

C/I: folate deficiency

Dosage/form: 25 mg tablets

PLUS

Folinic acid (Leucovorin)**:** 10-20 mg/d

S/E: allergy

Dosage/form: 5 and 10 mg tablets

OR

Pyrimethamine and Folinic Acid (Leucovorin): (standard dose)

PLUS

Clindamycin: 600 mg q 6 hrs

S/E: toxicities include fever, rash, and nausea, diarrhoea (including pseudomembranous colitis or diarrhoea related to *Clostridium difficile* toxin)

OR

Pyrimethamine and **Folinic acid (Leucovorin):** (standard dose)

PLUS

Azithromycin: 900-1200 mg PO qd

However the 1st line regimen in the Ethiopian context is:

1. Sulfadoxine/pyrimethamine (Fansidar): 500 mg/ 25 mg po b.i.d for two days, followed by once daily both for four (4) weeks is given together with Folinic acid (10 mg daily)

S/E: Occasional: anaemia- need Folinic Acid

Rare: pancytopenia; hepatitis; GI intolerance

C/I: Foliate deficiency

Dosage forms: 500/ 25 mg tabs or IV vials

PLUS

Folinic acid: 10-20 mg/d

2. The alternative regimen in Ethiopia is cotrimoxazole 15 mg /Kg

Trimethoprim in three divided doses daily when Fansidar cannot be administered safely.

*__Corticosteroids (dexamethasone__ 4mg PO or IV q6hrs) used if cerebral oedema present, discontinued as soon as clinically feasible. Corticosteroids might mask the evaluation of the clinical response particularly when therapy is initiated empirically.

3.3.2. Management of seizure associated with toxoplasmosis and other CNS OIs

CNS toxoplasmosis or other CNS OIs can present with seizure activity which can be focal or generalized. When such conditions occur, due attention should be given to control the seizure on top of managing the underlying conditions.

Management of seizure or epilepsy

Approach for patients with seizures or epilepsy

- The seizure type(s) and epilepsy syndrome, aetiology, and co morbidity should be determined
- All individuals with epilepsy should have a comprehensive care plan at primary and secondary health care providers
- The antiepileptic drug (AED) treatment strategy should be individualized according to the seizure type, epilepsy syndrome, co-medication, co- morbidity, lifestyle, and individual preference
- All patients noted or suspected of having seizures should be seen urgently by a care provider, for early diagnosis and initiation of therapy appropriate to their needs

Seizure is a common manifestation of toxoplasmosis and rarely crypto meningitis. Other rare causes of seizure include mass lesions like lymphoma, metabolic disorders, systemic infections or idiopathic causes. Seizure activity may be detected during jctal or post ictal period and the management approach includes the following:

Ictal phase

- Apply ABC of seizure
    - secure airway and put gag in the mouth
    - administer oxygen
    - give 40% glucose and B1 when applicable
    - draw blood for appropriate laboratory tests
    - slowly administer Diazepam 5-10 mg possibly repeat dose according to need and then Dilantinization
    - refer or consult specialist while stabilizing or after ictal period

Post-ictal phase

- Consider long term management
- Start with phenytoin 100 mg t.i.d following Dilantinization or Phenobarbitone 100 to 200 mg / day can be given
- Form long term treatment plan or refer to specialist

Monitoring Adverse Events

- Changes in antibody titers are not useful for monitoring responses to therapy
- Patients should be routinely monitored for adverse events and clinical and radiological improvement. Common pyrimethamine toxicities include rash, nausea, and bone-marrow suppression
- Laboratory monitoring to assess bone marrow depression to detect neutropenia, anaemia, and thrombocytopenia that can often be reversed by increasing the leucovorin to 50-100mg/day administered in divided doses
- Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhoea, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhoea (including pseudo membranous colitis or diarrhoea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity.
- Drug interactions between anticonvulsants and ARVs should be carefully evaluated and doses adjusted according to established guidelines
- Restart secondary prophylaxis if CD4 of patient with history of previous clinical toxo drops <100 cells/μL (i.e. while on ART)

Prevention of Recurrence

Primary prevention: CNS toxoplasmosis in HIV infection in advanced stage of immuno-suppuration. TMP-SMX administered for prophylaxis of PCP can be used to prevent CNS toxoplasmosis.

Indication: Patients whose CD4 count drops below <100 cells/mm with positive toxoplasma serology test

Secondary prevention

- Patients who have successfully completed a 6-week course of initial therapy for Toxo should be administered lifelong secondary prophylaxis (i.e.chronic maintenance therapy) unless immune reconstitution occurs because of ART.
- TMP-SMX can be substituted as a secondary prophylaxis after the initial phase of therapy is completed particularly for patients on Fansidar.
- Adult and adolescent patients appear to be at low risk for recurrence of CNS toxoplasmosis when they have successfully completed initial therapy, remain asymptomatic and have a sustained (i.e., $\geq$6 months) increase in their $CD4^+$ T lymphocyte counts to >200 cells/μL on ART.
  Secondary prophylaxis should be resumed if the $CD4^+$ T lymphocyte count decreases to <200 cells/μL

3.3.3 Cryptococcosis

HIV-associated cryptococcal infections are caused by *Cryptococcuss*. Before the advent of ART, approximately 5-8% of HIV infected patients in developed countries acquired disseminated cryptococcosis, but incidence declined substantially with the use of effective ART. The majority of cases are observed among patients with $CD4^+$ T lymphocyte counts of <50 cells/μL.

Clinical Manifestations: Cryptococcosis among patients with AIDS most commonly occurs as a sub acute meningitis or meningoencephalitis with fever, malaise, and headache.

Classic meningeal symptoms and signs (e.g., neck stiffness or photophobia) occur in approximately one fourth to one third of patients. Certain patients might present with encephalopathic symptoms e.g. altered mentation, personality changes and memory loss.

The CSF usually indicates a mildly elevated serum protein, normal or slightly low glucose, and a few lymphocytes and numerous organisms. The opening pressure in the CSF is elevated (with pressures >200mm of water) in the majority of patients. Disseminated disease is a common manifestation, with or without concurrent meningitis. Approximately half of patients with disseminated disease have evidence of pulmonary involvement. Skin lesions might be observed.

Diagnosis depends on laboratory evidence of infection in the CSF. Indian ink staining of CSF demonstrates the organism in up to 60% of cases. Cryptococcal antigen is almost invariably detected in the CSF at high titer in patients with meningitis or meningoencephalitis. Up to 75% of patients with HIV-1-associated cryptococcal meningitis have positive blood cultures. The serum cryptococcal antigen is also usually positive and detection of cryptococcal antigen in serum might be useful in initial diagnosis. Deep coma, high opening pressure and/or high CRAG titer in the CSF often indicate a poor prognosis.

Treatment Recommendations: Untreated cryptococcal meningitis is fatal.

First-line treatment: The recommended initial treatment for acute disease is **amphotericin B**, usually combined with **flucytosine**, for 2 weeks, followed by fluconazole alone for 8 weeks.

Non-liposomal amphotericin B is the standard treatment during induction of crypto treatment in the Ethiopian context. The dose is 0.1 mg/kg testing dose to be escalated to 0.6-1 mg/Kg for 2 weeks. Lipid formulations of amphotericin B appear effective and safe but very expensive. The optimal dose of lipid formulations of amphotericin B is 4 mg/kg body weight/daily.

After a 2-week period of successful induction therapy, consolidation therapy should be initiated with **fluconazole** administered for 8 weeks or until CSF cultures are sterile.

Alternative treatment: Therapy with **fluconazole alone** at a dose of 400-800 mg/daily is effective for treating AIDS-associated cryptococcal meningitis.

Increased intracranial pressure might cause clinical deterioration despite a microbiologic response, probably reflects cerebral oedema, and is more likely if the CSF opening pressure is >200mm H_2O. The opening pressure should always be measured when a lumbar puncture is performed.

The principal initial intervention for reducing symptomatic intracranial pressure is repeated daily lumbar punctures. CSF shunting should be considered for patients in whom daily lumbar punctures are no longer tolerated or signs and symptoms of cerebral oedema are not relieved.

***Corticosteroids (Dexamethazone)** – Unlike with other situations of intracranial pressure, these drugs have no beneficial effect.

Seizure activity associated with Cryptococcus meningioencephalitis
See CNS toxoplasmosis associated seizure

Monitoring Adverse Events

- Infusion of test dose (0.1mg/kg) before initiation of Amphotericin standard dose is important to avoid anaphylactic reaction
- A repeat lumbar puncture to ensure clearance of the organism is not required for those with cryptococcal meningitis and improvement in clinical signs and symptoms after initiation of treatment. If new symptoms or clinical findings occur after two weeks of treatment, a repeat lumbar puncture should be performed.
- Serial measurement of CSF cryptococcal antigen or culture or Indian ink staining might be more useful but requires repeated lumbar punctures and is not routinely recommended for monitoring response.
- Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Infusion-related adverse reactions (e.g., fever, chills, renal tubular acidosis, hypokalemia, orthostatic hypotension, tachycardia, nausea, headache, vomiting, anaemia, anorexia, and phlebitis) might be ameliorated by pre-treatment with acetaminophen, diphenhydramine, or corticosteroids administered approximately 30minutes before the infusion. Lipid formulations of amphotericin B are less toxic.

Prevention of Recurrence

Secondary prevention: Patients who have completed initial therapy for cryptococcosis should be administered lifelong suppressive treatment (i.e. secondary prophylaxis or

chronic maintenance therapy), unless immune reconstitution occurs as a consequence of ART.

Secondary prevention can be discontinued when CD4 remains above 200/dl for 3-6 months.

Adult and adolescent patients appear at low risk for recurrence of cryptococcosis when they have successfully completed a course of initial therapy, remain asymptomatic regarding cryptococcosis, and have a sustained increase (i.e. $\geq$6 months) in their $CD4^+$ T lymphocyte counts to >100-200 cells/μL after ART. On the basis of these observations and inference from more extensive data regarding safety of discontinuing secondary prophylaxis for other opportunistic infections during advanced HIV-1 disease, discontinuing chronic maintenance therapy among such patients is a reasonable consideration.

Maintenance therapy should be re-initiated if the $CD4^+$ T lymphocyte count decreases to <100-200 cells/μL.

3.3.4 CNS Tuberculosis

Central nervous system tuberculosis includes three clinical categories: meningitis, intracranial tuberculoma, and spinal tuberculosis. All three forms of CNS infection are encountered frequently in regions of the world where the TB incidence is high and prevalence of post-primary dissemination common among children and young adults.

Early recognition of TB meningitis is of paramount importance, particularly in Ethiopia, where TB prevalence is high and because the clinical outcome depends greatly upon the stage at which therapy is initiated. Empirical antituberculous therapy should be started immediately in any patient with meningitis syndrome and cerebrospinal fluid (CSF) findings showing low glucose concentration, elevated protein, and lymphocytic pleocytosis with or without evidence of TB elsewhere in the body, and when prompt evaluation fails to establish an alternative diagnosis.

Meningitis develops most commonly as a complication of post-primary infection in adults with HIV infection. Signs and symptoms may include a prodromal phase characterized by insidious onset of malaise, lassitude, headache, low-grade fever, and personality change. The meningitis phase follows with more pronounced neurological symptoms, such as meningismus, protracted headache, vomiting, confusion, and varying degrees of cranial nerve palsy followed by confusion, stupor and coma, seizures, and at times hemi paresis. Fundoscopic examination should be done routinely to exclude papilloedema before doing a lumbar puncture.

Abnormalities on chest X-ray occurs in 50%of patients, ranging from focal lesions to a subtle miliary pattern. A tuberculin skin test will be positive but may not be important in our setup, although a negative result does not exclude the diagnosis.

As noted above, diagnosis of CNS TB can be difficult. Maintaining a high degree of suspicion is vital in order to initiate therapy promptly. The proper examination of CSF specimens is of critical importance to early diagnosis. Typically, the CSF formula shows elevated protein and lowered glucose concentrations with a mononuclear pleocytosis. CSF protein ranges from 100- 500 mg/dL in most patients. The CSF glucose is less than 45 mg/dL in 80% of cases. The usual CSF cell count is between 100 and 500 cells/µL.

Treatment: Specific antituberculous chemotherapy should be initiated on the basis of strong clinical suspicion and should not be delayed until proof of infection is obtained. The clinical outcome depends greatly on the stage at which therapy is initiated; much more harm results from delay, even for only a few days, than from inappropriate therapy as long as efforts are continued to confirm the diagnosis.
All patients should initially receive a combination regimen of isoniazid (INH), rifampin, pyrazinamide (PZA), and ethambutol (EMB) as category I. The recommended regimen is a four drug combination that includes INH, rifampin, PZA, and EMB for two months followed by INH and rifampin/ETM for 10 months. There is evidence to recommend adjunctive corticosteroid therapy both adults and children with tuberculous meningitis.

Recommended regimens:

- Prednisone 60 mg per day tapered gradually over six weeks or
- Dexamethasone intravenously for the first three weeks (initially 0.4 mg/kg per day, tapering to 0.1 mg/kg per day), followed by oral administration beginning 4mg per day, tapered over three to four weeks at the rate of 1 mg decrease in the daily dose each week

Unit 4: Management of Skin Disorders

The skin is an organ frequently affected by OIs; early manifestations of HIV infections frequently occur in the skin. Different kinds of OIs, such as herpes zoster, and other viral, fungal and bacterial infections occur in the skin. Manifestations of adverse drug reactions and non-infectious conditions also occur in the skin. Some skin reactions to drugs such as Nevirapine may be life-threatening. In most instances diagnoses of skin disorders with HIV disease are made on clinical grounds. Most skin disorders in HIV disease can be cured or ameliorated, but a few fail to improve even with good general clinical and immunological responses to ART.
Pruritis is the most common dermatologic symptom in HIV infected patients. It can be localized indicating primary skin lesion, or generalized that may or may not indicate primary skin lesions. In many patients pruritus may be severe and not amenable to available therapy. The most common skin conditions associated with pruritis in patients with AIDS include the following:

1. excessive dryness of the skin (Xerosis cutis)
2. eczemas like seborrheic dermatitis or contact dermatitis
3. folliculitis that may include infections by *Staphylococcus aureas* or hypersensitivity to insects
4. drug eruptions
5. scabies
6. intertrigo (candida, tinea, herpes simplex)

In most patients, diagnosis can be established by examining the lesions. However, as immune deficiency advances it may be useful to use investigations such as biopsy to diagnose specific dermatosis or use staining and culture to diagnose specific infections.

4.1 Aetiological Classification of Skin Disorders in HIV Disease.

Skin disorders in HIV infected patients can occur due to infections, neoplasm, and hypersensitivity to foreign agents including drugs, or to unknown causes. Nevertheless, infections are commonly seen in clinical practice; refer to the following table:

Table 7: Aetiological Classification of Skin Disorders in HIV Disease

Infections	***Disease***	***Clinical presentations***	***Treatment***	***Remark***
Bacterial	Cellulitis	Poorly defined erythema. Pus and crust at the site plus signs of inflammation	Amoxicillin 500mg tid for ten days or erythromycin 500mg qid if allergic to penicillin.	Mostly encountered in lower extremities and often unilateral.
	Impetigo	Erythematous small papules usually limited to few lesions coalescing in to crusted plaques.	Use topical antibiotic; use amoxicillin for extensive disease.	Usually a superficial lesion
	Carbuncle	Nodular lesion with extensions to the deeper structure. Signs of inflammation present.	Use cloxacillin 500 mg qid for ten days.	Involves the trunk as well as extremities.
Viral	Herpes simplex	Painful vesicular lesion around mouth or genitalia. Recurrent and extensive; difficult to eradicate during advanced immune deficiency	Acyclovir 400 mg tid for ten days.	If chronic (> one month) indicates eligibility for ART.
	Herpes zoster	Painful and vesicular eruptions with dermatomal distribution. When healed, scar will remain.	Acyclovir 800 mg 5 X per day for seven days. Monitor renal function.	When it involves the eyes it is a medical emergency. Do not give acyclovir if duration is >72 hours.
	Warts/veruccae	Painless flat to raised warts over fingers or genitalia. In advanced	Podophyllin Imiquimod Cryotherapy	premalignant and risk for cervical cancer

		immune deficiency, they tend to be multiple and exophytic.	Consult experts.	
	Molluscum contagiosum	Umbilicated and raised facial lesions that tend to be very big during immune deficiency state.	May not require therapy; HAART if eligible	Contagious
Parasitic infestation	Scabies	Pruritic lesions ranging from pinpointed erythematous papules involving interdigital and gluteal places to varying degrees of hyperkeratotic plaques associated with significant skin thickening and crusting.	BBL, lindane or permethrin to be applied to whole body. Ivermectin 200 microgram/kg stat orally.	Burrows are visible in mild infestations but in crusted scabies may not be evident leading to misdiagnosis.
Fungus	Dermatophytosis	Superficial causing ringworm or athlete's foot.	Topical antifungal for limited skin affected. Fluconazole for extensive lesions 100mg daily for ten days.	
	Thrush	White plaques on the buccal mucosa including the tongue that can be scraped off leaving red base. Can be associated with candida paronychia or intertrigo.	Miconazole gel 2% apply bid Fluconazole 100 mg daily for ten days for recurrent or oropharyngeal thrush.	
	Deep fungal infection	Presentation varies from fungating nodules and tumors to ulcers and diffuse papulonodular disease	Disseminated Cryptococcus can be confused for molluscum contagiosum. Treat with amphotericin induction and/or fluconazole maintenance.	

4.2. Selected skin conditions in patients with HIV infection

4.2.1 Seborrheic Dermatitis: Seborrheic dermatitis is often associated with HIV infection and the extent of disease is inversely correlated with patient's CD4 level. It presents with greasy and erythematous scales localized to nasolabial folds, ears and scalp. Treat with topical steroids and antifungal agents; e.g. candicort cream to be applied on the lesions bid and ketoconazole cream or shampoo for the scalp.

Adverse Drug Reactions: Adverse drug reactions involving skin are common among HIV infected patients because of the large number of medications they require and the underlying altered immune status. Clinical manifestation ranges from simple morbilliform eruptions with erythematous macules and papules to life-threatening bullous eruptions or palpable purpura. Systemic symptoms like fever, rigors and intolerable pruritis often indicate severity of the reaction. Management includes discontinuation of the offending drug if the reaction is severe, or desensitization for

mild reactions, if treatment with the offending drug is absolutely necessary; e.g. cotrimoxazole treatment for PCP. Do not continue offending drug if the reaction is severe with wet lesions (blisters) and/or is accompanied by systemic symptoms like fever and when mucus membranes are involved. Commonly-used drugs associated with ADR involving the skin include;

1. Sulphonamide drugs (fansidar and cotrimoxazole)
2. anti TBC drugs (rifampin, INH and thiacethazone)
3. NNRTI (nevirapine and efavirenz)
4. NRTI (abacavir)
5. Penicillin
6. Anticonvulsants (carbamazepine and phenytoin).

4.2.2 Pruritic Papular Eruption

Pruritic papular eruption is common among HIV infected patients causing substantial morbidity in sub-Saharan Africa. Its prevalence ranges from 12-46% and it is uncommon in HIV negative patients (PPV of 82-87%, and may play role in diagnosing HIV). The pathogenesis is unknown but it may be related to hypersensitivity to arthropod bites. In extreme form, eosinophilia and eosinophilic infiltrates of the skin are present. Severity of rash often correlates with CD4 count.

The clinical manifestation is intensely pruritic, discrete, firm papules with variable stages of development and predilection for extremities, though they can involve trunk and face. Excoriation results in pigmentation, scarring and nodules. Treat with topical steroid and oral antihistamines; however it is often refractory to treatment and hence short course prednisolone may be used. HAART is often effective.

4.2.3 Kaposi's Sarcoma

This is a tumour caused by human HSV type 8 viruses. It was common in North America before the advent of ART but the incidence of KS in HIV-infected individuals is increasing in sub-Saharan Africa, where there is limited access to ART. In fact, AIDS-related KS has become the most frequently diagnosed tumour in several African countries though rarely seen in Ethiopia. The clinical features of KS are described below.

Skin lesions: KS usually manifests dermatologically as pigmented macules, plaques, papules, or nodules, commonly involving the tip of the nose. They range from a few millimetres to large confluent areas several centimetres across. Usually KS lesions look purple but in dark-skinned people appear dark brown or black.

Lesions of the oral cavity occur in about one third of patients with AIDS-associated KS. Hard palate lesions are most common. These flat, red or purple plaques, either focal or diffuse, may be completely asymptomatic and easily overlooked. In other patients, however, larger nodular lesions involving the hard or soft palate, or both, may become exophytic and ulcerated, and may bleed. Other oral sites of KS involvement include the

gingiva, tongue, uvula, tonsils, pharynx, and trachea. These lesions may interfere with eating and speaking, cause tooth loss, or compromise airway.

Gastrointestinal KS may occur throughout the GI tract, and although most patients are asymptomatic, some experience pain, obstruction, or bleeding. Digital examination may reveal rectal KS, but diagnosis generally requires endoscopy. Most lesions are sub mucosal and readily visible on contrast-enhanced radiographs.

Other sites of KS include the lungs, lymph nodes, many visceral organs, including liver, spleen, heart, pericardium, bone, and bone marrow.

Poor prognostic indicators include a disseminated tumour with CD4 count below 200/µL and/or presence of systemic symptoms like fever, weight loss and sweating.
Treatment of KS depends on extent of tumour spread. Localized lesions could resolve with ART alone. Disseminated or locally aggressive tumours require radiation therapy or chemotherapy in addition to ART and hence require referral to centres with this expertise.

Unit 5: Management of Fever.

Fever is a common result of opportunistic infections in patients infected with HIV. However causes of febrile illnesses in the general population can also be responsible. Unexplained fever occurs frequently in HIV-infected patients and in most patients with advanced immune deficiency. The purpose of this unit is to understand common aetiologies of fever among patients infected with HIV and principles of its management.

Definition of Fever:

- Fever is defined as elevation of body temperature >37.2°C in the morning or >38°C after 4 p.m. in the afternoon. Take temperature orally as axillary readings are often unreliable.

- Unexplained chronic fever (>one month) is suggestive of advanced immune deficiency state. This scenario is called “Fever of Unknown Origin” and is defined as fever >38°C lasting more than four weeks as an outpatient or four days following patient admission and remains unexplained despite exhaustive clinical and laboratory evaluation.

Aetiology: Causes of fever in HIV-infected patients can be identical to those in the general population. These include malaria, typhoid fever, typhus, relapsing fever, measles and meningitis. However, unexplained fever in HIV-infected patients often signifies advanced immune deficiency. Opportunistic infections are responsible for unexplained fever and of these; tuberculosis is the most common in patients with very low CD4 count. Consequently, empirical treatment for TB is recommended when blood culture for Mycobacterium tuberculosis is unavailable and other causes are ruled out. One should not start Isoniazid Preventive Therapy (IPT) and it is advisable to delay ART until the cause of fever is identified; otherwise IRIS will be a serious complication shortly after initiation of ART.

OIs presenting with unexplained fever in HIV-infected patients.

1. Bacterial infections: *Salmonella species, Pneumococcal bacteraemia.*
2. Fungal infections: *Pneumocystis jiroveci, Cryptococcus.*
3. Mycobacterium infections: *M. tuberculosis, MAC*
4. *Protozoa infection: Leishmania donovani.*
5. Viral infections: CMV
6. Non infectious disorders: lymphoma

Diagnosis: The clinical history should elaborate onset, duration, pattern, severity, accompanying symptoms and related complaints. Travel history to areas endemic for malaria and Kala-azar is essential. History of exposure to animals can indicate source of fever in some patients. Inquire about drug intake as medication could be the cause. Perform systematic meticulous physical examination. Focus on HEENT, intercostal areas and the precordium to elicit tenderness or abnormal findings

- Do not omit a pelvic examination in women because pelvic abscess is a recognized cause of chronic fever. Similarly, rectal examination can reveal perianal abscess, which could explain fever. Examination of fundi by ophthalmoscope is useful to see retinal changes or papilloedema
- The epidemiology of febrile illnesses and clinical onset of symptoms should direct types of investigations required.

Treatment: Management of fever includes supportive care, palliative care and treatment of underlying cause. Supportive care includes correction of fluid and electrolyte deficit; and because fever enhances catabolism, offer adequate nutritional supplement. The fever should come down to normal using antipyretics such as a standing dose of paracetamol. Avoid aspirin as it may cause stomach irritation. Fanning and cold compression are adjuvant treatment modalities whenever fever is difficult to control with paracetamol.

- Definitive treatment of the cause depends on isolation/detection of the organism responsible. The following table should guide treatment.

Table 8: Summary of febrile syndromes in Ethiopia

Disease *	Clinical presentation	Investigation	Recommended Treatment	Remarks
Malaria	Acute onset of fever, chills, headache, hepatosplenomegaly	Thick and thin blood film	Coartem for uncomplicated falciparum malaria; Quinine for complicated falciparum malaria; Chloroquine for vivax malaria.	Severe manifestations (severe anaemia, altered mental state, hypotension, renal impairment, bleeding tendency, hypoglycaemia in pregnancy) should warrant admission. PI and NNRTI can reduce serum level of Coartem
Relapsing fever	Acute onset of fever, chills, headaches , epistaxis, hepatosplenomegaly	Blood film	Admit patient, establish IV line Procaine penicillin 400,000 units IM followed by doxycycline 100mg orally next day.	Observe for Jarish-Herxheimer reaction and manage by fluid replacement with normal saline solution. Digitalize if indicated. Delouse scalp, hair and clothes.
Typhus	Acute onset of fever, chills, headache , epistaxis, hepatosplenomegaly ; severe prostration if louse born	High titer of Weil-Felix serology with clinical setting where patient has body louse or exposure to rat flea.	Doxycycline 100mg bid for seven days. Chloramphenicole 500mg qid for seven days.	Delouse scalp hair and clothes. Observe for complications such as renal impairment and stroke.
Typhoid fever.	Acute onset of fever chills, headache, epistaxis, hepatosplenomegaly , often diarrhoea.	Positive blood culture Four-fold rise in titer of anti body against somatic antigen of Widal test	Ciprofloxacin 500mg bid for seven days	Check for renal function and substitute chloramphenicole if impaired.
Leishma-niasis	Chronic fever, cachexia, anaemia, hepatosplenomegally and patient from endemic `area.	Spleen aspirate show amastigote on Wright or Giemsa stain DAT for presumptive diagnosis	SSG(pentostam 20mg/kg daily IM for 28 days Liposomal Amphotericin B or Miltefosine for resistant cases	Recurrence and drug interaction with ART can create problem.
MAC	Chronic fever, anaemia, cough, hepatosplenomegaly , hepatitis and diarrhoea.	Culture of atypical mycobacteria from sputum or blood. CD4 < 50cells/µL.	Clarithromycin 500 mg bid+ ethambutol 25 mg/kg daily Add rifabutin 300mg daily for severe symptoms	Rare in Ethiopia

** Refer to respiratory disease unit for treatment of TB and PCP and neurology unit for treatment of Cryptococcal meningitis.*

5.1 Selected causes of fever in AIDS patients.

5.1.1 Malaria

Three-quarters of the Ethiopian population is at risk of acquiring malaria. In most areas of the country, transmission is unstable from late July to early October following the heavy rainy season; minor transmission occurs in March to April after the Belge (small) rains. In parts of the country where the water body is sufficient to maintain breeding of mosquitoes throughout the year (e.g. around lakes, rivers and marshes), stable (continuous) transmission occurs.

Aetiology: The dominant parasite is Plasmodium falciparum, accounting for 60% of cases, and the remaining are caused by P. vivax. Mortality predominantly caused by P. falciparum, usually affecting children, pregnant women and non-immune individuals.

The effects of HIV on malaria in adults are now well documented. Malaria infection and fever rates are higher in areas of stable transmission, especially for individuals with low CD4 counts or high viral loads. In areas of unstable transmission, HIV is associated with more severe disease and death. Antimalarial therapy appears less effective in HIV-infected than in uninfected adults because of more rapid re-infection. In pregnant women, HIV is associated with more episodes of malaria, more fever, and more adverse birth outcomes. In the other direction, malaria up-regulates HIV transcription transiently during acute episodes and increases CD4 decline.

Several questions still need to be answered, such as how HIV affects malaria in children, whether the current HIV epidemic is affecting malaria control programs in Africa, and whether improved clinical management of malaria in HIV-1-infected subjects (e.g. avoidance of mosquito bites or chemoprophylaxis) slows the progression of HIV disease. We also need to establish whether acute malaria episodes accelerate clinical HIV disease progression and increase transmission. The effects of ART and cotrimoxazole on susceptibility to malaria parasitemia and fever should be studied in a range of endemic settings. We also need more information about pharmacokinetic interactions between antimalarials and antiretrovirals and the implications of widespread cotrimoxazole use in areas of high malaria prevalence.

5.1.2 Visceral Leishmaniasis

Visceral leishmaniasis (VL) is a systemic parasitic illness, transmitted primarily by the phlebotomine sand fly from animal or human reservoirs. Visceral Leishmaniasis is endemic in Ethiopia, with patchy distribution in the southern and north-western lowlands. The causative parasite is L. Donovani. VL has emerged as a major OI associated with HIV. In HIV patients, VL represents reactivation of latent infection with Leishmania parasite.

Clinical features: The cardinal signs of VL in patients with HIV infection are unexplained fever, splenomegaly and pancytopenia (anaemia, leucopenia and thrombocytopenia). Presentation may not be typical. The bone marrow is packed with parasites but two-thirds of cases have no detectable anti Leishmanial antibodies. CD4+ cell count in co-infected patients is usually <300cells/ml.

Diagnosis:
Parasitological diagnosis: Isolation of the organism from material taken from reticuloendothelial tissue and examined with Giemsa, Wright's or Leishmanial stain.

Immunological diagnosis

- Antibody detection
- Leishmanial test is negative

Treatment: Pentavalent antimonial 10-20mg/kg for 3-4 weeks, require longer treatment and more liable to relapse.

Treatment of relapsed patients: These are patients who are slower to respond and have a higher chance of further relapse and of becoming unresponsive to antimonial.
Treatment- 20mg Sb/kg daily for 8weeks; monitor by splenic aspirates.

5.1.3 Sepsis

This diagnosis is formulated whenever patients with HIV present with high grade fever, tachycardia, tachypnea and low blood pressure. Though these signs are clinical evidence of infections, it is difficult to predict the aetiology without laboratory support. In clinical practice in Ethiopia nearly all patients with this type of presentation are empirically put on parentral ceftraixone. Although enteric fever and non typoidal salmonellosis can be common among AIDS patients, incidence of gram negative sepsis is not different from HIV negative individuals.

Clinical features: 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 nuccal rigidity can suggest underlying pathology. Examination typically will elicit fever, tachycardia, tachypnea with low blood pressure and altered mental status. Fever can be absent and hypothermia can present concurrently in severe sepsis. A detailed examination is necessary to check the skins, lungs, rectum, female pelvis and full HEENT including the fundi.

Factors to consider before empirical treatment:

1. Do CBC including BF examinations to exclude haemo parasites.
2. Take three blood cultures if possible.
3. Do chest X-ray and abdominal sonography to determine sites of infection.
4. Identify if the source of sepsis is a community or hospital-acquired pathogen.

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

- treat the underlying infection
- preserve vital organ perfusion and maintain tissue oxygenation
- prevent complications

Table 9: Empiric choice of antibiotic for the treatment of sepsis

Suspected site of infection	Antibiotic
Lungs 1. Community acquired 2. Hospital acquired	Amoxacillin 500mg IV QID for 10 days Ceftriaxone 1 gm BID for ten days
Skin 1. Community acquired 2. Hospital acquired	Cloxacillin 500 mg qid for ten days Cloxacillin plus ceftriaxone 1gm BID for ten days.
Intra- Abdomen	Ampicillin 1 gm QID plus Gentamycin 5mg/kg in three divided doses or ceftriaxone 1gm BID
Urinary tract 1. Community acquired 2. Hospital acquired	Ciprofloxacin500mg BID or Norfloxacin 400mg BID Same as above or ceftriaxone 1 gm BID

Supportive therapy

1. Maintain mean arterial pressure at 50-60mmHg using IV fluids. Measure the daily urine output and calculate fluid balance
2. Prevent bedsores by frequently changing patient's position
3. Give oxygen if patient is complaining of air hunger
4. Correct anaemia by blood transfusion if haemoglobin is below 10gm%
5. Monitor liver and kidney functions
6. Ensure adequate nutritional support
7. Treat fever and pain as required
8. Do not give steroids as they may produce deleterious effect

Unit 6: Some Special Conditions in OI Management

6.1 Initiating ART in Context of an Acute OI

Certain OIs have no specific treatment. ART may be the only answer for these, such as diarrhoea due to cryptosporidiosis. Early initiation of ART is warranted under these circumstances. In general the initiation of ART for patients having active OIs, in particular life-threatening OIs, may pose pill burden, drug interaction, overlap toxicity and intolerance problems.

The preferred approach when a patient with active OI also requires ART initiation is to address the OIs first since the OI is the more immediate threat to life. After the OI is adequately addressed and patient tolerates the associated drugs ART can be initiated with standard preparation. TB is the best example of this situation: if a patient with severe

immunodeficiency presents with active TB, priority is given to controlling the TB and then after two weeks or so ART can be considered.

Another situation involving OIs that must be considered in HIV infected patients within three months of starting ART is immune reconstitution inflammatory syndrome (IRIS). IRIS is characterized by fever and worsening clinical manifestations of existing or newly manifesting OI, weeks after initiation of ART. IRIS may manifest as atypical mycobacterial infections: *Pneumocystis jiroveci* pneumonia (PCP), toxoplasmosis, hepatitis B and hepatitis C viruses, cytomegalovirus (CMV) infection, Varicella-zoster virus (VZV) infection, cryptococcal infection and PML, among others.

6.2 When to initiate ART in context of an acute OI

When a patient with severe immunodeficiency presents with active life-threatening OI, the latter must be addressed first. Consider the following before initiating ART in a patient with an acute OI:

- Availability of effective treatment for the OI
- Risk of drug interaction
- Overlapping drug toxicity and intolerance
- The risk and consequence of the development of IRIS
- Pill burden and tolerance when considering simultaneous use of ARV and OI drugs.
- Patient willingness and ability to take and adhere to their regimen.
- Status of the immunity (or CD4 level)

In cases of cryptosporidiosis, microsporidiosis, PML, and Kaposi sarcoma, the early benefits of potent ART outweigh any increased risk, and potent ART should be started as soon as possible. ART should never be denied to a patient because of fear of IRIS, and when IRIS occurs the OI is appropriately managed but the ART is not stopped, unless there is intolerance or other contra-indications that warrant withholding the ARV drugs.

Some data from observational studies of disseminated MAC, tuberculosis, and cryptococcal meningitis suggests that delaying ART for 4-8 weeks after initiating antimicrobial therapy for the opportunistic infection is associated with decreased risk of IRIS. As mycobacterial IRIS, in particular, may be clinically severe, delaying ART for 4-8 weeks after starting antimycobacterial therapy may be prudent. However, this must be weighed against the severity of the immunodeficiency. When CD4 is less than 200, delay in initiating ART may predispose the patient to other life-threatening OIs.

When an opportunistic infection occurs after three months of ART, the patient should be assessed for treatment failure and thorough adherence assessment done. Repeat the CD4 count after treating the patient and decide about treatment failure. Since viral load is not widely available detection of early treatment failure is difficult in resource-limited settings.

PART II

GUIDELINES

FOR

ANTI RETROVIRAL TREATMENT IN

ADULTS AND ADOLESCENTS

(March 2008, updated version)

Table of Contents

Tables

Acronyms and Abbreviations

3TC	Lamivudine
ABC	Abacavir
AFB	Acid fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
ART	Antiretroviral Therapy
AZT/ZDV	Zidovudine
CBC	Complete Blood Count
CD4 cells	Cells with CD4 marker
d4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic acid
DOTS	Directly Observed Therapy Short Course
FBS	Fasting Blood Sugar
EFV	Efavirenz, also abbreviated as EFZ
ELISA	Enzyme Linked Immunosorbent Assay
GOE	Government of Ethiopia
HAART	Highly active antiretroviral therapy
HAPCO	HIV/AIDS Prevention and Control Office
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency Virus
IDV	Indinavir
LFT	Liver Function Test
LPV	Lopinavir
MTCT	Mother-To-Child Transmission (of HIV)
NFV	Nelfinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside Analogue Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PI	Protease Inhibitor
PLWHA	People living with HIV/AIDS
PMTCT	Prevention of mother-to-child transmission (of HIV)
RNA	Ribonucleic acid
RTV, r	Ritonavir
PI/r	Ritonavir boosted Protease Inhibitor
RFT	Renal function test
RT	Reverse transcriptase
SQV	Saquinavir

STD/STI	Sexually Transmitted Disease/Sexually Transmitted Infection
TLC	Total Lymphocyte Count
UNGASS	United Nations General Assembly Special Session on HIV/AIDS
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization
ZDV	Zidovudine (also abbreviated as AZT)

1. Introduction

According to the calibrated single point estimate (2007) based on "AIDS in Ethiopia-6th Report" and EDHS, there are 977,394 people living with the virus, and of these 258,264 require ART[2]. Twenty four percent of adults requiring treatment were started on ART by December 2006. Children are disproportionately accessing HIV care, with only 15% ever starting treatment. Although coverage significantly increased after the launching of free ART program in Ethiopia in 2005 (from 900 to 62,000 by the end of December 2006), and a trend of decline in AIDS deaths was documented[1], there remains much suffering and death due to AIDS in both children and adults. The plan for the end of 2006 was 100,000 on treatment, but only 62% of this target was achieved.

The challenges of making ARV drugs available are multiple and complicated. The human resource shortage and its disproportionate distribution, grossly skewed to urban centres, together with low retention, morale and job satisfaction causing high turnover among health care workers of all categories at all levels have become the most prominent challenges of the free ART program. Other challenges such as inadequate infrastructure, networking and capacities of delivery at all levels remain to be addressed if the planned level of scale up is to be achieved.

The first guideline on safe and effective use of ARV drugs came out three years ago. It played an important role in setting a national standard and guiding HIV care services. It also served as a tool of quantifying and forecasting ARV drugs procurement, and training. A need to update the guideline was felt by care providers even before the WHO 2006 update of "Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-limited Settings" appeared. This feeling emanated from local experiences and needs, together with current level of knowledge and experiences in using ARV drugs in resource-limited settings.

The major departure of this third edition is that the paediatric ART is excluded; a separate guideline for ART for Children and Infants will come out shortly. The critical focus in this edition is ARV drug use for adults and adolescents. Issues of decentralization, task shifting, post exposure prophylactic medication, treatment adherence, are highlighted in this edition. The issue of resistance is not addressed in this document in sufficient detail, although it is a very important issue in relation to adherence and to ART program implementation in Ethiopia. Finally, in this 3rd edition first and second-line drug regimens have been updated to reflect current scientific knowledge, best practices and local experiences. It is strongly recommended that the 3rd edition is distributed in different forms, such as pocket sized (OI guidelines combined) volumes, posters and flow charts.

The 2008 update of the adult and adolescent guidelines of ART, has been made in order to address the rapidly increasing knowledge in antiretroviral treatment science. TDF has become first line drug in treatment naïve patients. This provides the best first line

[2] Calibrated Single Point Estimate (2007)

regimen (TDF/FTC/EFV as a triple FDC) to the Ethiopian program of adult HIV care/ART. This does not preclude the use of thymidine analogues and ABC in the first line regimens. They are used in the appropriate circumstances based on the judgement of the treating health care worker. Appropriate sequencing is done in selection of the 2nd line drugs in treatment failure. Hence, more individualization of the treatment selection is important in deciding which 2nd line regimen to start. Patients who have been on treatment so far will continue their regimens as long as it is effective. Switching of effective 1st line regimen to another 1st line regimen consisting of TDF for patient convenience alone may be counterproductive for the future selection of 2nd line regimen. This will be addressed in the implementation directives that come out with this update.

2. Objectives and Targets:

2.1 Objectives

- To provide a standardized and simplified guide to use of antiretroviral drugs in the comprehensive HIV/AIDS service delivery setting
- To promote evidence-based, safe and rational use of antiretroviral drugs
- To serve as a training tool and reference material for health service providers, program managers, and people living with HIV.

2.2 Targets

- Health care workers (physicians, health officers, nurses, pharmacy personnel, laboratory technicians and case managers) providing care to people infected and affected with HIV
- HIV/AIDS program managers, health planners, and researchers
- Organisations involved in antiretroviral drug procurement, supply management, and ART service delivery.

3. Antiretroviral Therapy in adults and adolescents:

With the advent of ARV drugs, AIDS has become a treatable chronic disease. Even in a Third World setting with increasing people with AIDS accessing services, a decline in death rates is clearly visible. ART is a complex health care intervention with a number of challenges; in order to benefit maximally nearly 100% adherence is necessary, therefore the support of family, friends, health care workers and other care providers is mandatory for the patient to achieve this level of adherence. Failure to comply with treatment results in the emergence of drug resistant viruses that are usually difficult to manage especially in resource-limited settings. That is why it is said, "*The first regimen is the best regimen*".

In resource-limited settings patients accessing ART have a number of non-medical needs including nutrition, shelter, transportation etc. A social system addressing these supports drug adherence.

The public health approach, recommended by WHO for resource-poor settings, is an overarching principle of the Ethiopian ART program. By this approach, large numbers of people are facilitated to access ART and survival is maximized. These guidelines standardise and simplify the initiation and monitoring of ART; Standardized formulary for first and second-line ART, with the use of two NRTIs and an NNRTI as the standard first-line approach, reserving PIs for second-line is the centre piece of the public health approach to ART.

3.1. Goals of Antiretroviral Therapy:

3.1.1 Primary goals:

- Maximum and durable suppression of viral replication
- Restoration of immunologic function, resulting in reduction of HIV-related morbidity and mortality, and improvement of quality of life and survival of people living with HIV

3.1.2 Secondary goals:

- increase uptake of HIV testing contributing to prevention as well as care of HIV infection
- Change in the perceptions of HIV, so that society regards AIDS as a treatable chronic disease, this reduces stigma
- Raise the hope of individuals, families and community, thereby reducing HIV-related stigma and discrimination and enhance affected persons' participation in HIV intervention activities
- Increase uptake of PMTCT
- Reduce transmission of HIV in the population
- Reduce incidence of TB

3.2. Initiation of Antiretroviral Therapy in adults and adolescents

3.2.1 General considerations

The decision to initiate ART in adults and adolescents is guided by clinical and immunological assessment. In situations where immunological assessment is unavailable it is recommended to initiate ART on clinical grounds with total lymphocyte count when applicable.

ART initiation demands thorough assessment of patient readiness and commitment. The patient must understand that treatment is life-long, and its implications (possible adverse effects, 100% adherence, etc). Access to nutrition, psychosocial and basic social supports are important when deciding to start ART in patients.

The entry points of ART include VCT sites, ANC/PMTCT services, OPD/IPD, TB clinic, public and private health facilities, workplace health services, CBO/FBO social support systems, etc. These must be strengthened and networked in order to scale up ART uptake.

3.2.2 Clinical assessment of HIV-infected adults and adolescents to decide eligibility

- In resource-limited settings, initiation of ART is predominantly dependent on clinical assessment, despite increasing availability of CD4 testing as a guide to ART decisions. With the decentralisation of HIV care to health centres, there will be even more use of clinical criteria to decide initiation. WHO recommends clinical decision-making where CD4 counts are unavailable in order to increase access to ART. The lab networking and sample transportation must be established and strengthened to make CD4 testing available for providers at health centres.

- The most important purpose of clinical assessment to initiate treatment is to stage a patient according to WHO criteria. Before the process of clinical or immunological assessment however, the HIV positive status of the patient must be confirmed.

3.2.3 Immunological assessment of HIV-infected adults and adolescents to decide eligibility

- Immunological assessment using the CD4 count identifies the disease progression and determines initiation of treatment. CD4 testing can monitor the ART response as well.

- A patient with a CD4 count below 200 cells/microLt. is at increased risk of developing life-threatening opportunistic diseases. To ensure patient safety, treatment must not be delayed until CD4 count falls below 200. The optimum time to initiate ART is when a patient's CD4 count is 200-350. CD4 count levels do not determine treatment initiation in stage IV patients; regardless of CD4 count, stage IV patients are promptly started on ART, once readiness is assured. In stages I and II, immunological assessment is important to initiate ART; in stage III, treatment can be considered under certain clinical conditions with CD4 count of 350 and below. ***In this document all stage III patients with a CD4 of 350 or below are recommended for initiation of ART to avoid confusion with advanced and early stage III***.

- Various factors require consideration when interpreting CD4 results. The test itself has an inherent variation of +/- 30%. It is important to consider all factors in making decisions to start or change treatment based on CD4 counts.

- Automated total lymphocyte count (TLC) may be used where a CD4 count is unavailable. However, it correlates poorly with CD4 counts, particularly in asymptomatic patients (stage I). A TLC of 1,200 or below is considered indication for starting treatment in stage II patients.

- Because of limitation of resources, viral load has not been considered as a standard benchmark of initiation or follow up of ART in the Ethiopian setting.

3.2.4 Clinical and immunological criteria to initiate first-line antiretroviral therapy:

Ideally, use CD4 count to guiding ART initiation; lack of CD4 should not preclude ART initiation in patients clinically eligible for treatment however.

Table 1: Criteria for initiation of ART in adults and adolescents

CD4 count not available	CD4 count available
WHO clinical stage IV and III irrespective of Total Lymphocyte Count (TLC)	WHO clinical stage IV, irrespective of CD4 count
WHO Clinical stage II if TLC $\leq$1200/ mm^3	WHO clinical stage III, if CD4 cell counts $\leq$ 350/mm^3 [a]
Do not treat WHO clinical stage I, in absence of CD4 count	All WHO clinical stages, if CD4 cell counts $\leq$ 200/ mm^3
WHO clinical staging in adults and adolescents is given in Appendix 1 TLC is only useful in deciding when to initiate ART in symptomatic patients with WHO clinical stage II disease. The use of CD4 cell count to guide treatment decision is advisable. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non - HIV aetiologies.	

4. First-line ARV regimens for adults and adolescents in Ethiopia:

The preferred first-line regimen consists of NRTI backbone with one of the NNRTIs. Both NNRTIs are given equal preference; choice is based on patients' conditions. TDF and ZDV are preferred first line NRTIs in the treatment naïve patients. They can be combined either with 3TC or FTC and given with one of the NNRTIs. Fixed Dose Combination, triple or double, are much preferred to loose compounds since they ensure patient convenience and adherence to ART. The other NRTIs—d4T and ABC—are used as alternative to TDF or ZDV in selected patient, such as renal affection or adverse effects of ZDV. Apparently, the selection of the 2nd line regimen depends on the first line regimen that patient has been taking. In particular, the cohort of patients that have been put on ART so far, should be carefully handled in order to avoid inadvertent switching from 1st line to 1st line because of patient preference. This will be addressed with the implementation guide that comes out with this updated guidelines.

FDCs are convenient for the patients in terms of pill burden in addition to logistics implication and dispensing, therefore, as long as GMP ensured the national program opts them. In particular in this update FDCs have been given high priority, unless there are complaining reasons to use the loose compounds, FDCS are preferred regimens of the Ethiopia regimen. The currently available FDCs include:

- Triple FDCs: TDF/FTC/EFV (ATRIPLA)—preferred first line regimen in all treatment naïve patients without contraindications: ZDV/3TC/NVP ---preferred first line regimen for treatment naïve patients in child bearing age without reliable

contraception, and have no contraindications to the regimen (good number of patients among the cohort on first line ART with this combination will be switched to this FDC, with 1 pill twice a day); d4T/3TC/NVP---this is an alternative regimen to the above 2 FDCs. Since most of the patients in the "on-ART cohort" are in this regimen with loose compounds, they will be switched automatically to this FDC. The combination of ABC/3TC/ZDV may be in rare situations such as pregnancy of first trimester with newly diagnosed TB warranting the use of Rifampicin.

- Double FDCs: the double FDCs that have been included in the national drug list are---ZDV/3TC (Combivir) and d4T/3TC. They can be used in combination with NNRTIs.

FIRST LINE REGIMEN: ETHIOPIAN ART PROGRAM 2008

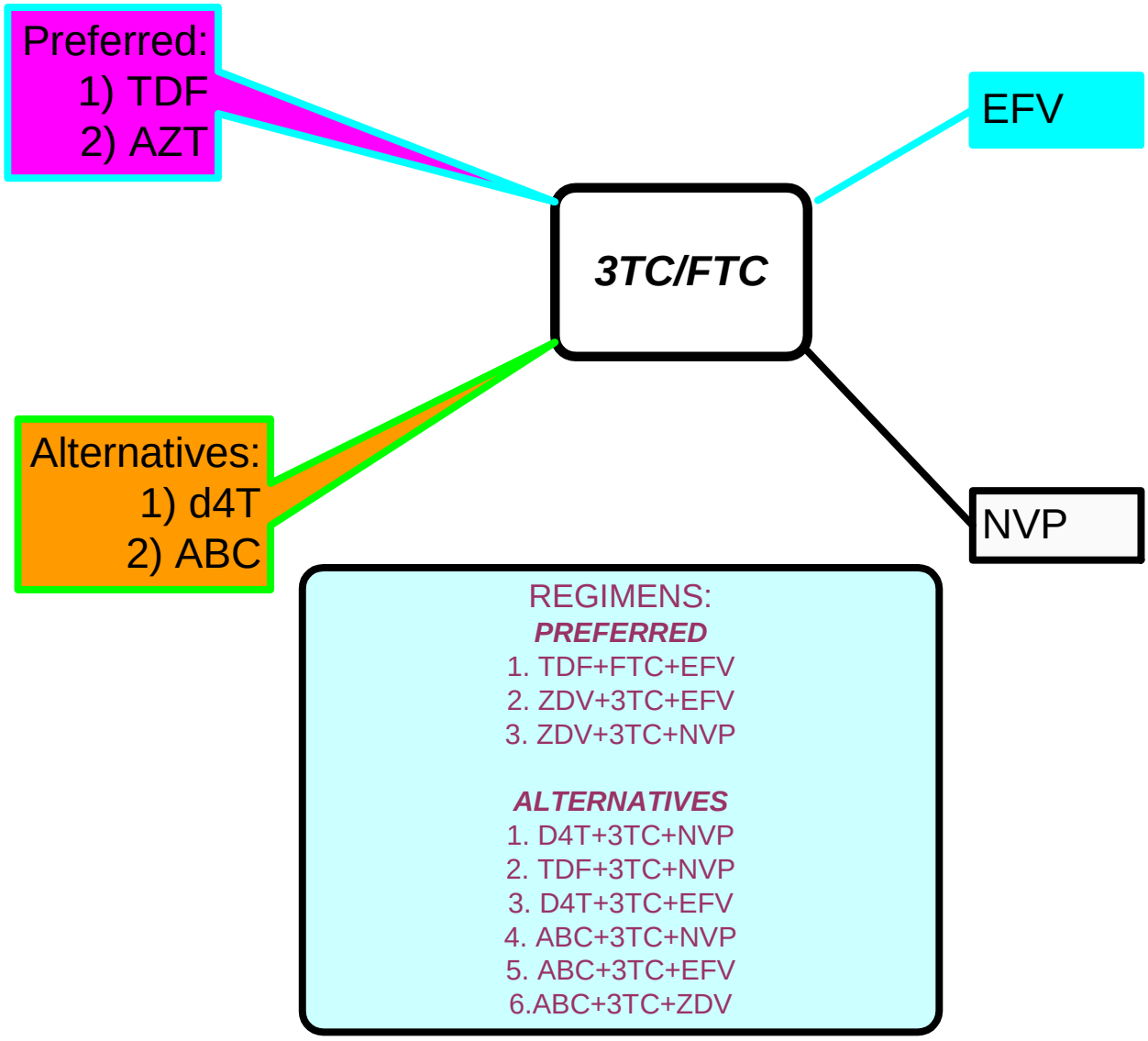

Table 2: First-line Regimens

Recommended ARV Regimens for Adults and Adolescents: One of the following should be used unless there are contraindications:
Preferred : • TDF+FTC+EFV = triple FDC • ZDV+3TC+EFV = combivir + EFV • ZDV+3TC+NVP = triple FDC
Alternatives: • D4T/3TC/EFV = double FDC (d4T/3TC) + EFV • TDF/3TC/NVP • D4T/3TC/NVP = triple FDC • ABC/3TC/EFV • ABC/3TC/NVP • ABC/3TC/ZDV = combivir + ABC

Table 3: ARV Drugs Dosage

First-line antiretroviral drugs dosage
Zidovudine (AZT) 300mg every 12 hours
Lamivudine (3TC) 150mg every 12 hours or 300 mg once a day
Emtracitabine (FTC) 200mg daily
Stavudine (d4T) 30mg every 12 hours
TDF 300mg daily
ABC 300mg every 12 hours
Nevirapine (NVP) 200mg daily for the first 2 weeks, followed by 200mg every 12 hours
Efavirenz 600mg daily at night

5. Essential steps in baseline assessment, initiation of antiretroviral treatment and follow up of patient

Standardized clinical assessment of patients and, when available immunological, are mandatory at baseline to decide on initiation of antiretroviral therapy. Patients who do not qualify for this have a follow up protocol that monitors disease progression and starts antiretroviral therapy before life-threatening immunodeficiency sets in. Patients qualifying for antiretroviral therapy are thoroughly evaluated at baseline and for the rest of their lives to monitor toxicity, intolerance, response or failure to treatment. Before ART initiation and thereafter patient readiness and adherence to therapy are always assessed and necessary support provided. Opportunistic infections including TB, IRIS,

and co morbidities are always looked for and managed. Such standardized procedures ensure HIV- infected persons a reasonable quality of care.

Table 4: Procedure of Baseline Assessment and Follow up

Baseline assessment, week 0		
Objectives	**Activities**	**Decision**

Assess patient eligibility	• Check HIV test document or request test
	  • For transfer-ins check referral form
	• Register, fill intake format
	• Clinical assessment: Hx of any HIV related illnesses in the past, OIs, co-morbidities, pregnancy, past and current medication
	• Stage
	• Counselling and education: determine treatment readiness, social background, disclosure,
	  • Lab assessment: CD4, TLC, (if stage III and IV CBC, ALT, creatinine). If TB suspect sputum smear. Pregnancy and other tests as necessary.
		• Develop impression on treatment readiness
		• Start CPT if clinically indicated
		• Treat OI
		• Determine eligibility in III and IV
		• Advise to come with support
		• Refer if necessary
		• Continue ART for in transfer-ins
		• Give appointment of 1 week

2nd Visit, 1 week after baseline visit		
To decide on initiation	• Review clinical and lab data • Adherence counselling and ensure readiness • Drug counselling and education • Discuss with family or closest support	• Decide eligibility for stage I and II • Non-eligible patients come every 3/12 for CPT and every 6/12 for clinical evalution/CD4 count • Start CPT or IPT (as indicated) • Treat OI including TB • Manage toxicity and intolerance • Determine treatment readiness • Decide on regimen • Refer • Appointment to return after 2 weeks
3rd visit, 2 weeks after initiation		

To determine toxicity/intolerance, adherence, and IRIS	• Clinical assessment • Counselling to assessment adherence and support • Lab tests if necessary	• Decide escalation of nevirapine • Decide on continuation ARV drugs • Treat OI if diagnosed • Give appointment to return in 2 weeks
4th visit 4 weeks after initiation		
Same as third visit	• Same as 3rd visit • Hg if patient is on ZDV	• Refill ART and CPT for one month • Treatment of OI • Manage toxicity and intolerance • Refer • Appointment to return after 4 weeks
5th visit 8 weeks after initiation		
Same as 4th visit	• Same as 4th visit	• Refill ART and CPT for 1 month • Treatment of OI • Manage toxicity and intolerance • Refer • Appointment to return after 4 weeks
6th visit 12 weeks after initiation		
Same as 5th visit	• Same as 4th visit	• Refill ART and CPT for 2 months • Treatment of OI • Manage toxicity and intolerance • Refer • Appointment to return after 8 weeks

After the 12th week of initiation of antiretroviral therapy patients are scheduled to return every eight weeks. At each visit antiretroviral drugs and CPT for two months are given, counselling of positive living, safe sexual practice, adherence assessment and support are done. Lab tests including ALT are requested when indicated. CD4 is repeated every 6/12.

Table 5: Summary of Laboratory Monitoring for Adolescents and Adults on ART

Regimen	Drugs	Monitoring Tests	Frequency
First-line Regimens	**TDF/FTC/EFV**	CD4	Baseline and every 6 months
		Pregnancy test	Baseline and as indicated
		ALT	Symptom-directed
		Creatinine	symptom-directed
	D4T/3TC/NVP	CD4 count	At baseline and 6 monthly (if available)
		ALT	Symptom-directed
	ZDV/3TC/NVP	Haemoglobin	At baseline, 4th, 8th, and 12th weeks. thereafter symptom-directed
		ALT	Symptom-directed
		CD4 Count	Baseline and 6 monthly (if available)
	d4T/3TC/EFV	Pregnancy Test	Baseline, thereafter as indicated
		ALT	Symptom-directed
		CD4 Count	At baseline and 6 monthly
	ZDV/3TC/EFV	Haemoglobin,	At baseline, 4th, 8th, and 12th weeks; thereafter symptom-directed
		Pregnancy test	At baseline, thereafter as indicated
		ALT	Symptom-directed
		CD4 count	At baseline and 6 monthly

6. What to expect in the first six months of antiretroviral therapy

This is a critical period because drug intolerance, toxicities, IRIS, challenges of changes in the quality of life due to starting HAART and mortalities occur more frequently during this time. Immunological and clinical improvement usually takes place, but some cases may deteriorate, in particular those who start treatment late with severe immunodeficiency. Therefore this period of antiretroviral therapy requires more attention from providers.

6.1 Early antiretroviral Toxicity and Intolerance

Some mortalities in the first six months are due to drug toxicities; therefore, they must be closely monitored. They occur from few weeks to months. The major ones include:

- Toxicities of NRRTIs (NVP and EFV) occur in the first few weeks, and may be life-threatening
- Anaemia and neutropenia due to ZDV occur in the first several months

The clinical manifestations due to hypersensitivity reactions (ABC and NVP) may be confused with IRIS. Intolerance to certain drugs, in particular ZDV induced gastrointestinal problems, are important barriers to adherence unless appropriate measures are taken.

Table 6: Common early adverse effects of First-line ARV drugs

ARV drug	Common associated toxicity
AZT	Gastrointestinal intolerance Anaemia, neutropenia lactic acidosis
D4T	Peripheral neuropathy lactic acidosis
EFZ	CNS toxicity, teratogenicity Very rare fatal skin reaction (SJS)
NVP	Hypersensitivity reaction Hepatitis Fatal skin reaction (SJS)
3TC	Safe drug
FTC	Safe drug
TDF	Renal toxicity
ABC	Hypersensitivity

6.2 Rapid reduction in viral load occurs during this period

With institution of antiretroviral therapy the level of the virus falls rapidly, starting in the first week. At six months LDL is expected (lower than detection level). In treatment failure, the first sign is rising viral load. Because of limited resources viral load is not used to monitor response or failure.

6.3 Immune recovery happens during this time

In most patients CD4 rises and continues rising for many years as long as treatment is effective and adherence optimal. Most of the time with low baseline CD4 the response may be blunted. Some patients may not exceed CD4 of 200 cells/miroL and thus never leave the zone of severe immunodeficiency. Progressive fall in the CD4 count after

significant increase suggests immunological failure, if there is not intercurrent infection. To monitor this, six-monthly CD4 is done for patients on antiretroviral therapy

6.4 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is an inflammatory syndrome occurring days to months after the start of antiretroviral therapy, with outcome ranging from minimal morbidity to fatal (usually 2 - 12 weeks after initiation). It occurs as immune restoration due to effects of HAART. The incidence is said to be 10% among all patients, reaching 25% among those with a baseline CD4 count below 50 cells/mirol. There are a number of conditions presenting as IRIS. Mycobacterial infections (atypical TB or MAC) are more common presentations. However, other sub-clinical and latent infections present as IRIS (Herpes virus, CMV, PML, cryptococcal meningitis, brain toxo, PCP, etc). The approach with IRIS is to treat the opportunistic infections, continue with HAART and use NSAIDS or steroids depending on the individual patient's condition.

IRIS is not indicative of treatment failure or drug side effect. It is a transient phenomenon and is not a reason to stop antiretroviral therapy or to change the ARV regimen.
The OIs should be treated using standard guidelines and in critically sick patients short-course corticosteroid might be indicated to control severe symptoms.

6.5 Mortality is also high during this time

HAART in general reduces mortality, but during the first six months mortality may be relatively high,, particularly among patients with stage 4 disease, severe immune suppression and very low CD4 count. Various studies in sub-Saharan Africa have shown that mortality is highest in the first six months in patients with disseminated TB and/or CD4 count below 50cells/mirol.

7. Second-Line regimens for adults and adolescents in Ethiopia:

In the event of first-line treatment failure, there is indication to start second-line regimens. However, both diagnosis of first-line treatment failure and initiation of second-line regimen should be made by a trained physician. In some facilities, this might require referring the patient to higher level facilities.
Treatment failure is defined:

- **Clinically:** based on indication of clinical progression of HIV-infection e.g. Emergence or recurrence of OIs, or other HIV-related illnesses
- **Immunologically**: Decline in CD4 counts (refer to table 7)
- **Virologically**: Rise in viral load

Clinical disease progression should be differentiated from Immune Reconstitution Inflammatory Syndrome (IRIS), which can occur early with ART. Immune reconstitution does not signify treatment failure, and opportunistic infection should be treated as usual, in most cases without alteration in the antiretroviral regimen.

Definitions of clinical and CD4-related treatment failure are listed in the following Table. As viral load is not often available, it is recommended that programmes primarily use clinical and CD4 count criteria, in order to define treatment failure.

Table 7: Definitions of treatment failure in adults and adolescents

	Definition
Clinical Failure [a]	New or recurrent WHO stage 4 condition [b c]
Immunologic Failure [d]	• Fall of CD4 count to pre-therapy baseline (or below); • 50% fall from the on-treatment peak value (if known); • Persistent CD4 levels below 100 cells/MM^3
Virological Failure	Plasma viral load above 10,000 copies/ml in duplicates after six months on ART.

[a] Should be differentiated from Immune Reconstitution Inflammatory Syndrome (IRIS).

[b] Certain WHO clinical conditions (e.g. pulmonary TB, severe bacterial infections), may indicate treatment failure and should be investigated.

[c] Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy.

[d] Without concomitant infection to cause transient CD4 cell decrease. If patient is asymptomatic and treatment failure is being defined by decreased CD4 cell criteria alone, consideration should be given to performing a repeat CD4 cell count before establishing diagnosis of treatment failure.

"T staging" refers to clinical events on ART

Table 8: Clinical staging events to guide decision making on switching

New or recurrent event on ART [3] ("T" staging)	Recommendations	Additional Management Options
Asymptomatic (T1)	Do not switch regimen	• Maintain scheduled follow-up visits, including CD4 monitoring (if available) • Continue to offer adherence support
Stage 2 event (T2)	Do not switch regimen	• Treat and manage staging event • Assess and offer adherence support • Check if on treatment for at least six months • Assess continuation or reintroduction for OI prophylaxis • Schedule earlier visit for clinical review and consider CD4 (if available)
Stage 3 event (T3)	Consider switching regimen	• Treat and manage staging event, and monitor response • Assess and offer adherence support • Check if on treatment for at least six months • Check CD4 cell count (if available) • Assess continuation or reintroduction of OI prophylaxis • Institute more frequent follow-up
Stage 4 event (T4)	Switch regimen	• Treat and manage staging event, and monitor response • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Check CD4 cell count (if available) • Assess and offer adherence support

- In case of treatment failure, it is recommended to change the entire regimen from first-line to second-line.
- The new second-line regimen should involve drugs that retain activity against the patient's virus strain and should preferably include at least three new drugs, one or more from a new class, in order to increase likelihood of treatment success and minimize the risk of cross-resistance.

- Before changing to second-line regimen, thorough assessment of the patient including possible reasons for treatment failure should be done in order to identify any problem related to treatment adherence. This is followed by treatment readiness assessment and patient education on adherence. Patients on second-line regimen should be monitored closely for adherence.
- In patients who have taken ARV therapy for six months or less when they come for treatment as new patients, the same regimen can be continued as long as there are no features of disease progression. If there are features of disease progression or ARV was taken for more than six months, patients should be assessed for treatment failure, at the appropriate level of facility.

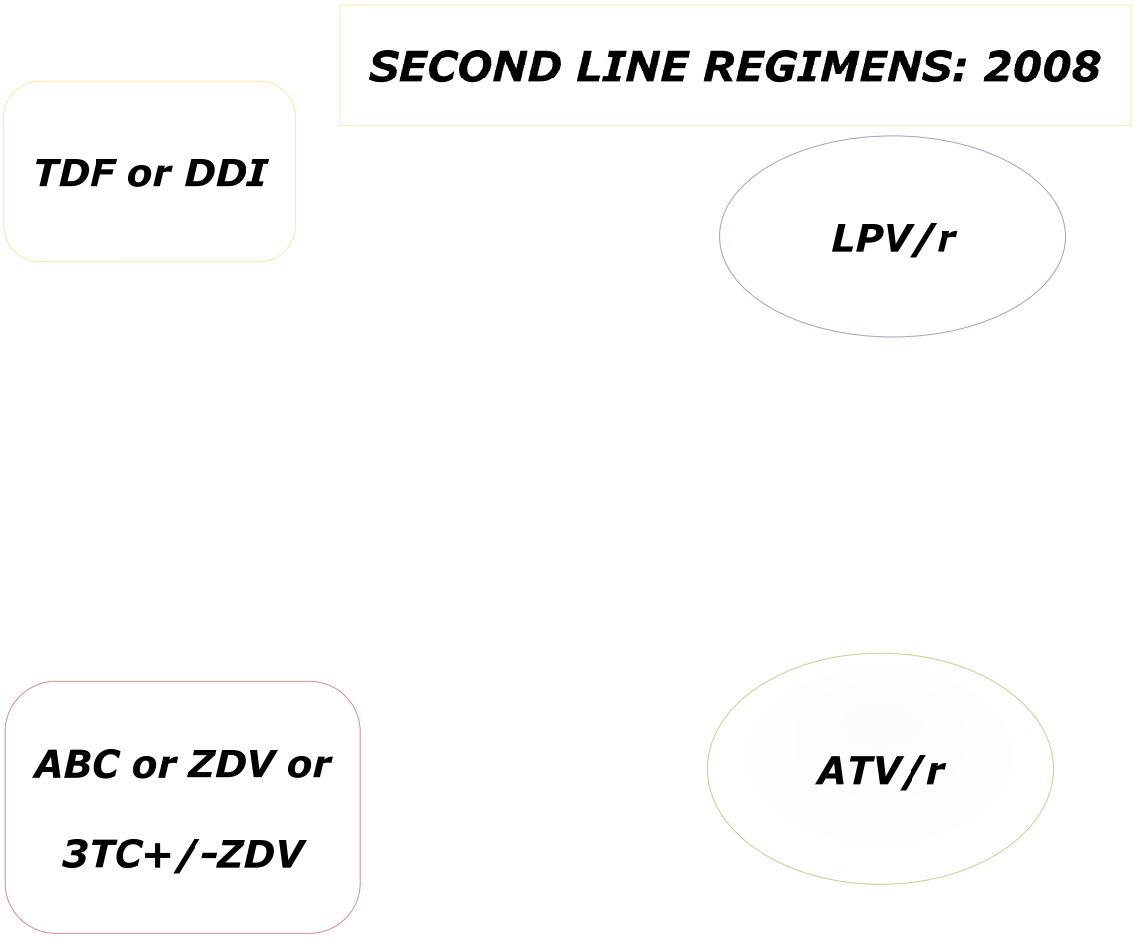

Table 9: Second-Line ARV Regimens in Adolescents and Adults

First-line Regimen	Second-line Regimen (*during treatment failure*)
TDF+FTC or 3TC +EFV or NVP	ZDV ±3TC +LPV/r or ATV/r Or ZDV+ABC+LPV/r or ATV/r
ZDV or d4T+3TC+EFV or NVP	TDF+3TC±ZDV+LPV/r or ATV/r Or ABC + ddI[a] +LPV/r[b] or ATV/r
ABC + 3TC + ZDV	EFV or NVP + LPV/r or ATV/r

[a] Didanosine alone must be taken on an empty stomach, at least one hour before or at least 2 hours after (<50% absorbed after) a meal. Tablets should be dissolved in at least 30 ml of water; no other liquids may be used to dissolve the tablets. The enteric coated version will not need to be dissolved.
[b] LPV/r use the heat stable tablet (200/50 mg).

- Atazanavir/ritonavir is has equivalent efficacy to LPV/r and has advantage of being given once a day and in patients with dyslipedimia.
- If TDF and ABC have been used in the first-line regimen, patients may be referred to experienced physicians for selection of the second-line drugs.
- Drug hypersensitivity and high-level cross-resistance to long term use of thymidine analogues (ZDV and d4T) are concerns of using ABC.
- TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but often retains activity against nucleoside-resistant viral strains. It is attractive in that, like ddI, it is administered once daily.

8. TB-HIV co-management

- Approximately 20-50% of patients with TB are co-infected with HIV, and many patients eligible for antiretroviral therapy will have active TB. Hence, TB diagnosis is an important entry point for a significant percentage of persons eligible for ART. TB is also an important manifestation of Immune Reconstitution Inflammatory Syndrome, and patients already receiving ART may also develop TB.
- HIV testing and care are important entry points to intensify access to TB-care. Therefore, all HIV-positive persons should be routinely screened for TB, at entry to care and during each subsequent visit
- ART is recommended for all patients with active PTB (smear positive or negative) with CD4 counts < 350 cells/mm3, and Extrapulmonary or disseminated TB patients irrespective of CD4 count
- If CD4 count is not possible, all patients with active TB are eligible for ART
- Suspect tuberculosis if patient presents with one or more of the following signs and symptoms:
    - Cough > two weeks
    - Other constitutional symptoms e.g. weight loss, fever,
    - Chest X-ray suggestive of lung tuberculosis
- Any patient with suspected TB should be assessed with three sputum smears and chest X-ray, and be offered HIV testing if status is unknown or reasonable time has elapsed since the last negative test result.
- The major issues in the clinical management of patients co-infected with HIV and active TB are: when to start ART, possibility of high pill burden, risk of drug interactions, drug toxicity, and IRIS. However, in HIV-infected patients who present with TB, priority must be given to initiate DOTS.

8.1 In co-managing TB-HIV there are two scenarios to consider:

A. Patient developing TB while on antiretroviral therapy:

A.1. If a newly-initiated ART patient (i.e. treatment naive patient) develops TB within the first 3-6 months after treatment, proceed as follows:

- Start DOT without delay, per national recommendation;
- If the patient is on nevirapine, substitute it with EFV when possible, while patient is on Rifampicin. If this is not possible (e.g. due to intolerance or other major efavirenz related side effects or significant risk of pregnancy), use triple nucleoside analogues, i.e., ABC/3TC/ZDV. Other than changing nevirapine to efavirenz, continue with the same nucleoside/nucleotide backbone.
- Start CP.

A.2 If a patient develops active TB after more than six months of ART, the possibility of treatment failure should be considered when diagnosis is extra-pulmonary tuberculosis and there are concomitant diseases suggesting advanced immune deficiency. If treatment failure is established, the patient should be managed with an appropriate second-line regimen decided by an experienced physician. This must be started as soon as the patient tolerates the anti TB drugs. Since PIs are usually used in 2nd line regimens, delaying the initiation of the 2nd line until completion of he intensive phase is better since refabutine is not available. It is also recommended to do a liver function test every two weeks for at least eight weeks to determine the risk of added hepatic toxicity. In the absence of evidence for ARV treatment failure, the patient should be managed per A.1.

8.2. Patient on anti-TB or newly-diagnosed active TB:

- If an HIV-infected patient *not on ART* presents with TB, the first priority is treating the TB per the national TB-treatment guidelines. As TB treatment requires a relatively long period, the issue is decision with regard to eligibility and timing of ARV initiation:

Table 10: Guide for management of patients presenting with TB before initiation of ART

	Recommendation	Preferred ARV regimen
CD4 count <200/mm^3	▪ Start TB treatment. ▪ Start ART as soon as TB treatment is tolerated (usually between 2 -8 weeks of TB treatment)[1]	EFV containing regimen is preferred.[2] However, if drugs are unavailable or there are problems with EFV (adverse effects with intolerance and risk of pregnancy) use triple nucleoside regimen with caution(3). If patient develops ABC hypersensitivity continue NVP but monitor liver function every month.
CD4 count 200-350/mm^3	• Start TB treatment. • Start ART after 8 weeks (after intensive phase) of TB treatment	• Start NVP containing regimen if the continuation phase does not include rifampicin. • If a non-pregnant woman has CD4 of >250 use EFV • In pregnant women with CD4 >250 use triple NRTI containing ABC/3TC/ZDV • Start EFV containing regimen if the continuation phase includes rifampicin
CD4 >350/mm^3	• Start TB treatment • Defer ART	• Re-assess eligibility for ART at 24 weeks clinically and immunologically, in the course of TB-treatment, at completion of TB treatment, or as indicated.
CD4 not available	• Start TB treatment. • Start ART after 2-8 weeks TB treatment if patient has severe disease and/or other clinical indicators of advanced immune deficiency • Start ART after completion of intensive phase when patient is not seriously ill or other signs of advanced immune deficiency are absent	. • Start NVP containing regimen if the continuation phase does not include rifampicin. • If a non-pregnant woman has CD4 of >250 use EFV • In pregnant women with CD4 >250 use triple NRTI containing ABC/3TC/ZDV • Start EFV containing regimen if the continuation phase includes rifampicin

[1] Timing of ART initiation should be up to clinical judgment based on other signs of immunodeficiency indicating progression of HIV disease (Refer to Table 1). For TB patients in WHO clinical Stage IV, ART should be started as soon as TB treatment is tolerated irrespective of CD4 count.
[2] EFV containing regimens include d4T/3TC/EFV or ZDV/3TC/EFV.
[3] NVP (200 mg daily for 2 weeks followed by 200 mg twice daily) may be used in place of EFV in absence of other options. NVP containing regimens include: d4T/3TC/NVP or ZDV/3TC/NVP.
[5] Start ART if non-TB Stage IV conditions are present

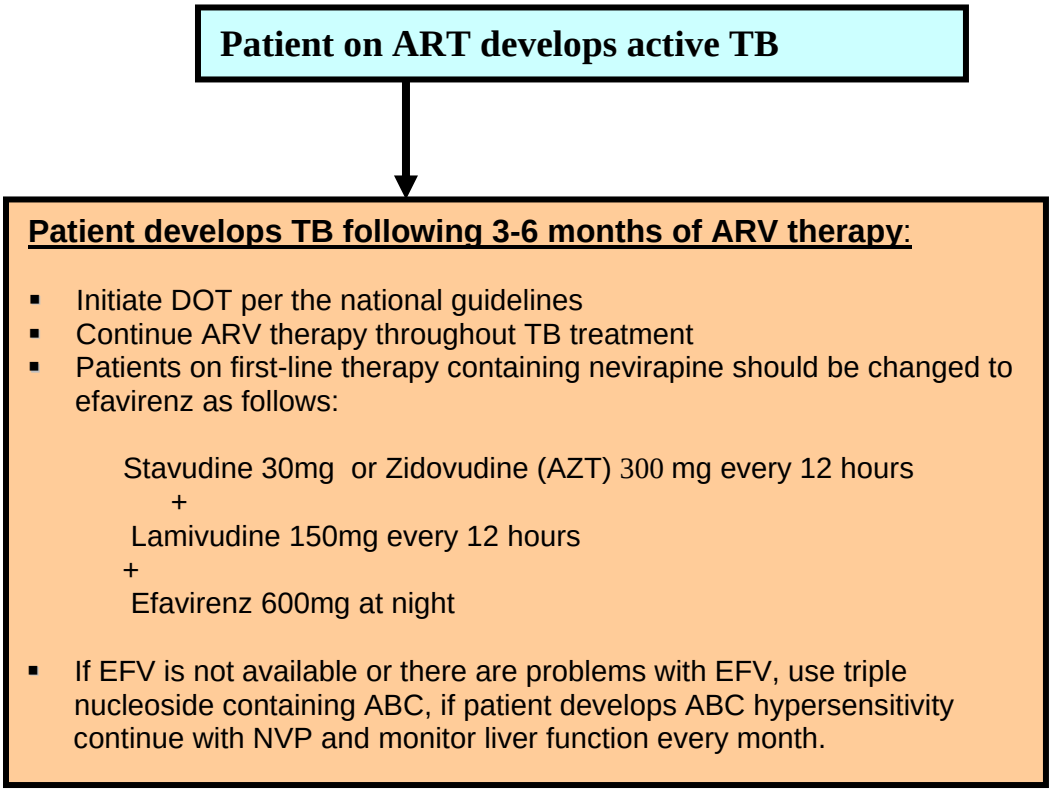

Table 11: shared side effects of anti-TB and ARV drugs

Side effects	ARV drugs	Anti-TB drugs
Nausea	ZDV, RTV, ddI	Pyrazinamide
Hepatitis	NVP, EFV	Rifampicin, INH, Pyrazinamide
Peripheral neuropathy	d4T, ddI	INH
Rash	NVP, EFV	Rifampicin, INH, Pyrazinamide

Remember:

- Patients on TB medication and antiretroviral drugs also probably take cotrimoxazole for prophylaxis, and therefore are on a large number of pills. Besides the pill burden, they might also experience side effects of the different drugs, and remembering the different dosages might also be difficult. Therefore, do pre-emptive counselling, provide support and continue education to improve treatment adherence.

- Patients should be routinely communicated with, counselled and educated about: When ART is started, TB symptoms may transiently worsen due to IRIS.

- HIV-positive persons should be routinely screened for TB at enrolment, and during each follow-up visit. The national TB/HIV guidelines recommend administration of INH Preventive Therapy (IPT) to HIV-infected persons after exclusion of active TB. Refer to the TB-HIV national guidelines for eligibility criteria to initiate IPT.

9. HIV-Hepatitis Co-infection

- Hepatitis B is endemic in many resource-limited countries, including Ethiopia. Since transmission of HBV follows the same model as HIV, the co-infection rate is also high. Hepatitis C virus infection occurs predominantly in injected drug users. HCV/HIV co-infection also occurs among this subset of the population.
- HIV influences the natural course of HBV: a higher rate of progression to advanced liver disease occurs in patients with HIV/HBV co-infection.
- Tests for HBV infection markers such as HBsAg are limited to a few hospitals and private laboratories in Ethiopia. The usual scenario in the care of HIV-infected cases in resource-limited settings is elevated transaminases. In such situations EFV is preferred to NVP, particularly when the transaminase level is above four times the upper limits of normal.
- Patients started on ART may develop mild or severe HBV related IRIS. Milder cases present with some elevation of transaminases. In such situations, continue ART. However, sort out the reason for liver disorder may be difficult because of limitations of lab capacities in most treatment centres in Ethiopia, thus there is high chance of discontinuing ART.
- ARV drugs such as 3TC and TDF are useful for treatment of HBV. 3TC is used as first-line drug in almost all ARV regimens; whether a patient has HBV infection or not. In order to select TDF for both HIV and HBV treatment, at least HBsAg must be determined. However, the preferred first line regimen in this guidelines is TDF/FTC/EFV, therefore, there is no need to do HBsAG to put patients on TDF based regimen now.
- Patients who have been on ARV regimens containing 3TC with or without TDF may develop flare up of HBV when treatment is discontinued.

10. Use of ARV in women of child-bearing potential or pregnancy

- Clinical staging is the same for a pregnant or postpartum woman as for any adult. Use the same staging criteria. The only modification is the weight loss criteria in clinical stage 2 and 3. For a pregnant woman, failure to gain weight during pregnancy can be considered the same as weight loss.

- The guiding principle for ARV use in women of childbearing age or pregnant women is that the therapeutic decision is based solely on their need and eligibility for ART as outlined in section 4.1.

- In situations of resource shortages priority should be given to CD4 testing for pregnant women. If CD4 testing is available but limited, priority should be given for pregnant women in stage 1, 2 or 3, in order to decide whether to start ART or to give ARV prophylaxis.

- A pregnant woman who came primarily for antenatal care and tested HIV-positive can be upset by the test result and might not want to think about ART. It is important to counsel her on the advantages and the urgency of PMTCT interventions, about accessing HIV care and treatment to maintain her health.

- Pregnancy does not preclude the use of ART. However, considerations related to pregnancy may affect the choice of antiretroviral regimen.

- EFV is not recommended for use in women in their first trimester of pregnancy due to its potential for teratogenic effect on the foetus. EFV is not also recommended for women with childbearing potential without provision of effective contraceptive.

- The combination of the dual NRTIs, d4T and ddI should be avoided during pregnancy due to the high risk of toxicity (e.g. Lactic acidosis).

- Make sure HIV-positive pregnant woman are offered the appropriate option:

    1. ART when the woman is medically eligible **plus** ARV prophylaxis to the newborn

    OR

    2. ARV prophylaxis both for the mother and the newborn when the woman **is not yet eligible** for ART.

There are three clinical scenarios for ARV drugs use during pregnancy:

10.1 Women who become pregnant while on ART:

- Women who become pregnant on d4T/3TC/NVP regimen should continue with the same regimen throughout pregnancy, and thereafter. ALT should be performed as indicated.
- For women on EFV and in first trimester, as soon as pregnancy is suspected or confirmed, the EFV should be replaced by nevirapine and the other drugs should be continued. In case the pregnant mother has CD4 >250, triple NRTI are preferred (ABC, 3TC, ZDV)

- Women who develop severe pregnancy-related nausea and vomiting (hyperemesis gravidarum) might require temporary discontinuation of treatment. When this is indicated, all drugs should be stopped and restarted at the same time. Treatment should be restarted after all symptoms of hyperemesis have subsided to ensure the drugs will be well tolerated

- Triple therapy (HAART) is most effective to reduce mother-to-child transmission of HIV. However, the neonate should be offered ARV prophylaxis as per the recommendation of national guidelines for exposed neonates

10.2 Pregnant women eligible for ART

- ART during pregnancy, when medically indicated, will improve the health of the woman and is most effective in decreasing the risk of transmission of HIV to the infant

- If ART is indicated, delay the initiation until 12 weeks (i.e. end of first trimester) unless the benefit of early treatment outweighs any potential for teratogenicity; e.g. mother has evidence for advanced HIV infection (i.e. clinical stage 3 or 4, CD4 under 200 in any clinical stage)

- In women eligible for ART, the benefit of early therapy clearly outweighs any potential foetal risks and thus therapy should be initiated

- HIV-infected women should be assessed for OIs and ART eligibility as part of routine maternal care; anaemia should also be routinely checked for by measuring haemoglobin on the first and follow up visits

- Start ART after the first trimester, with AZT containing regimen (i.e. AZT+3TC+NVP). In patients with moderate to severe anaemia d4T+3TC+NVP

can be used alternatively and the anaemia should be treated at the same time. In pregnant women with CD4 >250 cells/microliter use EFV. If there is contraindication to EFV consider triple NRTI (ABC/3TC/ZDV)

10.3 Pregnant women not eligible for ART:

- HIV-positive pregnant women not eligible for ART should receive ARV prophylaxis for PMTCT purposes, as per the national PMTCT guidelines.

In all the three clinical scenarios for the use of ARVs in pregnant mothers, ARV prophylaxis should be administered to the newborn, based on the national PMTCT guidelines

10.4 Monitoring therapy during antenatal care

- A pregnant woman needs determination of haemoglobin before and then at 4, 6 and 12 weeks after starting AZT. Because of the haemo dilution that occurs normally in pregnancy, severe anaemia is defined as less than 7 g/L
- If ART is provided in the antenatal clinic, the mother should return for weekly visits at least four times, then resume twice-weekly visits until 38 weeks gestation, when weekly visits should resume
- At each follow-up visit, providers should assess adherence to treatment, occurrence of any new signs and symptoms including adverse reactions to the ARV drugs, pregnancy-related problems or complications, IRIS or any other conditions (e.g. malaria)
- Routine lab testing should follow established national ANC guidelines
- Encourage institutional delivery, partner testing and testing of other children
- Inform/counsel the mother that treatment should continue through labour, delivery, postpartum period, and thereafter

An HIV-positive pregnant woman needs extra post-test counselling and support:

- She needs counselling to understand the benefits and accept taking either ARV prophylaxis or ART. Both prevent MTCT; and ART protects her health also
- She needs support to disclose her HIV status to her partner and to get her partner tested. Disclosure may not be simple, however, on-going counselling and understanding the problems of the pregnant and nursing mother are very important. Lack of disclosure is very much related with poor adherence to clinical and drug adherence.
- Extra support is needed if she is medically eligible for ART. Adherence preparation and initiation of ART might need to be rapid to ensure maximum benefit from ART to prevent MTCT
- HIV-positive women might suffer additional stigma and discrimination when they are pregnant, and they themselves might feel guilty about “giving HIV to their baby”. This feeling of guilt may in turn affect her ability to adhere to ART. It is important to address the guilt and assist her in getting beyond it.

- Women who have not disclosed their HIV status may be particularly reluctant about taking ART during pregnancy for fear that their HIV status will be discovered. Assure the woman of confidentiality and assist her in disclosing her status to her partner, family, or friends in whom she has confidence.

10.5 Monitoring Therapy during delivery:

- All ARV therapy initiated during the antenatal period should continue on the same schedule. [Refer to the revised national PMTCT guidelines]
- For patients undergoing caesarean section or other major obstetric intervention, efforts should be made to ensure they receive scheduled antiretroviral therapy.
- After delivery and in the postpartum period, patients should continue receiving the scheduled antiretroviral therapy.

10.6 Care from delivery until 6-weeks postpartum:

- When applicable, a mother discharged from the health facility after delivery should be asked to return weekly to the site where ARVs were administered during antenatal care for follow-up until 6-weeks postpartum. This should also enhance postnatal care for the mother
- At the weekly visits, health care providers should ensure the mother is coping and adhering to treatment
- Providers should ensure patients have adequate ARV supplies, and continue to monitor patients for complications related to pregnancy and delivery, HIV, or ARVs. Patients with complications should be referred to the appropriate health care provider
- Preparations should be made to transit the mother from delivery or antenatal care to an ARV treatment site. Patients should get:
  - An appointment and direction for care at the ART service point
  - Appointments for follow-up with suitable mechanism in place
  - Encouragement to seek support from family, partner and community
- Physical changes in the postpartum, delivery and post partum complications, the demands of caring for the newborn, apprehension related to the transmission of HIV to the baby, and postpartum depression can all make adherence difficult in the postpartum period. The health care provider should pre-empt these issues and provide counselling and support, as required.

Transition to community care as part of the continuum of care:

- Patients should be enrolled in the nearest ART service point
- Standard care should be provided from six weeks after delivery
- Patients who need palliative care should be referred to the appropriate agencies for home-based care with clinic backup

Remember to link the exposed neonate for paediatric care and treatment service after birth. The overall care model should family focused care, i.e., providing the care of the mother, children and male partner in holistic manner, together.

Managing HIV-infected Pregnant Women

All HIV-infected women should routinely be assessed for presence of OIs, including TB, and eligibility for ART during pregnancy, delivery and postnatal checkups. With regard to eligibility to ART, there are three scenarios:

1. **Pregnant women not eligible for ART:**

Manage per the national MCH and PMTCT guidelines.

Follow clinically and immunologically (every 3 to 6 months by CD4 count) to decide on initiation of ART.

2. **Pregnant women who are eligible for ART:**

Commence on first-line treatment:
AZT 300 mg every 12 hrs
3TC 150 mg every 12 hrs
NVP 200 mg daily for 2 weeks, then 200mg every 12 hrs

OR
Use d4T if the Hgb level is <10gm/dl
d4T 30 mg every 12 hours
3TC 150mg every 12 hours
NVP 200mg daily for 2 weeks, followed by 200mg every 12 hours

Plus manage per the national MCH and PMTCT guidelines

3. **Women who become pregnant while on ART:**

Women on EFV:
Consider possible teratogenicity during the first trimester, therefore, substitute EFV by NVP and continue treatment
Plus manage per the national MCH and PMTCT guidelines

Women on d4T/3TC/NVP or AZT/3TC/NVP:
Continue treatment
ALT monthly and when indicated
Monitor Hgb, if the mother is started on AZT (at baseline, 4th, 8th and 12th weeks)
Plus manage per the national MCH and PMTCT guidelines
If pregnant woman cannot take NVP (CD4 >250, history of toxicity, on DOTS intensive phase) put on triple NRTI including ABC/3TC/ZDV. If patients are in the 2nd or 3rd trimester EFV based regimen may be given (TDFor ZDV/FTC or 3TC/EFV) Such patients require attention of ART experienced physicians; therefore they require referral to facilities where these are available.
All infants born to HIV-infected women should receive a course of ARV drugs as post-exposure prophylaxis, per the national PMTCT guidelines

Fixed Dose Combination or Single ARVs	Dosage	Side-Effects	Interactions
Triple ART FDCs			
TDF+FTC+EFV	300mg TDF+ 200mg FTC+600mg EFV One tablet daily	CNS toxicity Teratogenicity in the first trimester pregnancy Rarely renal insufficiency	Avoid during first trimester pregnancy Avoid fatty meal
D4T+3TC+NVP	30 mg d4T+ 150 mg 3TC+ 200 mg NVP One pill twice daily after initial 2 weeks of NVP given as single 200 mg tablet daily	Skin Rash, Hepato-toxicity, pancreatitis Peripheral Neuropathy Lactic acidosis/ fatty liver Lipoatrophy	Avoid: NVP with Rifampin D4T with ddI D4T with AZT
(AZT)ZDV+3TC+NVP	300 mg AZT+ 150 mg 3TC+ 200 mg NVP One pill twice daily after initial 2 weeks of NVP given as single 200 mg tablet daily	Marrow suppresion (anemia/neuropenia), Myopathy, GI Disturbance (nausea/vomiting) Lactic acidosis/ fatty liver Lipoatrophy, Skin Rash, Hepato-toxicity	Avoid: NVP + Rifampin D4T + AZT D4T+ ddI
Dual ART FDCs			
D4T+3TC	30 mg D4T+ 150 mg 3TC One pill twice daily	Hepato-toxicity, pancreatitis Peripheral Neuropathy, Lactic acidosis/ fatty liver Lipoatrophy	Avoid: D4T +ddI D4T + AZT
ZDV+3TC	300 mg ZDV+ 150 mg 3TC One pill twice daily	Marrow suppression (anemia/neutropenia), myopathy, GI upset, Lactic acidosis/ fatty liver	Avoid: D4T + AZT
Single ARVs			
Zidovudine (ZDV)	300 mg Twice daily	GI upset, marrow suppression, asthenia, myopathy, rarely lactic acidosis	Avoid combination with d4T
Didanosine (ddI EC)	250 mg, 400 mg Once daily	Lactic acidosis/HS, pancreatitis, peripheral neuropathy, GI intolerance	Avoid ddI + TDF, d4T+ddI, ddI +Ribavrin Take on empty stomach
Lamivudine (3TC)	150 mg twice daily Or 300 mg once daily	Well tolerated; rare side effects	Avoid: 3TC+FTC (same drug)
Stavudine (d4T)	30 mg twice a day	Peripheral neuropathy, Pancreatitis, Lactic acidosis, fatty liver, Lipoatrophy	Avoid using with AZT
Tenofovir (TDF)	300 mg TDF One pill once a day	Rare renal insufficiency; Requires dose adjustment in renal failure	Avoid: TDF + ddI TDF + ABC
Abacavir (ABC)	300 mg ABC One pill twice daily	Hypersensitivity reaction	Avoid: ABC+TDF
Nevirapine (NVP)	200 mg po daily for first 14 days; then 200 mg po twice daily	Rash – mild and severe, SJS Hepatoxicity	Avoid: NVP + Rifampin
Efavirenz (EFV)	600 mg EFV Once at bedtime	CNS toxicity Teratogenicity in first trimester pregnancy	Avoid: EFV + fatty meal Pregnancy

Fixed Dose Combinations and Single ARVs Available in Ethiopia April 2008-04

The following table summarizes the different special scenarios and the regimens to be used in those conditions

1.	First line: Standard regimen	• (TDF or ZDV) + (FTC or 3TC) + (EFV or NVP) (Preferred). • D4T + 3TC+ (EFV or NVP)(Alternative)
2.	First line: women who may become pregnant	• ZDV + 3TC + NVP (Preferred) • d4T + 3TC+ NVP (Alternative)
3	1st Line: • Pregnant women First trimester • Pregnant women beyond First trimester	• ZDV + 3TC + NVP (Preferred) • d4T + 3TC+ NVP (Alternative) First line standard: • (TDF or ZDV) + (FTC or 3TC) + (EFV or NVP) (Preferred). • D4T + 3TC+ (EFV or NVP)(Alternative)
4	First line: Concomitant TB Rx	• (TDF or ZDV) + (FTC or 3TC) + EFV (Preferred) • D4T + 3TC+ EFV (Alternative)
5	First line: Pregnancy and TB • First trimester • Beyond First trimester	• Triple nuke (ABC+3TC+ZDV) • (TDF or ZDV) + (FTC or 3TC) + EFV or NVP (Preferred) • D4T + 3TC+ EFV or NVP (Alternative)
6	First line: Toxicity to standard regimen (1)	• ZDV induced anemia substitute d4T • D4T related peripheral neuropathy and pancreatitis substitute ZDV • D4T related severe[4] Lipoatrophy substitute TDF or ABC same is true to d4T caused LA and HS
7	1st Line: toxicity to drug 1 after prior switch	TDF or ABC
8	1st Line: Toxicity to drug 1, pregnant	No difference
9	1st Line: toxicity to drug 1, contraindication to standard switch	TDF or ABC
10	1st Line: toxicity to drug 3	NVP to EFV in hepato-toxicity, severe skin reaction NVP to PI in severe life-threatening skin reaction(SJS and TEN) and NVP induced hepato-toxicity EFV to NVP in severe neuropsychiatric problems
11	1st Line: Toxicity to drug 3 after prior switch	PI
14	1st Line: Incident pregnancy	If on EFV in 1st trimester switch to NVP If on EFV in 2nd and 3rd trimester continue If on NVP continue with NVP
15	1st Line: incident TB	Switch NVP to EFV If duration of ART is > 6/12 consider Rx failure

[4] Severe Lipoatrophy is: 1) changes noticed by the patient, 2) stigmatizing 3) affecting quality of life and 4) accompanied by dyslipidemia.

How to switch to Fixed Dose Combination (FDC) in patients who are taking ART now:

1. Patients on d4T+3TC+NVP will be switched to triple FDC of same drugs to be taken one pill bid.
2. Patients on AZT+3TC+NVP will be switched to triple FDC of same drugs to be taken one pill bid.
3. Patients on d4T+3TC+EFV will be switched to double FDC of d4T+3TC and EFV.
4. Patients on ZDV+3TC+EFV will continue taking combivir and EFV.

Treatment naïve patients who will be started with the updated ART guidelines will take:

1. TDF+FTC+EFV as triple FDC unless there is contraindication to this combination. For the alternative regimens see the above table.

11. Adherence

11.1. General Consideration

- High level of adherence to ART is mandatory in patients for the success of the treatment. Poor adherence results in emergence of drug resistance with implications to the individual patient and the community.

Table 12: Correlation between adherence and virologic response to ART

Adherence to ART*	Viral Load <400 copies/ml
>95% adherence	78%
90- 95% adherence	45%
80- 90 % adherence	33%
70- 80 % adherence	29%
<70% adherence	18%

- Multiple factors contribute to optimal treatment adherence. As ART is life long, patients might easily develop “treatment fatigue”; transport costs, lack of support, non-disclosure, drug side effects, pill burden, stigma, undiagnosed depression, poor quality service delivery set up, and substance use also contribute to poor adherence.

- Health care providers cannot accurately predict who will adhere to treatment. However, poor adherence to earlier medications, substance abuse, poorly-managed psychiatric problems including depression, non-disclosure of HIV status and lack of a treatment supporter, indirect or "hidden" costs of care, presence of internalized stigma and shame related to HIV-infection are common risk factors.

11.2 Role of the Health Care Team in Adherence Assessment, Support and Monitoring:

Patients are not started on ART without adequate adherence assessment counselling. The counselling encourages disclosure and involves the family, friends, social support systems such as home based care

- Adherence might wane with time; therefore, it has to be ongoing whenever patients encounter providers
- Building trust between the patient and care provider/health care system supports good treatment adherence. Optimal adherence requires full participation by the health-care team, with patient interaction representing an opportunity for trust building and adherence message reinforcement.
- Adherence assessment and support is primarily the responsibility of the adherence counsellor and pharmacist. Clinicians should also be involved in adherence counselling and ongoing adherence monitoring at each clinical visit making timely response to adverse events or interim illness. Interim management during clinician vacations or other absences must be clarified with the patient.
- New patients and high risk patients (low educational level, family and social problems, alcohol or drug abuse, patients on treatment not doing well, patients with sub-optimal adherence or poor adherence) need more focus in adherence counselling. More visits and family or support system engagement are necessary for this

Table 13: Some Adherence Strategies

Strategies to Promote Treatment Adherence
• Spend time and have multiple encounters with clients, their family and treatment supporter to explain goals of therapy and need for adherence • Assess the level of compliance in using current or previous medications to predict adherence to ARV drugs • Negotiate a treatment plan the patient can understand and to which s/he can commit. Encourage disclosure to family members, friends, or support groups who can support the treatment • Inform patient of potential side effects – degree of severity, duration, what to do about side effects, when to return to the facility, and coping mechanisms. Even "minor" side effects can lead to poor treatment adherence. Therefore anticipate, monitor, and manage side effects. • Establish level of 'readiness' to take medications before ARV initiation • Provide adherence tools where available: written calendar/daily schedule of medications, pill boxes or other tools, as deemed appropriate for the local context • Provide tips and skill to support adherence: Encourage use of alarms or other available mechanical aids for adherence • Avoid adverse drug interactions; advice patients to avoid use of over-the-counter drugs and traditional medicines • Create links with support groups and patient advocates and encourage discussions on adherence. Develop links with associations of PLWHA and community-based organizations to support adherence. • Should distance be a barrier and patient accepts it, transfer patient to their nearest ART site for subsequent follow up • Ensure same follow-up appointment dates for family members, and coordinate for same day visit for different services e.g. TB and ART clinic, ANC and ART clinic, etc. • Provide accurate information with regard to follow-up schedule; provide written schedule

12. Management of adverse ARV drug reactions

Adverse drug reactions are common, ranging from mild to life-threatening conditions. They usually occur within the first 6- 12 weeks but metabolic toxicities happen following prolonged use of ARVs. The mild toxicities require symptomatic therapy as they are self-limiting but these toxicities require counselling so that patients need to continue treatment. Some toxicities are due to class-specific effects while others are related to individual drugs. Adverse drug reactions can produce a diagnostic challenge with IRIS e.g. viral hepatitis versus nevirapine hepatotoxicity. In Ethiopia, where options for

regimen selection are limited it is important to minimize premature substitutions of ARVs during mild to moderate drug reactions.

12.1 Strategies for managing adverse drug reactions:

Step 1 Establish whether the problem is due to antiretroviral drugs, other medications, OIs, non-HIV related problems or clinical condition.
Step 2 Try to identify the responsible ARV drug.
Step 3 Assess the degree/severity of the Adverse Event using the ACTG/PACTG adverse events grading system
Step 4 Manage the adverse event according to severity and also decide whether to substitute or discontinue ARV drug

- **Grade 1 (Mild reaction):** are bothersome but do not require changes in therapy
- **Grade 2 (Moderate reaction):** consider continuation of ART as long as feasible. If the patient does not improve in symptomatic therapy, consider single-drug substitution.
- **Grade 3 (Severe reaction):** Substitute offending drug without stopping ART. Closely monitor using laboratory and clinical parameters.
- **Grade 4 (Severe life-threatening reaction):** Immediately discontinue all ARV drugs, manage the medical event with symptomatic and supportive therapy, and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilised. STOP all drugs at the same time. Life-threatening toxicity includes severe hepatitis, pancreatitis, lactic acidosis or Steven-Johnson syndrome.

Step 5: If there is an urgent need to discontinue antiretroviral therapy, ALL antiretroviral medications must be stopped at the same time, until the patient stabilizes. Never stop just one or two.

12.2 Grading adverse reactions in adults and adolescents

- Adverse reactions will be graded according to the AIDS Clinical Trial Groups (ACTG) grading. Consider grading both clinical and laboratory abnormalities and manage them as shown in the tables below.

Table 14: Clinical adverse events in adults and adolescents

ITEM	GRADE 1 MILD TOXICITY	GRADE 2 MODERATE TOXICITY	GRADE 3 SEVERE TOXICITY*	GRADE 4 SEVERE LIFE-THREATENING TOXICITY
Peripheral neuropathy	• Transient or mild discomfort, no limitation of activity • no medical intervention/treatment required	• Moderate limitation of activity, some assistance might be needed • Non-narcotic analgesia required	• Marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalization possible • severe discomfort and/or severe impairment (decrease or loss of sensation up to knees or wrists) narcotic analgesia required	• Life-threatening, extreme limitation in of activity, significant assistance required, significant medical intervention/ therapy required, hospitalization/ hospice care • Incapacitating or not responsive to narcotic analgesia • Sensory loss involves limbs and trunk
Cutaneous/Rash /Dermatitis**	Erythema, pruritus	Diffuse, maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration*	Erythema multiforme or suspected Stevens-Johnson syndrome or Toxic Epidermal Necrolysis (TEN)
Management	Continue ARV Provide careful clinical monitoring Consider change of a single drug if condition worsens		substitute responsible drug	Stop ARV and consult experienced physician

* Additional clinical indications to change ARVs due to grade 3 toxicity (See Table 16 for substitution)

Nausea: Severe discomfort or minimal intake for $\geq$ 3 days
Vomiting: Severe vomiting of all foods/fluids in 24 hours, orthostatic hypotension, or necessity for IV therapy
Diarrhoea: severe diarrhoea, with orthostatic hypotension, or necessity for IV therapy
Headache: Severe or requires narcotic therapy
Allergic reaction: Angioedema or anaphylaxis
Fatigue: Normal activity reduced $\geq$50 %

** For a patient on nevirapine, rash with mucosal involvement or associated with fever and/or systemic symptoms, and/or derangement in liver functions should be treated as Grade 4 toxicity.
ALL antiretroviral drugs should be stopped immediately.

- Primary care centres should consult with more experienced physician before recommencing ART after a serious adverse effect
- Never re-challenge with nevirapine

- Do not substitute EFV for nevirapine after G4 toxicity but when there are no alternatives to substituting NVP it may be possible to use EFV cautiously[5]. Triple NRTI may be used.

Table 15: Laboratory Grading of Adverse Events in Adults and adolescents (ACTG)

Laboratory Test Abnormalities				
ITEM	**GRADE 1 TOXICITY**	**GRADE 2 TOXICITY**	**GRADE 3 TOXICITY**	**GRADE 4 TOXICITY**
Haemoglobin	8.0-9.4 g/dL	7.0-7.9 g/dL	6.5-6.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1,000-1,500 mm3	750-990 mm3	500-749 mm3	<500 mm3
Platelets	-75,0000- 99,000	50,000-74,999	20,0000-49,999 mm3	<20,000
ALT	1.25-2.5 X upper normal limit	2.5-5 X upper normal limit	5.0-10 X upper normal limit	10 X upper normal limit
Bilirubin	1-1.5XULN	1.5-2.5 X ULN	2.5-5 x upper limits of normal	>5 x upper limits of normal
Amylase/lipase	1-1.5XULN	1.5-2 X ULN	2-5 x upper limits of normal	>5x upper limits of normal
Triglycerides *	200-399mg/dL	400-750 mg/dL	751-1200mg/dL	>1200mg/dL
Cholesterol *	1.0 –1.3 X Upper normal limit	1.3-1.6 X Upper normal limit	1.6-2.0 X Upper normal limit	2.0 X Upper normal limit
MANAGEMENT	Continue ARV Repeat test 2 weeks after initial test and reassess		substitute responsible drug	Stop ARV and consult experience physician
	Lipid imbalances could be managed with diet, exercise and pharmacologically with the use of fibrates. ALWAYS SEEK EXPERT ADVICE IN CASE OF DOUBT			

[5] Continue with the NRTI back bone and substitute EFZ after 1-2 weeks.

- ***Refractory hyperlipedemia after treatment with lipid-lowering agents is indication to substitute the offending drug.***

Decision checklist not to start or stop ARV drugs

- ***Jaundice***
- ***Hg <6.5 gm/dl***
- ***Severe vomiting (not capable of taking food or medication)***
- ***Severe skin rash (vesicles, desquamations, mucosal involvement, conjunctivitis, systemic manifestations such as fever***
- ***ALT > 5 X upper limit***
- ***Fatigue, nausea, vomiting, hepatomegaly---- as manifestations of lactic A.***

12.3 Some complications and their management:

Nausea:

- Seen with ZDV, ddI and PIs
- Nausea due to antiretroviral medication must be actively managed, as it can potentially be a barrier for treatment adherence
- Antiemetics such as metoclopramide, promethazine given half an hour before the antiretroviral dose up to three times daily may be helpful. If the nausea does not settle, refer for expert advice or consider changing ARV regimen (see Table 16).

Rash:

- Both nevirapine and efavirenz may cause skin reactions. This usually occurs within the first two months of treatment. Concomitant TB therapy may confound the situation as these drugs can cause similar adverse events.
- Clinical assessment to rule out other causes of rash (Table 16). Enquire about systemic symptoms, and check the temperature in a patient presenting with a rash.
- For nevirapine, liver function tests also need to be evaluated

Abdominal pain:

- Abdominal pain in a patient on antiretroviral treatment can be caused by a number of serious problems, and should never be ignored
- Important causes include lactic acidosis, pancreatitis, hepatitis, and disseminated tuberculosis
- Recommended investigations: liver functions, lipase, and serum lactate. (Refer for further investigations as needed)
- Seek expert help and refer if you are unsure of the cause of the pain

Acute pancreatitis:

- Seen with ddI and d4T, particularly when used in combination (i.e.d4T+ddI).
- Symptoms include peri-umbilical abdominal pain, nausea and vomiting
- Diagnosis is confirmed by determining level of serum amylase
- Management: discontinue all ARVs. Treatment is supportive– IV fluids, pain controls and NPO.
- When all symptoms resolve restart ART with change to different NRTI (i.e. ZDV or ABC).

Hyperlactataemia and lactic acidosis:

- Asymptomatic elevation of lactate is common in patients taking antiretroviral therapy: 1-2% per year develops symptomatic hyperlactataemia and (more rarely) 0.1-0.2% develops lactic acidosis.
- Risk factors for lactic acidosis include female gender, obesity, prolonged antiretroviral therapy, and excellent adherence with therapy, chronic renal failure and pregnancy, etc.
- It is seen as a complication of d4T, ddI or both; AZT is a less frequent cause.
- Symptoms are non-specific and include;
    - Unwellness, generalized fatigue, weakness
    - Gastrointestinal symptoms (nausea, vomiting, abdominal pain, abdominal distension and bloated ness)
    - Shortness of breath, dyspnoea, tachypnoea
    - Neurological symptoms (disequilibrium, motor weakness)

  Suspect lactic acidosis in presence of risk factors mentioned above and when the following conditions happen after prolonged (>6 months) use of offending drugs, clinical onset is insidious, and duration of illness more than two weeks.

    1. unexplained tachypnea.
    2. unexplained GI upset
    3. unexplained fatigue
    4. hepatomegally with steatosis on sonography of the liver.
    5. unexplained elevation of liver enzymes and/or reduced serum albumin.
    6. widening of the anion gap >16; anion gap is the difference between (sodium + potassium) - (chloride+ bicarbonate).
- Diagnosis is confirmed by laboratory test (determination of serum lactate).

Management of lactic acidosis*:*

- STOP all antiretroviral therapy and seek urgent expert help
- Symptoms associated with lactic acidosis may continue or worsen following discontinuation of antiretroviral therapy
- Therapy is primarily supportive (fluid, bicarbonate administration and respiratory support)
- After recovery, seek expert advice regarding antiretroviral selection. Stavudine and didanosine should be avoided. Drugs to consider for restarting ART include TDF, ABC and PIs; they should be initiated at least four weeks after discontinuation of the previous regimen.

Lipodystrophy:

- Lipodystrophy consists of two components that may be seen together or independently: fat accumulation and fat atrophy. Fat mal-distribution is seen in distinct regions of the body, such as the abdomen and dorso–cervical fat pad (buffalo hump) and breasts (gynecomastia). Another feature of lipodystrophy is of sunken cheeks due to lipoatrophy with loss of buccal fat. In addition, thinning of extremities and buttocks due to fat loss can happen at the same time.
- Fat accumulation is primarily associated with PI use, while atrophy is usually seen with NRTIs, especially d4Tand to a lesser extent with AZT, TDF and ddI.
- Some patients show a combination of abdominal obesity, hypertension, dyslipidemia, and insulin resistance that simulates the metabolic syndrome, or "syndrome X".

Management: There are no established methods for treating lypodystrophy. Encourage a low fat diet and exercise to reduce fat accumulation. Some patients improve if changed from a protease inhibitor to an NNRTI and from d4T to other NRTI.

Hyperlipidaemia:

- Patients who develop hyperlipidaemia should be counselled about lifestyle modification (weight-loss if obese, increasing exercise, stopping smoking, reducing cholesterol and saturated fat intake) and referred to a dietician, if available, for dietary advice.
- Severe hyperlipidaemia may require drug management. In patients with HIV infection pharmacologic therapy of dislipidemia should be guided by standard guidelines. When statins are indicated, avostatin and pravastatin could be used safely. However use of simvastatins and lovastatin should be avoided to prevent drug interactions with ART. If triglyceride >5.6 mmol (>500 mg/dl) after dietary changes or LDL >4.9 mmol (>220 mg/dl) or LDL >3.4 mmol (>160 mg/dl) with two or more other ischemic heart disease risk factors, commence fibrates or atorvastatin respectively.

Table 16: Recommended Single-drug substitutions for specific side effects (grade 3 or 4 toxicity)

ARV drug	Common associated toxicity	suggested substitution
ABC	Hypersensitivity reaction	AZT or TDF or d4T
AZT	Severe anemia[a] or neutropenia[b] severe GI intolerance[c]	TDF or d4T or ABC
	lactic acidosis	TDF or ABC[d]
d4T	Lactic acidosis Lipoatrophy/Metabolic syndrome[e]	TDF or ABC[d]
	Peripheral neuropathy	AZT or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction	AZT or ABC or d4T
EFV	Persistent and severe CNS toxicity[f]	NVP or TDF or ABC (or any PI[h])
	Potential teratogenicity (1st trimester of pregnancy or women not using adequate contraception)	NVP or ABC (or any PI[h])
NVP	Hepatitis	EFV or TDF or ABC (or any PI[h])
	Hypersensitivity reaction	TDF or ABC (or any PI[h])
	Severe or life-threatening rash (Stevens-Johnson syndrome)[g]	

[a] Exclude malaria in the areas of stable malaria; severe anemia (grade 4) is defined as Hg < 6.6 gm/dl.
b Defined as neutrophil cell count <500/mm3 (grade 4)

[c] Defined as severe, refractory GI intolerance that prevents ingestion of ARV drug regimen (e.g., persistent nausea and vomiting).
[d] Reinstitution of ART should not include d4T or AZT in this situation. TDF or ABC is preferred.
[e] Substitution of d4T may not reverse lipoatrophy.
[f] e.g. persistent hallucinations or psychosis.
[g] severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema or conjunctivitis; Stevens-Johnson syndrome can be life-threatening rash, substitution with EFV is not recommended, although this approach has been reported in a small number of patients in Thailand without recurrence of rash.
[h] PI class should be preferentially reserved for second-line therapy as no potent regimens have been identified for recommendation following initial PI failure.

12.4 Drug interactions

Protease inhibitors (e.g. lopinavir/ritonavir) and non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine) can interact with a number of other drugs, through changes in drug metabolism in the liver.

- The active ingredients in traditional drugs in the Ethiopian situation are not known; therefore it is better to avoid traditional medicine once ARV drugs have been started.
- Table 19 shows examples of drugs that should be avoided when administered with efavirenz, nevirapine, some PIs or all 3 drugs. Beware of other drug interactions that may require dosage adjustment (anticonvulsant, psychiatric, anti-infective, cholesterol lowering drugs, oral contraceptives, etc). Seek expert advice if the patient is taking one of these drug combinations.
- There are NO KNOWN drug interactions with the NRTI class i.e. d4T, 3TC, and ZDV.

Table 17: Contraindicated ARV drug combinations

Agent by Class	Agents prohibited with lopinavir/ritonavir	Agents prohibited with NVP and EFV
Antiarrhythmic agents	Fleicanide Propafenone	Amiodarone Fleicanide Quinidine
Antihistamines	Astemizole Terfenadine	Astemizone Terfenadine
Anti-infective	Rifampicin [6]	Systemic Ketoconazole [a]
Cholesterol lowering agents	Lovastatin Simvastatin	
GI Motility	Cisapride	Cisapride [b]
Sedative/hypnotics	Midazolam Triazolam	Midazolam [b] Triazolam [b]
Other	Ergot derivatives Bepridil (Calcium Channel blocker) Pimozide Sildenafil(Viagra)• Anticonvulsant (phenobarbitone, carbamazepine and phenytion)♣ Warfarin ♥ Metronidazole ∗.	Ergot Derivatives [b] Sildenafil(Viagra)• Anticonvulsant (phenobarbitone, carbamazepine and phenytion)♣ Warfarin ♥

[a] Ketoconazole is prohibited with NVP only, but EFV can reduce its efficacy.
[b] Prohibited only with EFV.
• Don't exceed 25 mg over 48 hours.
♣ Consider valporic acid as alternative or if this option is not available consider serum levels of the anticonvulsants.
♥ use with caution
∗ Can cause disulfiram-like reaction.

[6] Rifampicin is not recommended with NVP.

13. Post Exposure management including Prophylaxis

13. 1 Management of occupational exposure to HIV:

- Health care workers and support staff have a low but measurable risk of HIV infection after accidental exposure to infected blood or body fluid
- Compliance with infection prevention recommendations is the mainstay in prevention of occupational HIV infection. The priorities therefore must be to train health personnel in infection prevention and provide them with necessary materials and protective equipment
- Risk of HIV infection after a needle stick or cut exposure to HIV-infected blood is estimated to be 0.3% (3 in 1000). Stated another way, 99.7% of needle stick/cut exposures do not lead to infection. The risk of HIV infection after exposure of mucous membranes to HIV-infected blood is estimated to be 0.1% (1 in 1000). However, risk could vary depending on severity of injury and viral load in the source patient.
- Antiretroviral treatment immediately after exposure to HIV can reduce risk of infection by about 80%.

13.2 Set up for post exposure management in health facilities.

- Regular prevention education for employees (health workers, cleaners and other staff involved in institutional care for PLWHA.
- Ensure availability of control mechanisms for effective observation of Universal Precaution (UP).
- Establish system for post exposure management to ensure urgent attention for victims who have sustained accidental blood exposure.

13.3 Assessment of exposure risk:

13.3.1 Low-risk exposure:

- Exposure to small volume of blood or blood contaminated fluids from asymptomatic HIV positive patients
- Following injury with a solid needle
- Asymptomatic source patient

13.3.2 High-risk exposure:

- Exposure to a large volume of blood or potentially infectious fluids
- Exposure to blood or potentially infectious fluids from a patient with clinical AIDS or acute HIV infection
- Injury with a hollow needle
- Needle used in source patient artery or vein
- Visible blood on device
- Deep and extensive injury

Table 18: Recommendations for post exposure prophylaxis (PEP) after occupational exposure to infectious material

Site of Exposure	HIV status of source person		
	Unknown	Positive	
		Low risk	High risk
Mucosal splash/ Non-intact skin	Consider 2-drug regimen	Recommend 2-drug regimen	Recommend 3-drug regimen
Percutaneous (sharps)	Recommend 2-drug regimen	Recommend 2-drug regimen	Recommend 3-drug regimen

Table 19: Recommended ARV drug regimens for PEP

ARV drug regimen	Dose	Frequency	Duration
2-Drug Regimen: Zidovudine (AZT) + Lamivudine (3TC)	AZT 300mg 3TC 150mg	12 hourly	28 days
3-Drug Regimen: Zidovudine (AZT) + Lamivudine (3TC) + EFZ. Lopinavir/ritonavir (LPV/r) can be used as alternative if available.	AZT 300mg 3TC 150mg EFZ 600mg (daily) LPV/r 400mg/100mg	12 hourly	28 days

13.4 Timing of initiation of prophylaxis:

- To be effective, post-exposure prophylaxis should commence as soon as possible (within 1-2 hours). The maximum delay for initiation of treatment which would prevent infection is not known in humans. In most developed countries, PEP is commenced within 2-4 hours. Don't consider PEP beyond 72 hours post exposure. Prophylaxis is to be given for 28 days.

13.5 Testing and monitoring after occupational exposure:

- Testing source: rapid test is done after counselling and consent has been secured. If the source patient is negative there is no need of further assessment of the exposed health care worker. If the result is positive the health care worker needs to be tested
- Testing of health care worker: HIV serology should be performed immediately after exposure. If result is positive there is no need for PEP, but if negative you should administer PEP as soon as possible as outlined above and then repeat serology at 6 weeks, 3 months, and 6 months

- Remember to initiate PEP immediately after exposure until test result confirms the HIV status of the victim. Stop PEP if the health worker is positive for HIV antibodies
- Following HIV exposure there is a need for psychosocial support

13.6 Prevention of the transmission of the Human Immunodeficiency Virus (HIV) after sexual assault:

1. All women 14 years and older presenting to a health facility after potential exposure to HIV during sexual assault should be counselled by the examining health care worker about the potential risk of HIV infection.

2. Parents/guardian of traumatized children should be counselled and informed on the risk of HIV infection after sexual assault.

3. The following points should be covered in the counselling:
   a. The exact risk of transmission is not known, but it exists
   b. It is important to know the victim's HIV status prior to any antiretroviral treatment
   c. It is the patient's choice to have immediate HIV testing or, if s/he prefers, this can be delayed until 72 hours post examination visit (management guidelines on sexual assault provides for a 3-day starter pack for those who prefer not to test immediately, or those that are not ready to receive results immediately). However, encourage the patient to be tested.
   d. PEP is not recommended after 72 hrs following sexual assault. Patients should be counselled about risk of infection and the possibility of transmitting infection during seroconversion. They should be instructed to return at 6 weeks and 3 months post sexual assault for voluntary counselling and HIV testing.

4. It is strongly recommended that the implementation of post-rape prophylaxis should be carefully monitored and evaluated for:
   - Psychosocial and legal support
   - Screening for conventional STIs and follow up management
   - Drug side effects
   - Seroconversion

Recommendations for HIV prophylaxis after sexual assault

PEP is not recommended a) if victim presents more than 72 hours after exposure b) Following condom leak or tear
Recommended regimen AZT/ 3TC/EFZ or d4T/3TC/ EFZ for 28 days. Alternatively, Kaletra can substitute for EFZ.

14: appendix

Appendix 1: WHO Clinical Staging for HIV Infection in Adults and Adolescents

ANNEX 1. WHO CLINICAL STAGING OF HIV DISEASE IN ADULTS AND ADOLESCENTS

CLINICAL STAGE 1
Asymptomatic
Persistent generalized lymphadenopathy
CLINICAL STAGE 2
Moderate unexplained[a] weight loss (under 10% of presumed or measured body weight)[b]
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections
CLINICAL STAGE 3
Unexplained[a] severe weight loss (over 10% of presumed or measured body weight)[b]
Unexplained[a] chronic diarrhoea for longer than one month
Unexplained[a] persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained[a] anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9 /l)

CLINICAL STAGE 4[c]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a Unexplained refers to where the condition is not explained by other conditions.

b Assessment of body weight among pregnant woman needs to consider the expected weight gain of pregnancy.

c Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

Source: *Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance.* 2006 (in press).

Appendix 2: Fixed Drug Combination of ARVs.

Three-drug fixed-dose combinations	d4T (40mg) + 3TC (150 mg) + NVP (200 mg) d4T (30mg) + 3TC (150 mg) + NVP (200 mg) ZDV (300mg) + 3TC (150 mg) + ABC (300 mg) ∗ ZDV (300mg) + 3TC (150 mg) + NVP (200 mg) TDF(300mg) + 3TC (300 mg) + EFZ (600mg)♥ TDF (300mg) + FTC (200mg) + EFZ (600mg)♥
Two drug fixed-dose combination	d4T (30 mg) + 3TC (150 mg) d4T (40 mg) + 3TC (150 mg) ZDV(300 mg) + 3TC (150 mg)
∗ This regimen should be used as alternative during co-management of TB and pregnancy when ever indicated. ♥ This is a once daily regimen and a preferred regimen for co management of HBV.	

Appendix 3: Dosages of Antiretroviral Drugs for Adults and Adolescents

Drug class/ drug	Dose [a,b]
Nucleoside RTIs	
Abacavir (ABC)	300 mg twice daily
Didanosine (ddl)	400mg once daily (250 mg once daily if <60 kg) (250 mg once daily if administered with TDF)
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (ZDV)	300 mg twice daily.
Emtricitabine (FTC)	200 mg daily.
Nucleotide RTI	
Tenofovir (TDF) 300 mg once daily (Note: drug interaction with ddI necessitates dose reduction of latter)	
Non-nucleoside RTIs	
Efavirenz (EFV)	600 mg once daily
Nevirapine (NVP)	200 mg daily for the first 14 days, then 200 mg twice daily
Protease inhibitors	
Lopinavir/ ritonavir (LPV/r)	400 mg/ 100 mg twice daily (533mg/ 133 mg twice daily when combined with EFV or NVP)
Nelfinavir (NFV)	1250 mg twice daily
Saquinavir/ ritonavir (SQV/ r)	1000 mg/100 mg twice daily or 1600 mg/100 mg once daily [bc]

[a] These dosages are in common clinical use. The dosages in this table were selected on the best available clinical evidence. Dosages that can be given once daily or twice daily were preferred in order to enhance adherence to therapy. The doses listed are those for individuals with normal renal and hepatic function. Product-specific information should be consulted for dose adjustments that may be indicated with renal or hepatic dysfunction or for potential drug interactions with other HIV and non-HIV medications

[b] zidovudine, lamivudine, emtricitabine and stavudine dosages should be adjusted for the creatinine clearance during renal insufficiency.

[c] Both the hard-gel and soft-gel capsule formulations can used when SQV is combined with RTV

Appendix 4: Characteristics of Available ART.

Generic Drug (Brand)	**Available adult Preparations in mg**	**Toxicities**	**Special considerations**
Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
Abacavir (ABC Ziagen)	300	Common: nausea, vomiting, fever, headache, diarrhoea, rash and anorexia -Severe: Hypersensitivity reaction (5%)	No food restriction With severe reaction drug should be discontinued immediately and there should not be re-challenge
Didanosine (ddI, Vidax)	25,50,100,125, 150,250,400	Common: Diarrhoea, nausea, vomiting and abdominal pain Less common but severe: Peripheral neuropathy, lactic acidosis and electrolyte abnormality and hyperuricemia	Food decreases absorption and hence has to be taken with empty stomach.
Lamivudine (3TC, Epivir)	150mg; same dose in combination with AZT and ABC.	Common: headache fatigue, nausea, diarrhoea, skin rash and abdominal pain mainly in children Less common but severe: pancreatitis, peripheral neuropathy, reduced neutrophil count and increased liver enzymes again in children.	Can be administered with food Decrease dosage in patients with impaired renal functions.
Stavudine (d4T, Zerit	Capsules of 15, 20,30 and 40 mg	More common: headache, GI	Can be administered

		disturbance and skin rash. Less common: (more severe)peripheral neuropathy and pancreatitis, lactic acidosis and hepatic steatosis. Rarely increased liver enzymes	with food Decrease dosage in patients with impaired renal functions.
Zidovudine (AZT,ZDV, Retrovir)	Tablets 300, capsules 100, injections 10mg/ml Also same dose in combination with 3TC and ABC	More Common: anaemia thrombocytopenia and headache Less common: myopathy, myositis and liver toxicity. Unusual but severe: lactic acidosis, hepatomegally with steatosis.	Can be administered with food Decrease dosage in patients with impaired renal functions. Reduce dosages in substantial hepatic dysfunction
Non nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
Efavirenz, Strocrin, Sustiva	200mg, 600mg	More common: skin rash, somnolence insomnia, vivid dreams, confusion, impaired concentration, agitation, euphoria, hallucinations) Increased aminotransferase levels, Teratogenic effect in first trimester.	Avoid administration with high fat meal Better given at bedtime to improve tolerability. Can be taken with food
Nevirapine (NVP,Viramune)	200 mg	More common: potentially life-threatening skin rash (SJS, TEN) and abnormal liver function tests. Less common: hepatitis and	Can be administered with food. Patient should be informed to contact the health facility for evaluation if signs and

		severe muco-cutaneous hypersensitivity reactions	symptoms develop.
Protease inhibitors.			
Lopinavir/Ritonavir (Kaletra,LPV/RTV	400mg Lopinavir/100mgRitonavir	More common; diarrhoea, headache, asthenia, nausea and vomiting. Rare bleeding episode, diabetes, hepatitis, dyslipidemia and pancreatitis	Administer with food. High fat meal can increase absorption If co-administered with ddI, ddI should be taken one hour before or two hours after Kaletra.
Nelfinavir (NFV, Viracept)	250 mg tablet.	More common; diarrhoea Less common; asthenia, abdominal pain, rash, diabetes, dyslipidemia and rarely bleeding tendency.	Administration with food to increases absorption If co administered with ddI, NLV should be administered one hour later or two hour after.
Saquinavir (SQV, Inverase or hard gel, Fortovase or soft gel)	200 mg capsules	Common; diarrhoea, abdominal discomfort, headache, nausea, paresthesias, and skin rash Less common: exacerbation of chronic liver disease, diabetes, dyslipidemia.	Administer within two hours of meal Sun exposure can cause photosensitivity and hence sun screen advisable.

ANNEX 7. SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES

(Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, USA – modified.)

For abnormalities NOT found elsewhere in the toxicity table use the scale below to estimate grades of toxicity.

GRADE 1 Transient or mild discomfort; no limitation of activity; no medical intervention/therapy required.

GRADE 2 Mild to moderate limitation of activity; some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 Marked limitation of activity; some assistance usually required; medical intervention/therapy required; hospitalization possible.

GRADE 4 Extreme limitation of activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care.

HAEMATOLOGY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Haemoglobin	8.0 – 9.4 g/dl OR 80 – 94 g/l OR 4.93 – 5.83 mmol/l	7.0 – 7.9 g/dl OR 70 – 79 g/l OR 4.31 – 4.92 mmol/l	6.5 – 6.9 g/dl OR 65 – 69 g/l OR 4.03 – 4.30 mmol/l	<6.5 g/dl OR <65 g/l OR <4.03 mmol/l
Absolute neutrophil count	1000 –1500/mm³ OR 1.0 – 1.5/G/l*	750 – 999/mm³ OR 0.75 – 0.99/G/l*	500 – 749/mm³ OR 0.5 – 0.749/G/l*	<500/mm³ OR <0.5/G/l*
Platelets	75000 – 99000/mm³ OR 75 – 99/G/l*	50000 – 74999/mm³ OR 50 – 74.9/G/l*	20000 – 49999/mm³ OR 20 – 49.9/G/l*	<20000/mm³ OR <20/G/l*
CHEMISTRIES	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SODIUM				
Hyponatraemia	130 – 135 meq/l OR 130 – 135 mmol/l	123 – 129 meq/l OR 123 – 129 mmol/l	116 – 122 meq/l OR 116 – 122 mmol/l	<116 meq/l OR <116 mmol/l
Hypernatraemia	146 – 150 meq/l OR 146 – 150 mmol/l	151 – 157 meq/l OR 151 – 157 mmol/l	158 – 165 meq/l OR 158 – 165 mmol/l	>165 meq/l OR >165 mmol/l

CHEMISTRIES	GRADE 1	GRADE 2	GRADE 3	GRADE 4
POTASSIUM				
Hyperkalaemia	5.6 – 6.0 meq/l OR 5.6 – 6.0 mmol/l	6.1 – 6.5 meq/l OR 6.1 – 6.5 mmol/l	6.6 – 7.0 meq/l OR 6.6 – 7.0 mmol/l	>7.0 meq/l OR >7.0 mmol/l
Hypokalaemia	3.0 – 3.4 meq/l OR 3.0 – 3.4 mmol/l	2.5 – 2.9 meq/l OR 2.5 – 2.9 mmol/l	2.0 – 2.4 meq/l OR 2.0 – 2.4 mmol/l	<2.0 meq/l OR <2.0 mmol/l
BILIRUBIN				
Hyperbilirubin-aemia	>1.0 – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 – 5 x ULN	>5 x ULN
GLUCOSE				
Hypoglycaemia	55 – 64 mg/dl OR 3.01 – 3.55 mmol/l	40 – 54 mg/dl OR 2.19 – 3.00 mmol/l	30 – 39 mg/dl OR 1.67 – 2.18 mmol/l	<30 mg/dl OR <1.67 mmol/l
Hyperglycaemia (nonfasting and no prior diabetes)	116 – 160 mg/dl OR 6.44 – 8.90 mmol/l	161 – 250 mg/dl OR 8.91 – 13.88 mmol/l	251 – 500 mg/dl OR 13.89 – 27.76 mmol/l	>500 mg/dl OR >27.76 mmol/l
Triglycerides	200 – 399 mg/dl OR 2.25 - 4.51 mmol/l	400 – 750 mg/dl OR 4.52 – 8.47 mmol/l	751 – 1200 mg/dl OR 8.48 – 13.55 mmol/l	>1200 mg/dl OR >13.55 mmol/l
Creatinine	>1.0 – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN
TRANSAMINASES				
AST (SGOT)	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
GGT	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN

CHEMISTRIES	GRADE 1	GRADE 2	GRADE 3	GRADE 4
TRANSAMINASES				
Alkaline phosphatase	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Pancreatic enzymes				
Amylase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Pancreatic amylase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Lipase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
GASTRO-INTESTINAL	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Nausea	Mild OR transient; reasonable intake maintained	Moderate discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalization required
Vomiting	Mild OR transient; 2–3 episodes per day OR mild vomiting lasting <1 week	Moderate OR persistent; 4–5 episodes per day OR vomiting lasting ≥1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR intravenous Rx required	Hypotensive shock OR hospitalization for intravenous Rx required

GASTRO-INTESTINAL	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Diarrhoea	Mild OR transient; 3–4 loose stools per day OR mild diarrhoea lasting <1 week	Moderate OR persistent; 5–7 loose stools per day OR diarrhoea lasting ≥1 week	Bloody diarrhoea OR orthostatic hypotension OR >7 loose stools/day OR intravenous Rx required	Hypotensive shock OR hospitalization required
RESPIRATORY	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O^2 therapy
URINALYSIS	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Proteinuria				
Spot urine	1+	2+ or 3+	4+	Nephrotic syndrome
24-hour urine	200 mg to 1 g loss/day OR <0.3% OR <3 g/l	1 g to 2 g loss/day OR 0.3% to 1.0% OR 3 g to 10 g/l	2 g to 3.5 g loss/day OR >1.0% OR >10 g/l	Nephrotic syndrome OR >3.5 g loss/ day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
MISCELLANEOUS	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Fever (oral, >12 hours)	37.7 – 38.5 °C OR 100.0 – 101.5 °F	38.6 – 39.5 °C OR 101.6 – 102.9 °F	39.6 – 40.5°C OR 103 – 105 °F	>40.5 °C OR >105 °F for ≥12 continuous hours

MISCELLANEOUS	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Headache	Mild; no Rx required	Moderate OR non-narcotic analgesia Rx	Severe OR responds to initial narcotic Rx	Intractable
Rash hypersesnitivity	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE OF: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25–50%	Normal activity reduced by >50%; cannot work	Unable to care for self