

Kingdom of Cambodia
Nation Religion King



Ministry of Health

National HIV clinical management guidelines for Adults and Adolescents

4th Revision in 2015



National Centre for HIV/AIDS, Dermatology and STD

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Preface

Cambodia is one of the successful countries in the Western Pacific Region in the national response to HIV epidemic by reducing the HIV prevalence among people aged 15-49 years-old from 1.7% in 1998 to 0.6% in 2015. It is estimated that there are 70, 885 people who are living with HIV (PLHIV) in 2015.

Since its launching in 2003, the Comprehensive Continuum of Care (CoC) Framework for PLHIV, Cambodia has achieved the universal access target for HIV treatment to provide ART to 54,755 patients on ART at the end of the first quarter 2016, at 65 for Adult ART sites, and 36 Paediatric ART sites country-wide.

These National HIV clinical management guidelines for adults and adolescents are substantially changes. It is the first consolidated guidelines which combines the two previously separated guidelines of antiretroviral therapy and opportunistic infection treatment. Furthermore, dealing with the long-term complications of life-long ART treatment, these guidelines also includes new section on non-communicable diseases. Cambodia is intent on harmonizing HIV clinical management guidelines to the WHO's HIV treatment guidelines version 2013, and the supplements up to September 2015. They key updates of ART initiation is the expansion of the criteria to all PLHIV regardless of CD4, "Test and Treat All".

I would like to congratulate NCHADS and all development partners who were actively participated in revising these important guidelines. The Ministry of Health has officially approved for the use of the national HIV Clinical Management Guidelines for Adults and Adolescents and hopes that all health care workers involved in Care and Treatment for PLHIV will implement these national guidelines successfully.

Phnom Penh, 09 August 2016

Minister for Health



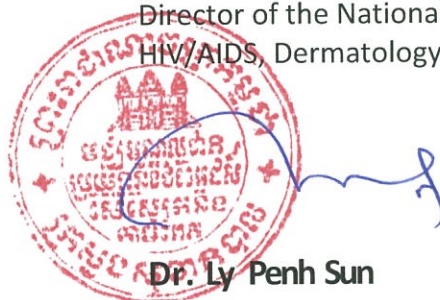
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The National Centre for HIV/AIDS, Dermatology and STD (NCHADS), together with development partners invested a significant amount of times, energy and resources in the development of the National ARV treatment guidelines in 2003, revisions in 2007, in 2011, and now 2015. The revised 2015 guidelines not only align with the recent WHO recommendations in 2015, but also build on the extensive experiences over the past decades in care and treatment for PLHIV by NCHADS and all its partners.

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Phnom Penh, 04 August 2016
Director of the National Centre for
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21. Representative	KHANA	Member
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Abbreviations

3TC	Lamivudine	HPV	Human papilloma virus
ABC	Abacavir	HSV	Herpes Simplex Virus
AFB	Acid fast bacilli	INH	Isoniazid
AIDS	Acquired immunodeficiency syndrome	ITP	Immune thrombocytopenia
ALT	Alanine aminotransferase	IPT	Isoniazid preventive therapy
ART	Antiretroviral therapy	IRIS	Immune reconstitution inflammatory syndrome
ARV	Antiretroviral drug (s)	Ix	Investigation
AUC	Area under curve	KS	Kaposi's Sarcoma
ATV	Atazanavir	LDH	Lactate dehydrogenase
ATV/r	Atazanavir/ritonavir	LFT	Liver function test
AZT	Zidovudine	LN	Lymph node
BMD	Bone mineral density	LPV	Lopinavir
BMI	Body mass index	LPV/r	Lopinavir/ritonavir
CBC	Complete Blood Count	MAC	Mycobacterium avium complex
CD4	CD4+ T-lymphocyte	MDR-TB	Multi drug resistant tuberculosis
CMV	Cytomegalovirus	MTB	<i>Mycobacterium tuberculosis</i>
CNS	Central Nervous System	Mx	Management
CrCl	Creatinine clearance	NCD	Non communicable disease
CRAG	Cryptococcal antigen	NCHADS	National center for HIV/AIDS dermatology and STIs
CrAg	Cryptococcal antigen	NHL	Non-Hodgkin's lymphoma
CSF	Cerebral Spinal Fluid	NNRTI	Non-nucleoside reverse transcriptase inhibitor
CTX	Cotrimoxazole	NRTI	Nucleoside reverse transcriptase inhibitor
CVD	Cardiovascular disease	NVP	Nevirapine
CXR	Chest x-ray	OHL	Oral hairy leukoplakia
DAA	Direct antiviral agent	OI	Opportunistic infection
DRV	Darunavir	ORS	Oral rehydration solution
DRV	Darunavir/ritonavir	PCP	<i>Pneumocystis jiroveci</i> pneumonia
D4T	Stavudine	PEP	Post exposure prophylaxis
ddl	Didanosine	PPE	Pruritic papular eruption
DOT	Directly observed therapy	PI	Protease inhibitor
DST	Drug Susceptibility Testing	PLHIV	People living with HIV
DTG	Dolutegravir	PMN	Polymorphonuclear leukocyte
Dx	Diagnosis	PrEP	Pre exposure prophylaxis
DDx	Differential diagnosis	PTB	Pulmonary tuberculosis
E	Ethambutol	RAL	raltegravir
EBV	Epstein Barr Virus	R	Rifampicin
eGFR	Estimated glomerular filtration rate	RBC	Red blood cell
EFV	Efavirenz	RPR	Rapid Plasma Reagin
EPTB	Extra-pulmonary tuberculosis		
ETV	Etravirine		
H	Isoniazid		
HIV	Human Immunodeficiency Virus		

RTV	Ritonavir		agglutination
/r	Low dose ritonavir	TST	Tuberculin skin test
Rx	Treatment	US	Ultrasound
SJS	Stevens Johnson syndrome	WBC	White blood cell
SMX	Sulfamethoxazole	WHO	World Health Organization
TB	Tuberculosis	XDR	Extensively drug-resistant
TDF	Tenofovir disoproxil fumarate	Z	Pyrazinamide
TMP	Trimethoprim		
TPHA	Treponemal pallidum particle		

Introduction

This HIV clinical management guideline is substantially changed from the 2012 guidelines.

This is a consolidated guideline, including sections on antiretroviral therapy and opportunistic infections, which were previously contained in two separate documents. In addition to avoiding repetition, the intention is also to make the format more concise, with more dot points, tables and algorithms than paragraphed text.

The changing clinical needs of PLHIV necessitate a broadening of the scope of the guideline. As more PLHIV are now established on combination antiretroviral therapy they will experience less late stage complications of advanced immunodeficiency. HIV itself, and long-term combination antiretroviral therapy (ART), increases the risks and complications associated with metabolic and non-communicable (NCD) diseases as people age. This guideline includes a new section on non-communicable diseases to guide the clinician to advise patients regarding the prevention of NCD, to incorporate screening for NCD into routine consultations, and for the investigation and management of NCD. The clinician is directed to Cambodian National NCD guidelines for management of hypertension and diabetes. Whilst the HIV clinician may not always lead the management of NCD if the patient has the opportunity to attend a specialised clinic, the HIV clinician must have a good understanding of these common conditions, and in particular drug interactions with ARV.

There is increased attention to meeting the needs of adolescents, and coordinating with the paediatric services to smooth the transition of adolescent PLHIV from paediatric to adult HIV clinics, and to provide “adolescent appropriate” care in the adult clinics.

The TB section is aligned with the National HIV/TB guidelines, and in addition outlines issues regarding drug resistant TB, introduces the use of the now widely available GeneXpert MDT/RIF test, and includes the expanded recommendation for all PLHIV to have a course of Isoniazid prevention therapy.

Hepatitis B (HBV) and hepatitis C (HCV) are common co-infections and impact on the care of PLHIV. It is anticipated that new highly effective and well-tolerated treatments for HCV will soon be made available to PLHIV with HCV co-infection in Cambodia. Tenofovir and 3TC are included now in standard ART for HIV, these are treatments also active against HBV. It is important the clinician has a good understanding of these common co-infections when managing ARV, and of their long-term complications; accordingly content has been expanded in this guideline.

Key content updates regarding antiretroviral therapy include the expansion of the criteria for starting ART to all PLHIV regardless of CD4 count. This guideline also includes the updated ART regimens including standard 1st line regimen of TDF + 3TC + EFV for all including pregnant women, and ATV/r as the preferred PI in 2nd line ART. It is expected that EFV 400mg FDC will be available soon, and therefore guidance is provided for whom to switch to this lower dose, which has been demonstrated to be equally effective to the 600mg dose for most patients.

Monitoring of PLHIV on ART is primarily focused on routine viral load (VL) monitoring which is being scaled up in Cambodia. As routine VL becomes available, CD4 testing will still be required in the early phases of HIV management; however it will be less frequently required once the patient is stable on ART. Algorithms for VL and CD4 monitoring are included in this guideline.

The guideline has increased the CD4 thresholds for cotrimoxazole prophylaxis as recommended by the World Health Organisation (WHO). And introduced cryptococcal antigen screening which will ultimately take the place of routine fluconazole prophylaxis.

The section on Post exposure prophylaxis (PEP) has been updated to include new ARV regimens, and has been expanded from provision to health care workers to also include victims of sexual assault, and exposure between discordant couples prior to viral load suppression. A PEP clinic visit and reporting form is included in the Annex.

This guideline has been written in accordance with the WHO guidelines 2013 and supplements up to September 2015. It is expected that the new WHO consolidated guidelines will be available at the end of 2015.

Background

Chapter1. HIV overview

1.1 Key points

- HIV is a blood borne virus, which is transmitted via blood and genital secretions.
- Acute HIV infection may be difficult to distinguish from other acute viral illnesses.
- Chronic HIV may be asymptomatic for many years, however during this time the underlying disease progresses and HIV can be transmitted to others.
- HIV cannot be cured, however can be effectively managed with combination anti-viral medicine (ART).
- Transmission may be reduced through implementation of safe sex and risk reduction strategies, including prompt initiation of combination antiretroviral therapy (ART).

1.2 HIV transmission

- HIV is transmitted through bodily fluids, particularly blood and genital secretions.
- HIV cannot be transmitted by normal social contact, kissing, and sharing food or by insects.

Table1- 1 Routes of HIV transmission, average transmission risk per episode

Exposure from an HIV infected source	Estimated risk of HIV transmission per episode ¹
<i>Sexual exposure (via blood, semen, vaginal fluids)</i>	
• Insertive vaginal intercourse (female to male transmission)	1/2500
• Receptive vaginal intercourse (male to female transmission)	1/1250
• Receptive anal intercourse (male to male (MSM) or male to female transmission) <i>without</i> withdrawal prior to ejaculation	1/70
• Receptive anal intercourse <i>with</i> withdrawal prior to ejaculation	1/155
• Insertive anal intercourse, uncircumcised (MSM)	1/160
• Insertive anal intercourse, circumcised (MSM)	1/900
• Oral sex: insertive or receptive (male or female)	Extremely low
<i>Blood exposure</i>	
• Intravenous Drug Use: contaminated injecting equipment	1/125
• Occupational needle stick (NSI) or other sharps exposure	1/440
<i>Other exposure</i>	
• Mucus membrane or non- intact skin exposure	< 1/1000

Factors that influence the risk of HIV transmission and acquisition

Factors that increase the risk of HIV transmission

- High HIV Viral load in the source individual - when seroconverting or advanced disease.

¹ Post-Exposure Prophylaxis after Non-Occupational and Occupational exposure to HIV National Guidelines. ASHM 2013. Available at www.ashm.org.au.

- Sexually transmitted infection in the source *or* exposed individual, particularly genital ulcer disease and symptomatic gonococcus infection.
- Breach in genital mucosa (trauma, infection).
- Breach in oral mucosa in the case of oral sex.
- Penetrating injury with a hollow bore needle, +/- or direct injection into vein or artery.
- Uncircumcised HIV negative male in the case of insertive vaginal or anal sex.

Protective factor against HIV transmission

- Early initiation of ART in HIV infected individuals, and maintenance of an undetectable serum HIV viral load is highly effective at reducing sexual transmission of HIV.

Factors that increase the risk of HIV acquisition

- Genital infections, particularly genital ulcerations.
- Receipt of blood or blood products.
- Intravenous or subcutaneous (“skin-popping”) drug abuse.
- Higher risk sexual behaviour:
 - Multiple sexual partners.
 - Sex with sex workers.
 - Sex partners with high-risk behaviour (many women with only one regular sex partner are at high risk because their partner has multiple sexual contacts).
 - Men who have sex with men (MSM).
 - Other injections, tattooing, scarification, ear piercing or body piercing using non-sterile instruments.

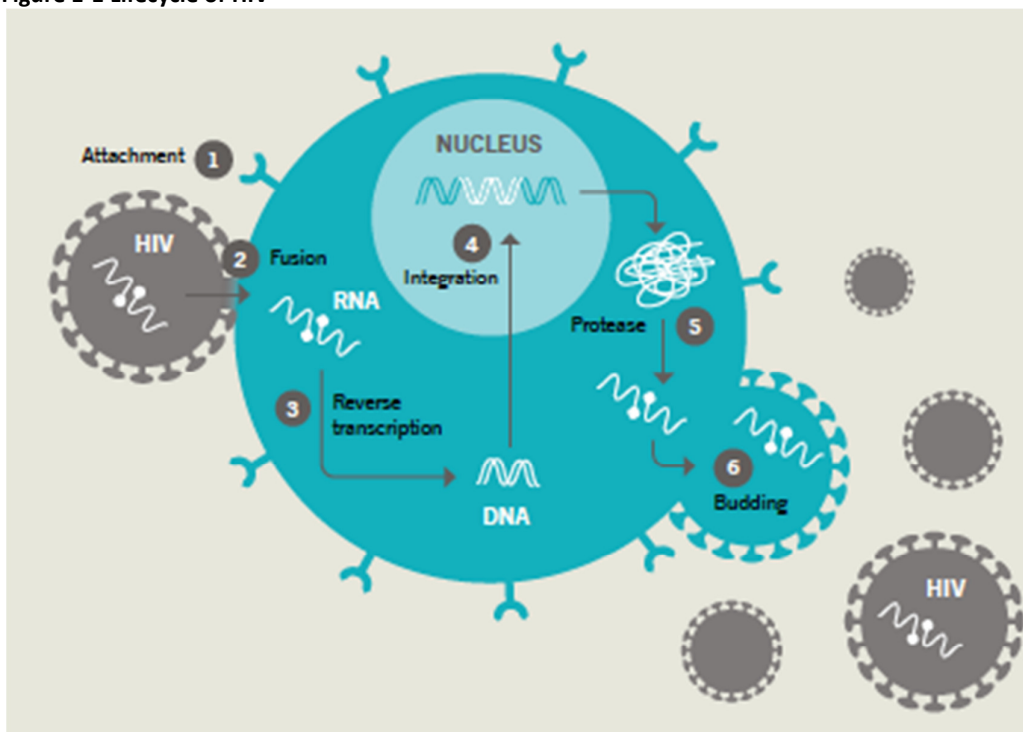
Protective factors against HIV acquisition

- Pre-exposure prophylaxis (PrEP) and Post – exposure prophylaxis (PEP) both reduce the risk of HIV acquisition in exposed HIV negative individuals (see below).

1.3 HIV Pathogenesis and natural history

- HIV is an RNA virus that infects cells in the body that possess a CD4 receptor. These cells include lymphocytes, monocytes, and macrophages, which help to coordinate the response of the immune system to infection.
- HIV attaches to the CD4 cells → fuses with the cell wall → HIV RNA is converted to DNA by viral reverse transcriptase → HIV DNA is inserted into the host genome → the host cell produces new materials to make HIV → HIV particles are then packaged and released.
- Antiretroviral drugs which treat HIV target each of these 6 stages.

Figure 1-1 Lifecycle of HIV²



1.3.1 Acute infection

- Following infection, there is a period of high-level HIV viraemia associated with a sharp reduction in the CD4 cell count.
- The host then develops an immune response which causes >50% of patients to develop a self-limiting mononucleosis-like seroconversion illness.
- The immune system response results in a marked decrease in the viral load (to a “virological set point”) and CD4 cell count increases back to near baseline levels.

1.3.2 Clinical latency

- A period where the HIV infected individual is relatively asymptomatic (WHO stage 1)
- High levels of viral replication continue.
- Sexual and other transmission of HIV is common.
- Unless ART is commenced → there will be continued decline in CD4 cell count; median loss of 80 cells/year.

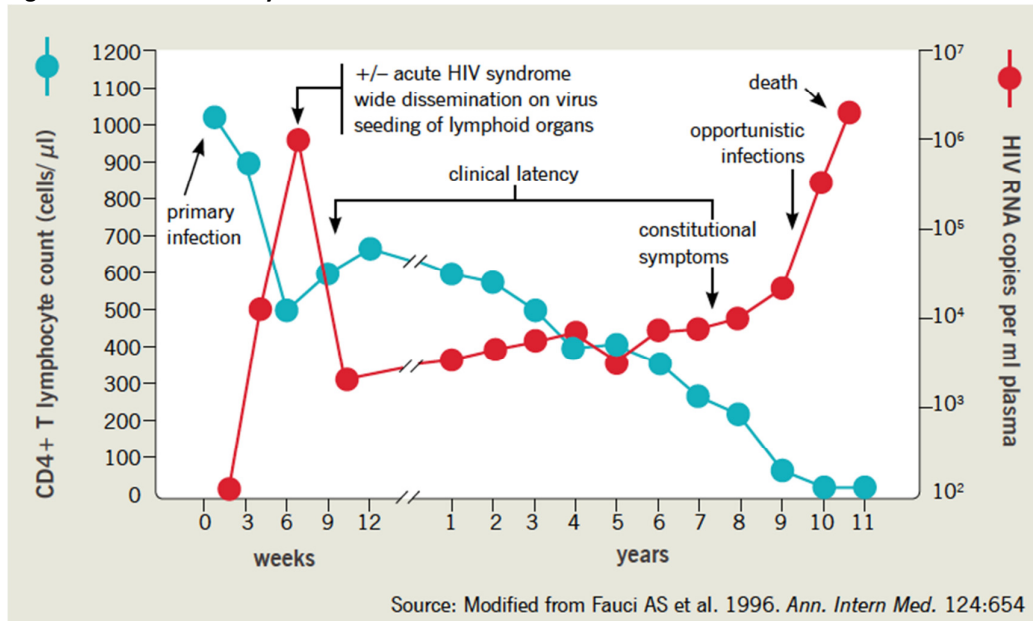
1.3.3 Advanced HIV infection

- Without treatment individuals ultimately progress to develop WHO stage 2 - 4 HIV related illness and AIDS.

² Copied from HIV/TB Clinical Guide 8th edition. Médecins Sans Frontières.. 2015.

- Progression to AIDS (WHO stage 4, CD4 < 200 cells/mm³) occurs a median of 10 years after initial infection with HIV. Factors which may cause faster progression to AIDS include age < 5 years, or > 40 years, and co-infections, especially tuberculosis.

Figure 1-2 Natural History of HIV infection³



Level of immunodeficiency	CD4 cells
• No significant immunodeficiency	>500 cells/mm ³
• Mild immunodeficiency	350-500 cells/mm ³
• Advanced immunodeficiency	200-349 cells/mm ³
• Severe immunodeficiency	< 200 cells / mm ³

1.4 Clinical presentations with HIV

1.4.1 When HIV infected individuals may present

PLHIV may present to clinicians at any time from seroconversion, to late stage disease;

1. Primary HIV = Seroconversion illness
2. Illness *related to undiagnosed* chronic HIV infection
 - Look for clues: demographic, clinical, laboratory, → test for HIV
3. Illness *related to already diagnosed* HIV.
4. Illness *unrelated* to their coexisting known or unknown HIV infection.

1.4.2 Causes of clinical presentations

1. Immunodeficiency
 - Infections

³ Copied from MSF HIV/TB Clinical Guide 2015

- Opportunistic infections
- Malignancy
- 2. Immune dis-regulation
 - E.g. Immune mediated thrombocytopaenia, inflammatory arthropathies, sjogrens syndrome.
- 3. Direct effects of HIV infection
 - E.g. HIV associated cognitive decline (HAND), nephropathy, gastropathy
- 4. Co-infections
 - Hepatitis B, C, TB
- 5. Medication - side effects / drug interactions
- 6. Immune reconstitution syndrome (IRIS)
 - Unmasking or paradoxical reactions to infections
- 7. Ageing and other chronic disease accelerated by HIV and ART
 - E.g. cardiovascular or renal disease

1.4.3 Primary HIV infection: clinical presentation

- HIV seroconversion is symptomatic in > 50% of patients.
- Incubation period: 10 –14 days.
- Symptoms can be mild to severe, and are very similar to other viral illnesses.
- Check for risk exposure +/- STI, and prompt HIV testing.

Clinical features:

- Sudden onset, fever, myalgia and arthralgia, lymphadenopathy, sore throat, maculopapular rash, oral ulcers, gastro intestinal symptoms, headache and aseptic meningitis.
- Rarely; neuropathies and Guillain–Barré Syndrome.
- Transient immunosuppression opportunistic → infections e.g. oral candidiasis, or PJP.

Laboratory features:

- Thrombocytopenia, leukopenia, raised liver enzymes.
- HIV antibody test may be negative for up to 3 weeks after onset of symptoms.
- If HIV Ab is negative at the time of illness, → repeat after 1 month.

1.4.4 Chronic HIV infection: HIV related conditions by CD4 count

- The following table lists the risk of HIV related conditions by CD4 count.
- See also the WHO classification system of clinical and laboratory conditions stage 1 – 4. (Annex: Table 44-1 WHO staging system for adults and adolescents (≥ 15 years))

Table 1-2 HIV related conditions, risk by CD4 count⁴

CD4 count	Condition
Any CD4 count	Persistent generalised lymphadenopathy (PGL) Parotid gland enlargement Herpes zoster (shingles) Tuberculosis Bacterial pneumonia Cervical intraepithelial neoplasia (CIN) Vulvo-vaginal candidiasis Chronic anaemia HIV-related thrombocytopenia Lymphocytic interstitial pneumonitis (LIP) (children)
<200 cells/ μ L Vulnerable to severe Opportunistic Infections	Oral candidiasis (thrush) Oesophageal candidiasis Oral hairy leukoplakia (OHL) Pneumocystis jiroveci pneumonia (PCP) Cryptosporidiosis Lymphoma (non-CNS) Kaposi's sarcoma (KS) HIV-associated dementia (HAD)
<100 cells/ μ L	Toxoplasmosis Cryptococcal meningitis (CM) Cytomegalovirus infection (eye) Wasting syndrome
<50 cells/ μ L	Non-tuberculosis mycobacterial (NTM) infection Lymphoma (CNS) Progressive multifocal leukoencephalopathy (PML) Cytomegalovirus infection (brain or disseminated)

1.5 HIV Testing

HIV testing in Cambodia is conducted at client initiated VCCT centres, initiated by health care providers (HPITC) or as Community/Peer initiated testing (C/PITC for Key populations) using 3 HIV Rapid tests according to a standard algorithm.⁵

If HIV is suspected:

- Provide information to the patient on the importance of HIV testing.
- Refer the patient to a HIV testing site.
- Provide information to the patient regarding HIV transmission, and safe sex/injecting whilst they wait for HIV testing and results.
- For those diagnosed with HIV refer to HIV treatment site and early initiation of ART.

⁴ Adapted from MSF HIV/TB Guide 2015

⁵ Standard Operating Procedures for HIV Testing and Counseling (HTC). NCHADS 2012

1.6 Antiretroviral therapy

- Antiretroviral therapy (ARV or ART) is the mainstay of HIV treatment and is now recommended for ALL PLHIV regardless of CD4 count.
- ARV drugs from multiple classes target the HIV lifecycle at different stages in the HIV attachment and replicative process. Combination ART (ART) rapidly suppresses the replication of HIV leading to a rapid fall in the amount of HIV in the blood (HIV viral load or VL) to below the limit of detection by viral load tests. This reduces the impact of HIV on the immune system and allows gradual restoration of immune function, which is represented by the CD4 lymphocyte count. As immune function is restored and maintained, the risk of HIV-associated illness and mortality decreases.
- ART is not a cure for HIV. It suppresses viral replication, but does not eradicate the virus. If ART is ceased, HIV replication as seen by the VL, quickly returns to pre-treatment levels and damages the immune system again.
- In addition to ARV drugs prescribed to PLHIV as ART, ARV drugs are also demonstrated to be effective at preventing HIV acquisition if taken by uninfected individuals. This may be taken as Post Exposure Prophylaxis (PEP) or as Pre Exposure Prophylaxis (PrEP) (see below).

1.6.1 Aims of antiretroviral therapy

1. Individual health benefits for PLHIV of improved quality of life and life expectancy, via:
 - Suppression of HIV replication, measured by viral load (VL)
 - Restoration and maintenance of immune function, represented by CD4 count.
 - Reduced morbidity and mortality from opportunistic infections and other HIV related conditions
2. Reduction in HIV transmission (TasP) and acquisition (PEP and PREP) for individual and population health benefits:
 - Sexual transmission
 - Mother to child transmission (PMTCT)
 - Injection drug use.
 - Occupational exposure.

1.6.2 Principles of combination ART

Combination antiretroviral therapy must be prescribed properly and taken correctly to prevent HIV ARV drug resistance leading to failure of ART regimens.

- A combination of at least 3 ARV drugs must be prescribed from at least 2 classes (ART)
- Adherence to the regimen must be near perfect.

HIV replication naturally results in a very high rate of spontaneous genetic mutations. Effective ART suppresses replication and so reduces the rate of development of mutations. If ART is suboptimal (for example, inappropriate combinations or poor adherence), viral replication in the presence of ARV will lead to emergence of HIV populations that carry genetic drug resistant mutations. Eventually this population will become dominant and the particular ART regimen being used will become ineffective.

Early detection of HIV virological failure is essential. If left untreated resistant viruses can accumulate more genetic mutations that make them less susceptible to other ARV drugs, resulting in 1) reduced efficacy of 2nd line ART; and 2) resistant virus can be transmitted to others. If virological failure is detected early a 2nd line regimen including at least 2 new drugs usually suppresses the VL once again.

1.6.3 Treatment as Prevention (TasP)

- Treatment as prevention refers to ART in PLHIV reducing the risk of transmission to others. Ongoing studies demonstrate that PLHIV with an undetectable VL are extremely unlikely to transmit HIV to their (heterosexual and MSM) sexual partners.
- PMTCT protocols rely on TasP, and hence the importance of achieving an undetectable VL during pregnancy.
- The term TasP was coined to advocate for treatment of some individuals for the protection of others, despite it not being clear that the ART would necessarily provide a physical health benefit to the PLHIV. However it has since been resolved that ART provides health benefits to PLHIV regardless of CD4 count.

1.6.4 Post exposure prophylaxis (PEP)

- PEP refers to the administration of regimens consisting of ARV drugs within a short time frame after a high-risk sexual or parenteral exposure. The regimen is continued for 1-month post exposure, with follow up HIV Ab testing at 3/12.
- Whilst there are no randomized controlled trial data, observational studies support the effectiveness of PEP in reducing HIV acquisition from occupational and non-occupational exposures.
- PMTCT protocols also utilize the principle of PEP for the newborn.
- For PEP management see: Chapter 43. Post exposure prophylaxis

1.6.5 Pre exposure prophylaxis (PrEP)

- Oral PrEP for HIV infection is the use of ARV drugs by HIV-uninfected people before the potential exposure to block the acquisition of HIV.
- PrEP is now recommended by WHO as an additional prevention choice for all people at substantial risk of HIV infection (> 3% incidence).⁶

⁶ Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. September WHO 2015

- PrEP intervention must be implemented within a comprehensive program of harm reduction, including baseline and regular HIV testing, monitoring for toxicity, and management of HBV co infection, and pregnancy etc.
- WHO will publish comprehensive implementation guidance for PrEP in 2016.

1.6.6 ARV drugs available in Cambodia⁷

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
 - Tenofovir (TDF)
 - Zidovudine (AZT or ZDV)
 - Lamivudine (3TC)
 - Abacavir (ABC)
 - (Didanosine (ddI) and Stavudine (d4T) are currently being phased out)
2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
 - Efavirenz (EFV)
 - Nevirapine (NVP)
3. Protease Inhibitors (PI)
 - Atazanavir combined with low dose Ritonavir (ATV/r)
 - Lopinavir combined with low dose Ritonavir (LPV/r)

Most are available as fixed dose combinations of 2 or 3 drugs (e.g. TDF + 3TC+ EFV, AZT + 3TC), which minimize the number of necessary tablets and maximize adherence.

It is anticipated that newer agents in these classes (eg PI Darunavir, NNRTI Etravirine), and Integrase inhibitor class agents (Dolutegravir, Raltegravir) will be available in Cambodia to be utilised in 1st and 2nd line ART regimens and for virological failure in highly treatment experienced individuals (salvage, or 3rd line regimens).

⁷ The drugs procured for the Cambodian National HIV program are manufactured to standards for WHO prequalification.

Provision of care for PLHIV

Chapter 2. Routine schedule of clinical consultations

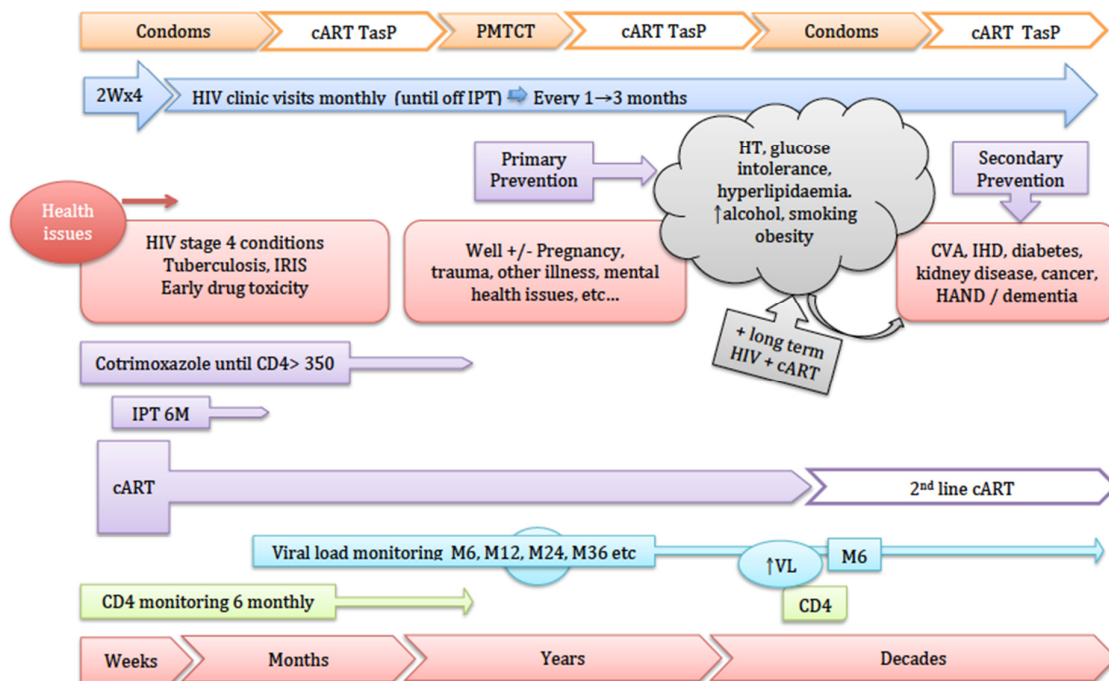
2.1 The objectives of the early clinical consultations

- Diagnose and treat any current OI or other medical illness.
- Screen for TB **at every visit**, and either refer for further Ix and Rx or commence IPT.
- Commence OI prophylaxis if required.
- Provide information to PLHIV regarding avoidance of HIV transmission, and prepare for the lifelong management of HIV with ART.
- Provide information and medical support to optimize general health.
- Establish the patient on ART.

2.2 The objectives of consultations once the PLHIV is established on ART

- Maintain good ART adherence and optimal control of HIV.
- Avoid and manage toxicities to ART.
- Manage co-infections.
- Prevent and manage non-communicable diseases, which are more prevalent with long term HIV, ARV and advancing age.

Figure 2-1 HIV clinical pathway



2.3 Laboratory testing timed with clinical consultations

- Laboratory tests should be performed on the *same day* as clinical visits.
- Clinicians should anticipate when the next VL or CD4 is due, and schedule the next visit on a day when laboratory testing is possible.

- Laboratory testing may be performed within 1 month either side of the scheduled test. On the following schedule this is indicated, as xY_z (e.g. 5_67 indicates the test planned for 6M can be performed at a clinic visit any time between 5 and 7 months).
- If, for whatever reason a patient misses their scheduled CD4, or VL test, it should still be performed as soon as possible.

The following schedules are for routine clinical visits, laboratory testing, ART and OI prophylaxis. Individual patient management may require additional visits or tests.

- **Complete the National Clinic Visit Forms**, which also serve as checklists of steps for assessment and management. Follow each point and document carefully, and keep in mind that data is entered into the National database and used for HIV program activity.

Regarding clinical assessments see Section 45 Annex: Routine Clinical consultation visit guide.

Table 2-1 Clinic visit routine schedule

Week	Clinical	Adherence counselling	Laboratory testing	Drugs start /Stop
Week 0	✓	✓	✓	Start Cotrimoxazole
Week 1		✓		
Week 2	✓	✓		Start ART Stop Cotrimoxazole if CD4 > 350 and no TB
After start ART				
Week 2	✓	✓		Start IPT
Month 1	✓	✓	✓	
Every 1 M whilst on IPT	✓	✓	✓VL at month 5_67	Stop IPT after 6 months
After stop IPT, still on Cotrimoxazole				
Every 1 – 3 months (According to clinical status, + adherence)	✓	✓	✓VL at M_{5_67} then $M_{11_12_{13}}$, $M_{23_24_{25}}$ $M_{35_36_{37}}$ etc. ✓CD4 every 5_67 M	Stop Cotrimoxazole according to criteria in Table 2-4 Primary Prophylaxis for opportunistic infection. Stop CD4 monitoring according to criteria in Chapter11. Monitoring response to A
After stop Cotrimoxazole and routine CD4 monitoring				
Every 1 – 3 months	✓	✓	✓VL at every 11_12_{13} Months	

Table 2-2 Clinical screening criteria for TB for PLHIV at every clinic visit

In the last 4 weeks ask the patient if there are ANY of the following?
1. Cough: any time, any duration
2. Fever: anytime, any duration
3. Drenching night sweats: ≥ 2 weeks duration
4. Loss of weight? AND weight the patient at each visit and compare with previous visit.

Table 2-3 Routine Laboratory investigation

Test	Pre ART	Monitoring on 1 st line	Treatment failure	Monitoring on 2 nd line
HIV Ab	✓			
CD4 count	✓ but no need to wait for the result before start ART	<p>✓CD4 every 6 Months if on OI prophylaxis +/or routine VL not available.</p> <p>No routine CD4 once off OI prophylaxis, and meet criteria in Chapter11. Monitoring response to A</p>	<p>✓If new OI including TB</p> <p>✓At time of switch to 2nd line ART regimen.</p>	<p>✓ CD4 every 6 Months if on OI prophylaxis +/or routine VL not available.</p> <p>No routine CD4 once off OI prophylaxis, and meet criteria in Chapter11. Monitoring response to A</p>
Viral Load	No	✓M6, M12, M24, M36 etc.	✓Confirm with VL if “targeted” monitoring	✓M6, M12, M24, M36 etc.
AST/ALT	✓	✓M1, M3	✓	✓M1, M3
Hb	✓if plan AZT	✓If on AZT, M1, M3 then every 6M	✓If plan AZT	✓If on AZT, M1, M3 then every 6M
Urine dipstick Serum creatinine, (calculate eGFR)	✓	<p>✓</p> <p>✓if on TDF M1, M3 then every 12M</p>	✓	<p>✓</p> <p>✓ If on TDF M1, M3 then every 12M. If not on TDF every 12 M</p>
HBsAg	<p>✓ if ↑ ALT</p> <p>✓if considering not starting TDF in ART</p>		✓ If not known and considering stopping TDF	
Diabetes screen			✓ If switching to PI	✓ If PI, every 12 M
Serum lipids			✓If switching to PI	✓ If PI, every 12 M

Table 2-4 Primary Prophylaxis for opportunistic infection

	Criteria to initiate	Dose	Criteria to stop
Cotrimoxazole	See: Chapter5. Primary Prophylaxis for Opportunistic Infections		
	<ul style="list-style-type: none"> • CD4 < 350 • TB at any CD4 • WHO stage 3 or 4 • All adolescents If not contraindicated	1 DS; (TMP-160mg, SMX-800mg) tablet daily <i>or</i> 2 SS; (TMP-80mg, SMX-400mg) tablets daily.	Age ≥ 20 years <i>and</i> No active TB, <i>and</i> VL undetectable <i>and</i> CD4 > 350 on two occasions > 6 months apart.
Isoniazid preventive therapy (IPT)	See Chapter6. Screening for TB and assessment for Isoniazid Preventive Therapy (IPT)		
	All PLHIV (including pregnant women) without active TB should have IPT one course If not contraindicated.	Isoniazid 300mg / day + pyridoxine 50mg/d (if weight < 40kg Isoniazid 200mg / day)	After 6 months.
Fluconazole Only if Crag screening is <i>not</i> available	See Chapter7. Cryptococcus screening and prevention		
	PLHA with CD4 < 100 If not contraindicated	Fluconazole 100mg/ day	VL undetectable and CD4 > 100 on two occasions > 6 months apart.

Table 2-5 Recommendations for prevention and management of NCD

The emphasis on diet and lifestyle modification will vary depending on whether the patient is under/over/normal weight and other risk factors, HT, diabetes etc.
<p>Diet: most people need to pay attention to eat:</p> <ul style="list-style-type: none"> • More protein (tofu, beans, chicken, fish) • More vegetables (5 x 400 – 500gm servings vegetables and fruit per day) • Less fat (avoid deep fried foods, cut/ skin the fat of meats e.g. pork /chicken) • Less sugar (soft drinks, sweets, condensed milk). • Less salt (prohok, MSG, fish sauce, soy sauce and salted meat or fish) instead use other flavours (e.g. lemon juice, pepper) and herbs. • Minimize processed foods (usually high in salt, fat, sugar)
Weight: Maintain BMI between 18.5 – 22.9 (see 33.3 Nutrition Screening and weight management)
Alcohol: maximum of 2 standard drinks per day, ≥ 2 alcohol free days per week.
No smoking
Exercise: 30 minutes per day (e.g. brisk walking) (more if need to lose weight)

Specific populations

Chapter3. Women of child bearing age

Female PLHIV have specific requirements particularly with regards to reproductive health.

- At each visit check with the woman what her current reproductive wishes are:
 - Wanting to get pregnant?
 - Or wanting to avoid a pregnancy?
- If the woman is established and adherent to ART *and the VL is undetectable*, there is minimal risk of transmission to a male partner in trying to become pregnant, and to a child through pregnancy or breast-feeding.

3.1 Planning pregnancy

- Advise the woman that the preferred timing of a pregnancy in relation to optimizing her own health and for PMTCT is after 6 – 12 months on ART with undetectable VL, evidence of CD4 recovery, and completion of treatment for OI.

3.2 Contraception

- For women wanting to delay or avoid pregnancy contraception should be discussed:
 - Promotion of dual methods of contraception rather than condoms alone, which have a high rate of failure to prevent pregnancy.
 - Contraceptives: the effectiveness of low dose oral contraception is reduced with NNRTI and PI. Injectable (Depo-Provera) or LARC (long acting reversible contraception) such as implants and IUD are preferred.

3.3 Emergency contraception for women on ART

- Emergency contraception (should be taken as early as possible ≤ 4 days).
- If on rifampicin, NNRTI or PI: prescribe double dose (usual dose is 1.5mg) = 3mg levonorgestral taken as single dose⁸.

3.4 Supporting adherence to ART, and VL monitoring during pregnancy

- Women who test HIV positive before, or during pregnancy or breastfeeding should be commenced immediately on lifelong ART, using the standard 1st line treatment regimen (TDF+3TC+ EVF), and cotrimoxazole if indicated.
- A special focus should be made on supporting adherence to ART in pregnancy.
- All pregnant women should have one viral load test during pregnancy.
- Additional Viral load monitoring outside routine testing may be required in pregnancy:
 - If a pregnant woman has just started ART check VL after 3M
 - If already on ART, check VL early in the pregnancy (then follow the VL algorithm)

⁸ MSF HIV/TB Clinical guide 2015 p 85

- The management for PMTCT and HIV prophylaxis and testing in the infant should follow the National PMTCT Guidelines and SOP for Boosted Linked Response⁹ the newly revised PMTCT guidelines and NCHADS Paediatric HIV treatment guidelines.

Cervical carcinoma, caused by HPV is significantly more common in PLHIV; invasive cervical cancer is a WHO stage 4 AIDS defining illness. Depending on the availability, women should undertake cervical cancer screening, and treatment of precancerous lesions (see Chapter 32. HIV associated malignancies)

⁹ Standard Operating Procedure for Implementation of the Boosted Linked Response between HIV and SRH for Elimination of New Pediatric HIV Infections and Congenital Syphilis in Cambodia. MCH and NCHADS 2013

Chapter4. Adolescents

- WHO defines adolescents as 10 – 19 years old.¹⁰
- Cambodia offers Paediatric Aids Care (PAC) services for children up to the age of 15, and thereafter, adolescents will be transferred to an adult ART clinic.
- **HIV infected adolescents (ALHIV)** includes those who:
 - Are living with *perinatally-acquired* infection, and will transition from a paediatric to adult HIV treatment service. (*This is the majority of ALHIV in Cambodia*).
 - Have *newly acquired* infection through sexual activity, injecting drug use, unsafe injections or blood transfusions, who would likely be treated at adult HIV service from the outset.
 - Female adolescents may also access and be diagnosed in maternity service
- **HIV Ab testing:** Adolescents must have access to HIV testing which is confidential and requires informed consent from the adolescent.

- **Psychosocial challenges:**

Adolescents are a heterogeneous group, who by nature are undergoing rapid physical, cognitive and social development, and so are at varying levels of maturity and have a range of responsibilities within their family and community.

By the time they reach adolescence, many perinatal infected children have faced the stigma of chronic illness, including stunted growth and development and poor school performance because of frequent absences. They may be orphaned or live in a household with chronically ill parents or caregivers who do not show empathy to their status. They may have delayed puberty, which leads to poor self-esteem.

Adolescents who have acquired HIV through horizontal means also have distinct needs; they may be from key populations e.g. MSM, transgender, PWID and/or engaged in sex work. This group is generally prone to risk-taking behaviour, which is likely to make medication adherence a challenge. They also have a need for family planning and STI services.

- **Transition into an Adult ART clinic**

Many adolescents experience worry and anxiety about transitioning to adult services and have a difficult time adjusting to the increased responsibility and expectations in the adult care setting.

The goals of successful transition are that the individual is retained in care, remains adherent to ART, develops the capacity to take measures to reduce the risk of onward transmission of HIV, and that they receive the clinical and psychosocial support required to transition into a physically and psychologically healthy adult. Most HIV-infected adolescents transition to adult care between **15 and 20 years of age**. Adolescents who demonstrate

¹⁰ HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV: recommendations for a public health approach and considerations for policy-makers and managers. WHO 2013.

independence in making their own decisions and show responsibility for their own care may be ready to transition sooner.

- **Supporting the transition and providing adolescent appropriate care**

The adult HIV care service needs to cooperate with paediatric care providers at operational and individual patient levels to support the transition of adolescents into their care and to ensure their service is “adolescent friendly”.

4.1 Organizational arrangements for Adolescent care in Adult HIV clinics

Clinic level organizational arrangements for transition of adolescents to adult care:
<ol style="list-style-type: none">1. Identify a focal point for communication between the adult and paediatric services.2. Develop a specific orientation procedure to acquaint the newly transitioned patient to the adult clinic environment that includes.<ul style="list-style-type: none">• Orientation to the physical layout of the clinic.• Introduction to clinic staff.• Explaining clinic visit flow.• Clearly explaining the policy for late arrivals and walk-ins.• Assignment one clinic staff member as point person for the patient, and have his/her contact information available, including hours when contact is possible

Organizational arrangements for improving the “adolescent friendliness” of the clinic:
<ol style="list-style-type: none">1. Create a specific clinic time each week for adolescent attendance.2. Structure this clinic time for shorter waiting periods, and longer consultation times.3. Invite a counsellor/PSW from the paediatric clinic to join this session.4. Enable MMM (peer support) adolescent specific activities.5. Ensure where possible that fees are not charged to the Adolescent.6. Partner with NGOs to provide specific adolescent support to complement clinic services.7. Foster a clinic culture where staff remains non-judgmental and respectful at all times.

The paediatric clinic staff will prepare the adolescent for transfer to the adult clinic as follows:

1. Develop a transition plan with the adolescent, families and care providers.
2. Provide education and skills training so that prior to the transition the adolescent has the capacity to:
 - Know when to seek medical care for symptoms or emergencies.
 - Identify symptoms and describe them.
 - Make, cancel, and reschedule appointments.
 - Arrive to appointments on time.
 - Call ahead of time for urgent visits.
 - Make sure that they have enough medication at home before medications run out before appointment date.
 - Understand the importance of health care follow up, and able to assume responsibility for his or her treatment and participate in decision-making.

3. The paediatric/adolescent healthcare team should assist the adolescent in choosing an adult clinic that best suits the individual.
4. Ensure that the transfer is made when clinically stable.

After transition to Adult clinic

The adult care provider must work with the paediatric team in the event that adolescents withdraw from care in the adult clinic and return to their previous paediatric clinic, to facilitate and encourage re-engagement in adult medical care.

4.2 Psychosocial support

The Adult HIV clinic will be required to provide ongoing psychosocial support to adolescents, which may include:

- Identifying and address crises (i.e., suicidal behaviour, homelessness).
- Reproductive health and sexuality, and promotion of safer sex behaviours.
- Providing access to benefits, entitlements, and services.
- Supporting youth in self-care and life-enhancing practices.
- Identifying and treating chronic problems (i.e., depression, substance abuse).
- Promoting skills to live independently and to make the transition to adulthood.

Counselling for adolescents includes; support for adherence to ART, sexual and reproductive education, support for intimate romantic relationships, as well as disclosure to partners and significant others.

Care providers should show respect, and listen carefully and in a non – judgmental way to the adolescent’s concerns and choices.

Care providers need to talk with the adolescent by themselves about risk reduction, as it may not be possible to have an open discussion in front of their parents or care takers.

Group counselling should be facilitated to help these teenagers develop better self-esteem. By providing a meeting space in the clinic and inviting skilled individuals, health care workers can help facilitate the process and foster the formation of a group where adolescents can get together and through which they can develop some of these skills.

4.3 Specific issues to address with adolescents

4.3.1 Disclosure:

- **Disclosure to the adolescent:** WHO advises that children of \geq school age status should be told their HIV status, and that non-disclosure to adolescence is associated with poorer retention in care. Adolescents transferring into Adult HIV clinics should be clearly aware of their HIV status prior to transfer.
 - The moment of full disclosure should occur between the ages of 6 - 12 years.
 - If disclosure occurs after puberty has started, usually after the age of 12, there may be negative consequences, such as a treatment non-adherence and depression.

- **Disclosure to others, risks and benefits:** Adolescents should be counselled about:
 - *Potential benefits of disclosure;* such as disclosure (a) to others in order to obtain the support they need for HIV care and treatment and (b) to sexual partners in order to contribute to safer sex/HIV prevention.
 - *Potential risks of disclosure;* such as stigma, discrimination, abandonment and violence.
- Adolescents will need to be empowered and supported to determine if, when, how and to whom to disclose.
- In general, disclosure to sexual partners is different for adolescents than for adults;
 - Adolescents are often not in long-term stable relationships,
 - They may not have the knowledge and emotional skills to deal with the difficult issues raised by disclosure to partners, including dissolution of the relationship.
 - Unequal power dynamics are common among adolescents (e.g. between adolescent women and older partners) may leave the adolescent partner more vulnerable to isolation or abuse following disclosure.
- Adult carers of adolescents also need to be supported around the ALHIV disclosure to a wider community, as they may experience stigma and discrimination.

4.3.2. Reproduction and sexual health

Adolescents need to have a clear understanding regarding

- Basic reproduction and contraceptive measures to avoid pregnancy.
- Sexually active young women should be strongly advised to use dual contraceptive methods, preferably with a long acting hormonal contraceptive.
- Sexually transmitted infections: information regarding prevention, and where to access check-ups and treatment.
- Their individual right to control if, when and how they engage in sexual activity.

4.3.3. Adherence and retention in care

- Adherence to ART and retention in care are the most difficult challenges for adolescents and their clinicians, and have individual and public health ramifications.
- Providing a clinical service that is “adolescent friendly” and meets ALHIV needs is critical to provide the support that is required.
- Identify barriers to adherence by listening to the individual’s concerns, and work with them to address these issues in a non-judgmental way.
- Peer support, and NGO support should be recruited when available.
- Active case management should be employed to ensure that each adolescent is supported to remain in care.

4.4 Clinical issues regarding Adolescent care

Clinical issues regarding Adolescent HIV care

- **WHO clinical staging** for adolescents ≥ 15 years is the same as adults, and for < 15 years is the same as paediatrics.
- **Initiation of ART** in adolescents; same as adults
- **ART regimen** for adolescents ≥ 35 kg is the same as for adults, for <35 kg is same as for children.
- **NCD:** ALHIV who had perinatal transmission are at risk of long term ART toxicity and metabolic complications of HIV (e.g. hyperlipidaemia)
- **OI prophylaxis:**
 - Cotrimoxazole is prescribed routinely for all adolescents, and once they become an adult at age 20, the same stopping rules apply as to adult.
 - TB screening and criteria for IPT are the same for adolescents as adults.
 - Cryptococcal screening is also the same for adolescents as adults

Antiretroviral therapy and prevention of Opportunistic infections

Chapter5. Primary Prophylaxis for Opportunistic Infections

5.1 Cotrimoxazole primary prophylaxis

- The primary aim of cotrimoxazole prophylaxis is to prevent Pneumocystis Jirovecii Pneumonia (PJP or PCP), toxoplasmosis, and major bacterial illness.
- Cotrimoxazole can be initiated as either *primary prophylaxis* (given to PLHIV who have never had these infections) or *secondary prophylaxis* (given to PLHIV who have had an episode of these infections, to prevent recurrence).

- Cotrimoxazole is a combination tablet of trimethoprim TMP, and sulfamethoxazole SMP.

Formulations of cotrimoxazole:

- Cotrimoxazole DS (double strength) = TMP 160mg / SMX 800mg (or 960mg)
- Cotrimoxazole SS (single strength) = TMP 80mg / SMX 400mg (or 480mg)
- Cotrimoxazole oral suspension = TMP 40mg / SMX 200mg per 5 ml

Dosing and administration

- If ≥ 35 kg Cotrimoxazole DS x 1 daily or cotrimoxazole SS tablets x 2 daily.
If < 35 kg cotrimoxazole SS x 1 daily.
- If the standard dose of cotrimoxazole is not tolerated (depending on the reason) either reduce the dose to cotrimoxazole dose to 1 SS tablet daily, or use Dapsone 100mg orally once a day (for prevention of PJP only – see below).
- Take cotrimoxazole with food to prevent GIT side effects.

5.2 Criteria for Cotrimoxazole prophylaxis

Table 5-1 Criteria for starting, continuing and stopping Cotrimoxazole for Adults and Adolescents including pregnant women.

	Adolescent (11-19)	Adults (≥ 20 years)
When to start cotrimoxazole	All regardless of CD4 count	<ul style="list-style-type: none"> • CD4 < 350 cells/mm³* • All patients with TB • WHO stage 3 or 4 regardless of CD4 count
When to continue cotrimoxazole	ALL	<ul style="list-style-type: none"> • CD4 < 350 cells/mm³ and/or on TB treatment • If history of PCP with CD4 count > 200 cells/mm³ (secondary prophylaxis indefinitely)
When to stop cotrimoxazole	Never stop (until adult)	<ul style="list-style-type: none"> • CD4 count > 350 cells/mm³ on 2 measurements at least 6 months apart <i>and</i> undetectable VL <i>and</i> completed TB treatment

* Start cotrimoxazole at the first visit, and if the CD4 is > 350 then cease it at the next visit two weeks later.

5.3 Recommence cotrimoxazole if CD4 drops or active TB

- If the CD4 count drops < 350 cells/mm³ or active TB, cotrimoxazole prophylaxis should recommence, and the same stopping criteria used.

5.4 Contraindications to cotrimoxazole

- Severe allergy to cotrimoxazole or other sulfa containing drugs
- Severe liver disease
- Severe anaemia or neutropenia
- Severe renal disease: (eGFR < 15 mL/min), for moderate impairment (15 – 50 mL/min) → reduce dose to 1SS daily and watch potassium.
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency.

5.5 Cotrimoxazole in pregnancy and lactation

- The WHO endorses cotrimoxazole use as a priority intervention in pregnant PLHIV, that there is no conclusive evidence for teratogenicity and that the benefits of cotrimoxazole prophylaxis outweigh any potential risk.
- Cotrimoxazole prophylaxis regimens for PLHIV are non-inferior to intermittent preventive treatment (IPT) of malaria (do not use any additional malaria IPT).

5.6 Drug interactions

- *Drugs that cause potassium retention, e.g. ACE inhibitors*—increase risk of hyperkalaemia; monitor potassium concentration.
- Cotrimoxazole may potentiate the effects of oral hypoglycaemic agents (monitor BSL).

5.7. Monitoring

Frequency: monthly until stable, then 3 monthly

- Check adherence, and patients understanding.
- Monitor for hypersensitivity reaction; fever and rash.
- Monitor for other side effects; GIT, hyperkalaemia (especially if on ACE inhibitor), bone marrow suppression (anaemia, neutropenia, thrombocytopenia), hepatitis, rarely urinary stones/ obstruction, neurological issues.

5.8 Cotrimoxazole hypersensitivity

- Usually occurs within days – weeks of commencement; skin and systemic symptoms: (most commonly rash and fever).
- Skin: dry → wet rash, Stevens-Johnson syndrome, toxic epidermal necrosis.
- Systemic: fever, dyspnoea+ cough, eosinophilia, hepatitis, interstitial nephritis, lupus-like syndrome, multi-organ hypersensitivity syndrome, vasculitis and pancytopenia.

5.9 Management of side effects

- Minor rashes (dry rash) are common and can usually be managed with careful observation and continuing cotrimoxazole. Stop if persistent.

- Discontinue cotrimoxazole in the event of more severe (usually wet) rashes including Stevens Johnson syndrome, clinical hepatitis, severe anaemia or pancytopenia. Supportive management including hospital admission is sometimes necessary.
- Reductions in Hb or white cell count can be managed by dose reduction if not severe.

Table 5-2 Management of Cotrimoxazole hypersensitivity rash

Severity	Description	Management
Grade 1	Diffuse or patchy erythema May be pruritic.	Continue cotrimoxazole Follow-up in 3-4 days +/- antihistamines for symptom relief
Grade 2	Dry maculopapular rash Minimal exfoliation	Continue cotrimoxazole Follow-up in 1-2 days +/- antihistamines for symptom relief
Grade 3	Vesiculation, mucosal ulceration	Stop Cotrimoxazole until the adverse effect has completely resolved (usually two weeks), and then reintroduction with desensitisation
Grade 4	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation	Discontinue cotrimoxazole immediately Hospitalize for supportive care Never restart cotrimoxazole.

- Dapsone is less effective than cotrimoxazole in preventing PCP and also lacks the broad antimicrobial activity of cotrimoxazole. It is therefore desirable to attempt desensitization to cotrimoxazole among individuals with a previous non-severe reaction, before substituting with dapsone.

5.10 Desensitization in order to recommence Cotrimoxazole

- Desensitization can be attempted two weeks after a non-severe (grade 3 or less) cotrimoxazole reaction.
- Cotrimoxazole desensitization has been shown to be successful in 40-80 % of individuals with previous hypersensitivity, and rarely causes serious reactions.
- **Desensitization should not be attempted in individuals with a history of a grade 4 reaction to cotrimoxazole or other sulfa drugs.**
- Premedication with an oral antihistamine may reduce the risk of a hypersensitivity reaction, and can be commenced one day prior, or on the day of starting the regimen, and continue daily until completing dose escalation.

Table 5-3 Cotrimoxazole Desensitization Protocol (adults + adolescents)

Time	Dose cotrimoxazole *
Day 1	16 mg TMP / 80 mg SMX (2 ml oral suspension)
Day 2	32 mg TMP/ 160 mg SMX (4 ml oral suspension)
Day 3	48 mg TMP/ 240 mg SMX (6 ml oral suspension)
Day 4	64 mg TMP/ 320 mg SMX (8 ml oral suspension)
Day 5	One single-strength (SS) TMP 80mg /SMX 400mg tablet
Day 6 and continue:	One double- strength (DS) TMP 160mg/SMX 800mg tablet
* Cotrimoxazole oral suspension is 40 mg TMP + 200 mg SMX per 5 ml	

- The patient must come to the clinic daily for each dose, and stay for 1-hour post dose.
- Prior to each dose: check the patient for rash or fever.

- Severe reaction (Grade 3/4): cease the desensitization regimen immediately, and consider if hospitalization is necessary.
- Mild to moderate reaction (Grade 1/2): repeat the same dose for an additional day. If the reaction subsides, advance to the next dose and slow down the escalation protocol (e.g. 2 days at each dose); if the reaction worsens cease the desensitization regimen.
- Once maintenance therapeutic dosing has been established, treatment should not be interrupted.
- If desensitization fails Dapsone 100mg/d should be considered.

5.11 Accelerated Cotrimoxazole desensitization (hospital inpatients)

- In an urgent situation, and if resources allow, an accelerated cotrimoxazole desensitization regimen can be given as a hospital inpatient over 6 hours. This may be necessary for the prompt treatment of active PCP or toxoplasmosis infection.
- It requires a pharmacist to make up serial dilutions of the oral suspensions initially at 1:2000 to enable an hourly dosing schedule of TMP/SMX of: 0.004/0.02, 0.04/0.2, 0.4/2.0, 4.0/20, 40/200, 160/800 mg.

Chapter6. Screening for TB and assessment for Isoniazid Preventive Therapy (IPT)

- Globally TB is the most common cause of morbidity and mortality in PLHIV, TB is responsible for more than a quarter of deaths in people living with HIV.¹¹
- Cambodia has a high burden of TB infection in the population.
- PLHIV with TB infection have a 30-50% lifetime risk of developing active TB.
- Isoniazid preventive therapy considerably reduces the risk of development of active TB.

See Chapter13.Tuberculosis for assessment and management of active TB.

6.1 Screening for symptoms of active tuberculosis

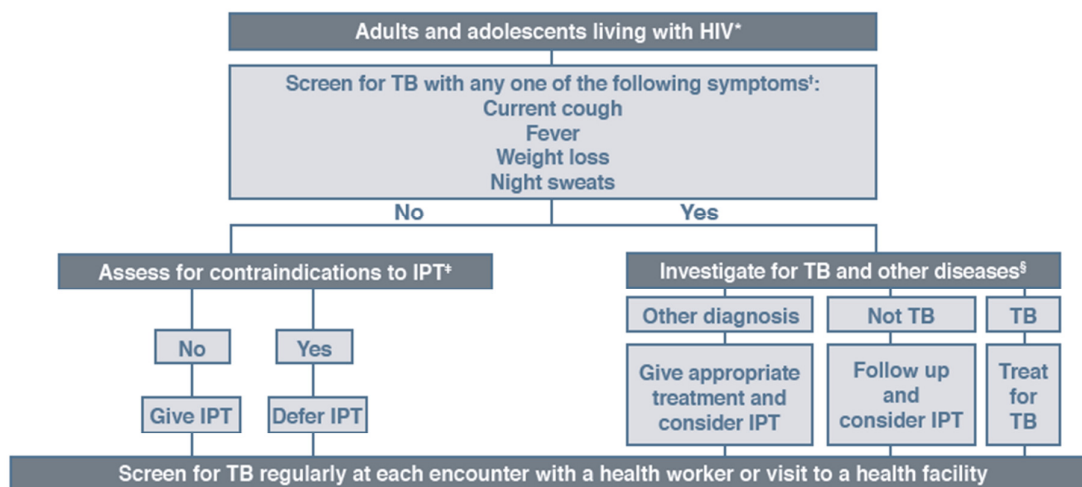
Adults and adolescents living with HIV should undergo clinical screening for TB at every clinic visit.

Table 6-1 TB clinical screening

In the last 4 weeks ask the patient if there are ANY of the following?
1. Cough: any time, any duration
2. Fever: anytime, any duration
3. Drenching night sweats: ≥ 2 weeks duration
4. Loss of weight? AND weigh the patient at each visit and compare with previous visit.

- PLHIV who present with cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.
- Those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

Figure 6-1 WHO Algorithm for TB screening for Adult and Adolescent with HIV



¹¹ Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource- constrained settings. WHO 2011

6.2 IPT: When to start, regimen and duration

Table 6-2 Criteria to start, continue, and stop Isoniazid preventive therapy (IPT)

IPT	TB symptom screening should be performed at EVERY clinic visit
When to start IPT (Adults and adolescents)	<ul style="list-style-type: none"> • All patients with TB symptom negative and no contraindications. Contraindications: peripheral neuropathy, heavy alcohol consumption, ALT/AST > 3 x ULN. • Patients who TB symptom screen positive; start IPT after elimination of active TB. • After completion of TB treatment (secondary prophylaxis)* <p><i>Start IPT at the first follow up visit after commencing ART, provided the patient is tolerating ART and is clinically stable. Otherwise start as soon as stable on ART.</i></p>
Continue IPT	<ul style="list-style-type: none"> • Complete 6 months (if treatment interruption, see below)
When to stop IPT	<ul style="list-style-type: none"> • If symptoms of hepatitis (anorexia, nausea, vomiting, abdominal pain, chills, icterus and dark urine), stop INH immediately and seek the HIV clinic • If increase of ALT/AST under monitoring of patients with risk of liver disease: <ul style="list-style-type: none"> • Asymptomatic and ALT/AST > 5 x ULN or • Symptomatic and ALT/AST > 3 x ULN • If persistent neuropathy after increase of pyridoxine to 100mg daily • After completion of 6 months on IPT

(*) To eradicate more recently acquired infection, and to protect against new infection whilst being established on ART.

6.3 IPT: Dose and duration

6 month course:

- If > 40kg: Isoniazid 300mg / day + pyridoxine 50mg / day
- If ≤ 40kg: Isoniazid 200mg / day + pyridoxine 50mg / day

6.4 Side effects:

- IPT is usually very well tolerated
- Main side effects are:
 - Gastrointestinal – including nausea and occasionally vomiting
 - Hepatitis – rate 0.3% in young adults, and ~2 -3% in the elderly
 - Peripheral neuropathy – largely prevented with pyridoxine, the dose can be increased to 100mg daily if symptoms appear. If persistent, cease INH.
 - Hypersensitivity reaction

6.5 Counselling on IPT to the patient

- The patient has been informed and understands to take IPT for 6 months duration.
- They do not have regular or heavy alcohol consumption, and agree to abstain.
- If they have symptoms of hepatitis; anorexia, nausea, vomiting, abdominal pain, chills, icterus (yellow eyes) and dark urine, that they should *stop the INH immediately* and seek medical attention, preferably at the HIV clinic.

6.6 Clinical Monitoring visits on IPT

The patient should return to clinic every month – at which time:

- Assess for any clinical indication of INH toxicity.
- Screen for active TB (every visit, continue whilst on, and after IPT).
- Dispense 1 month INH + pyridoxine.

6.7 Monitoring Liver function tests at baseline and on IPT

- ALT/AST should be checked at baseline ONLY with NO routine monitoring if the patient does not have increased risk for hepatic disease (see below)
 - If the ALT/AST > 3 x ULN at baseline: IPT is contraindicated.
 - If the ALT/AST is above ULN but < 3 x ULN: check HBsAg, and repeat ALT/AST at M1, and M2, and consider continuing to monitor monthly.
- In case of increased risk for hepatic disease (e.g. HBV, HCV, history of liver disease), ALT/AST should be monitored monthly
- In case of the emergence of symptoms +/- signs suggesting hepatitis (anorexia, nausea, vomiting, abdominal pain, chills, icterus and dark urine), INH SHOULD BE STOPPED IMMEDIATELY and ALT/AST should be performed urgently.

6.8 Interruptions to IPT

- Patients should be advised strongly that it is critical that IPT be taken as prescribed, continuously for 6 months.
- However if there is one interruption to IPT, the following can be considered.
 - If interrupted for < 8 weeks, *perform clinical TB screening* and if negative continue INH and extend so total taken is equivalent to 6 months.
 - If interrupted for ≥ 8 weeks, *perform clinical TB screening* and if negative re-start treatment for 6 more months.
- If the patient interrupts IPT more than once, then do not try to reinstitute again.

Chapter7. Cryptococcus screening and prevention

7.1 Primary prophylaxis for Cryptococcus vs screening CRAG

Cryptococcal meningitis (CM) is a significant cause of morbidity and mortality amongst Cambodian PLHIV. It occurs mostly in advanced disease in PLHIV with CD4 < 100 cells / mm³, with those with CD4 < 50 cells / mm³ at particularly high risk.

Detection of Cryptococcal antigen (CRAG)

- Simplified low cost antigen detection methods for Cryptococcal antigen (CRAG) using a Lateral Flow Assay (LFA) provides an opportunity to screen PLHIV for cryptococcal infection, and will be available soon in Cambodia.
- CRAG test enables detection of cryptococcal infection prior to the development of symptoms.
- Asymptomatic cryptococcal infection risks developing clinical life threatening cryptococcal disease in the following weeks – months.
- Two previous studies in Cambodia have found ~ 20% (symptomatic and asymptomatic), and ~ 8% (asymptomatic) patients with CD4< 100 were CRAG + at the time of entry into HIV treatment.

Clinical scenarios with CRAG + include

1. Symptomatic cryptococcal meningitis (CM) / other cryptococcal disease
 2. Asymptomatic cryptococcal meningitis (CM)
 3. Isolated positive cryptococcal antigenaemia (ICPA)
- PLHIV diagnosed with symptomatic or asymptomatic CM require hospitalization and standard treatment (see Chapter17. Cryptococcal meningitis).

7.2 Fluconazole primary prophylaxis

Fluconazole may continue to be prescribed until the CRAG test becomes available:

Table 7-1 Fluconazole prophylaxis (when CRAG test is not available)

When to start Fluconazole prophylaxis	CD4 < 100 cells / mm ³ and Not in the 1 st trimester of pregnancy and AST/ALT < 3x ULN*
When to stop Fluconazole prophylaxis	CD4 > 100 on 2 occasions > 6 months apart and VL undetectable Or if emergence of hepatitis: <ul style="list-style-type: none"> • AST/ALT > 3 x ULN and symptomatic, • or AST/ALT > 5 x ULN and asymptomatic

* Monitor AST/ALT at baseline, 1 and 2 months, then if clinically indicated. In case of HBV /HCV co-infection or abnormal at AST/ALT at baseline, continue to monitor AST/ALT monthly till month 4.

7.3 Cryptococcal antigen (CRAG) screening

- The CRAG testing is for screening purposes only. If a patient has symptoms of meningitis they should proceed directly to LP rather than wait for CRAG test result. (see Chapter 16. Meningitis)
- For all newly enrolled adult and adolescent PLHIV, if the CD4 < 100 cells/mm³ the laboratory performing CD4 test will automatically go on to perform a CRAG test on the same day.

What to do with the result of CRAG?

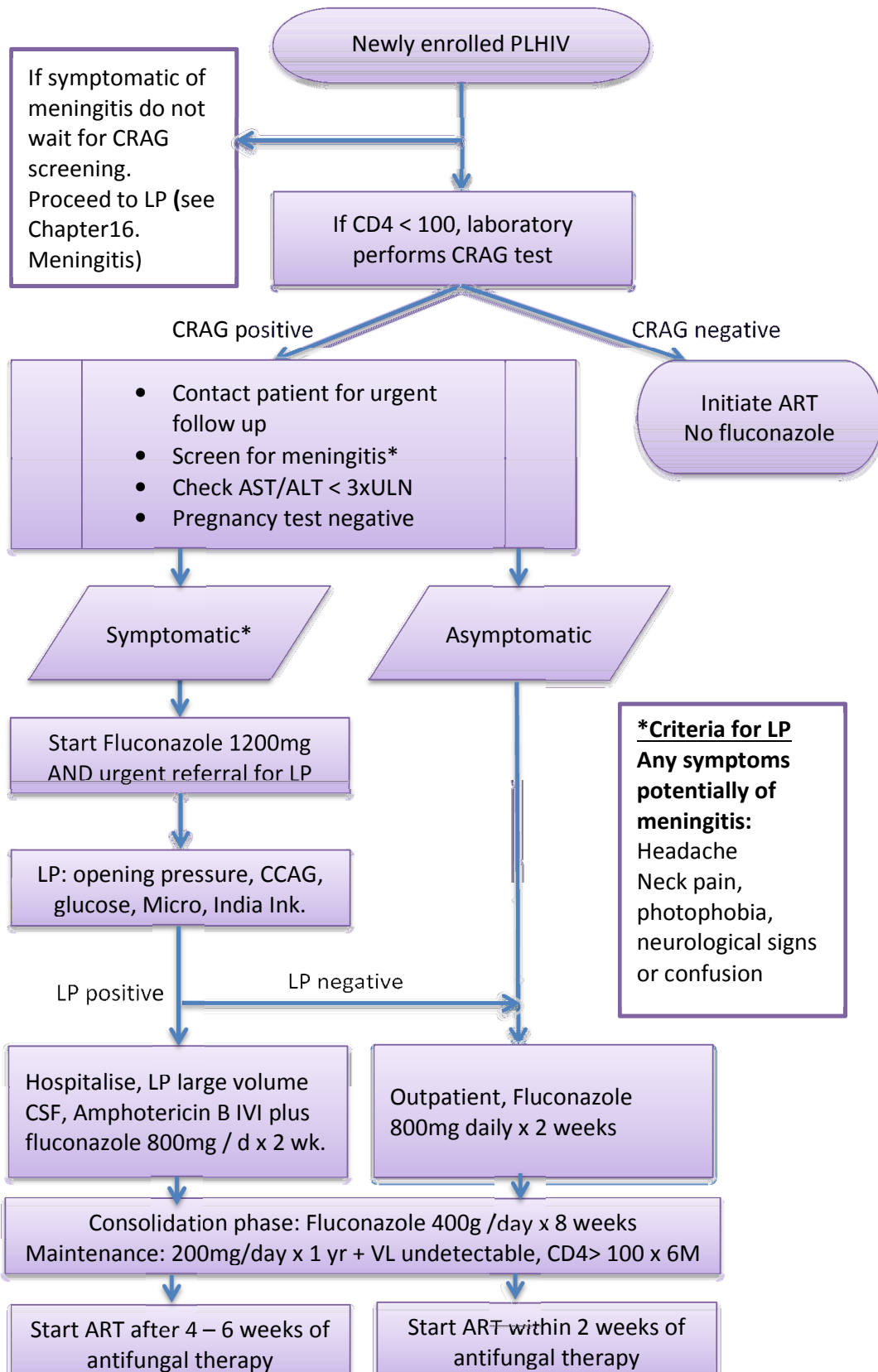
- CRAG + → call the patient to return to be evaluated for symptoms / signs of meningitis.
 - If any possible symptoms / signs of meningitis (headache, neck pain, photophobia, confusion, neurological signs, fever) → immediately start fluconazole 1200mg and refer for urgent lumbar puncture. (See Chapter 17. Cryptococcal meningitis)
 - If NO symptoms / signs of meningitis → start fluconazole 800mg/day x 2 weeks followed by 400mg x 8 weeks.
- If CRAG negative → No fluconazole.
- All CRAG positive should continue with maintenance fluconazole 200mg daily until ≥ 1 year *and* VL undetectable *and* CD4 > 100 cells / mm³ on two occasions > 6 months apart.

Pregnant women:

Women of childbearing age who screen CRAG positive should have a pregnancy test prior to starting fluconazole (teratogenic); those who are not pregnant and are started on fluconazole should be advised to avoid pregnancy during treatment.

- CRAG-positive patients who are pregnant should be offered an LP and discussed with an expert before a decision is made regarding management.

Figure 7-1 Cryptococcal Antigen screening



Chapter8. Starting Antiretroviral Therapy

8.1 Criteria to start ART and when to start ART in adults and adolescents

Table 8-1 Criteria to start ART and when to start ART in adults and adolescents

Who should start ART	<ul style="list-style-type: none"> • ALL regardless of CD4 count • Priority should be given to: <ul style="list-style-type: none"> • PLHIV with WHO clinical stage III/IV or CD4 \leq 350 • Pregnant and breastfeeding women (Option B+) • PLHIV with HBV, and TB co-infections
When to start ART	<ul style="list-style-type: none"> • Within 2 weeks after enrolment following preparedness and completion of ART counseling. • With some opportunistic infections, delay in ART initiation are required after initiating OI treatment* <ul style="list-style-type: none"> • Cryptococcosis meningitis: 4-6 weeks • TB with CD4 > 50: 2-8 weeks

* see Table 8-3 Timing of ART initiation in setting of active OIs

8.2 First line ART regimens

Table 8-2 Standard 1st line ART regimens

First line ART	Preferred first line	Alternative first line*
Adults Including pregnant/ breastfeeding, and with TB and HIV co-infection Adolescents > 35kg	TDF + 3TC + EFV	AZT+ 3TC + EFV (or NVP) TDF + 3TC + NVP
Adolescents < 35kg	TDF + 3TC + EFV	AZT+ 3TC + EFV (or NVP) TDF + 3TC + NVP ABC + 3TC + NVP
	*ABC or PI or when available Dolutegravir may be required in special situations as alternative 1 st line agents. Consult with an expert.	

8.2.1 Preferred 1st line regimen

TDF + 3TC + EFV fixed dose combination, once daily regimen

- TDF 300mg + 3TC 300mg + EFV 600mg FDC tablet is the preferred first line ART regimen provided there are no contraindications.
- The regimen is highly effective and well tolerated, to be taken once daily on an empty stomach, (food increases EFV side effects and may increase CNS side effects).
- This regimen is appropriate for adults, and adolescents including pregnant and breastfeeding women, and those on TB treatment.

- TDF and 3TC are also treatment for HBV so this NRTI combination is preferred for HBV co-infection.
- TDF has advantages over AZT with regards to sequencing to second line ART, as AZT failure results in the accumulation of thymidine analogue mutations which reduce the susceptibility of HIV to TDF (or ABC). However the K65R mutation that develops in the context of TDF failure does not reduce and may even increase susceptibility of HIV to AZT for second line use.

8.2.2 Contraindications to preferred 1st line ART: TDF + 3TC + EFV

- TDF is contraindicated in renal failure and should not be started if the eGFR < 50 ml/min.
 - Substitute AZT 250 – 300mg BD (as AZT + 3TC FDC)
- EFV should be avoided in the context of psychiatric illness, and dementia.
 - Substitute NVP 200mg BD (after lead in dose).

8.3 Efavirenz dosing

- EFV 400mg is now demonstrated to have equivalent efficacy to 600mg, with less side effects¹²
- However EFV 400mg is not recommended for pregnant women or those on rifampicin, which reduces the concentration of EFV.
- It is anticipated that EFV 400mg single tablets will soon be available, and, an FDC will come later.
 - Patients who are experiencing significant side effects due to EFV who are currently taking FDC of TDF+3TC+EFV 600mg, can be given the option to switch to EFV 400mg + FDC dual NRTI, which may be better tolerated. (Provided they are not pregnant or on TB treatment)
 - Patients currently doing well on FDC TDF+3TC+EFV 600mg should stay on this until the triple FDC EFV 400mg becomes available.
 - Patients starting ART should commence on FDC TDF+3TC+EFV 600mg.

8.4 Alternative first line agents

AZT + 3TC FDC (+NVP or EFV)

- AZT 250 - 300mg + 3TC 150mg taken twice daily can be used as an alternative to TDF provided the Hb > 8.0 g/dl.
- AZT + 3TC FDC twice daily dosing can be combined with separate EFV daily dose.
- AZT + 3TC + NVP is available as a FDC to take twice daily (after lead in NVP dose).

Nevirapine (NVP)

- NVP can be used as an alternative to EFV in the event of contraindication to EFV.

¹² Encore 1 Study Group. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis* 2015;15: 793–802

- NVP is contraindicated if the patient is also on rifampicin as rifampicin reduces NVP drug concentrations.
- NVP is contraindicated in severe hepatic impairment (ALT/ AST> 5 x N)
- Risk factors for hepatotoxicity include women with CD4> 250 and men with CD4> 400, concomitant hepatotoxic drugs, and underlying hepatic disease.
- A lead in dose of 200mg NVP daily should be prescribed for 2 weeks prior to increasing to 200mg twice daily.
- ALT/AST should be monitored at baseline, at 2 weeks prior to dose escalation, again 2 weeks after and monthly for the following 3 months.

Abacavir (ABC)

- ABC may be substituted for AZT or TDF if both the latter are contraindicated.
- However ABC/3TC combined with EFV, or ATV/r have been demonstrated to have higher rates of VL failure if pre-treatment HIV VL is > 100,000. If these combinations are being considered prior to ART commencement check the VL prior to starting ART, however as pre-treatment VL is not routinely performed in Cambodia the opportunity may have been missed.
- ABC hypersensitivity reaction occurs in ~3% of patients, in which case ABC should never be restarted (rechallenge may be fatal).

8.5 Starting ART in the setting of an opportunistic infection

- Early initiation of ART in the setting of an opportunistic infection may increase the risk of IRIS, however in the majority of situations early commencement of ART improves morbidity and mortality.
- An exception is in PLHIV with drug susceptible (DS) TB and CD4 > 50 it is reasonable to wait 2 – 8 weeks prior to commencing ART, as this reduces the risk of IRIS and there is no mortality disadvantage.
- In addition IRIS is more likely to be fatal with CNS infections, so ART should be delayed for 2 – 8 weeks with TB meningitis and 4 – 6 weeks with Cryptococcus meningitis.
- Otherwise ART should be initiated **within two weeks of treatment of opportunistic infections**

Table 8-3 Timing of ART initiation in setting of active OIs

Opportunistic Infection	Time from start treatment for OI and start ART
Tuberculosis¹³ CD4 < 50 cells/mm ³ CD4 > 50 cells/mm ³	Within 2 weeks 2 – 8 weeks
Cryptococcal meningitis (CM)	4 – 6 weeks
Cryptococcus non-meningeal disease including Cryptococcal Ag + CSF neg	Within 2 weeks
All other OI	Within 2 weeks

¹³ WHO TB guidelines 2010: recommends start ART as soon as possible within 8 weeks of TB treatment. The above schedule is consistent with the TB CARE I. International Standards for Tuberculosis Care, Edition 3. TB CARE I, The Hague, 2014, and MSF HIV/TB Clinical guide 2015. See also Uthman O.A et al Optimal Timing of Antiretroviral Therapy Initiation for HIV-Infected Adults With Newly Diagnosed Pulmonary Tuberculosis A Systematic Review and Meta-analysis. Annals of Internal Medicine • Vol. 163 No. 1 • 7 July 2015

8.6 Issues that may arise with concurrent ART and treatment of OI

- Pill burden and side effects
- Patients being overwhelmed by new medication regimens.
- Drug-drug interactions
- Toxicity – liver, renal, bone marrow
- Immune Reconstitution Inflammatory Syndrome.

Chapter9. Immune Reconstitution Inflammatory Syndrome

After the commencement of ART, a reduction in viral load allows immune recovery, and this increased capacity for immune reaction to infections sometimes leads to new, or increase in severity of clinical manifestations.

9.1 The main contexts in which Immune Reconstitution Inflammatory Syndrome (IRIS) occurs

1. Previously asymptomatic infections becoming symptomatic (unmasking IRIS).
 2. Apparent worsening of symptomatic infections even if they are being successfully treated (paradoxical IRIS).
 3. Reaction to remnants or antigens of previous OIs after ART treatment.
- **The risk of IRIS is higher if:**
 - ART is commenced in advanced HIV; at lower CD4 counts and higher viral loads.
 - There is a high pathogen burden such as in disseminated infection.
 - There is a short interval between treatment of OI and initiation of ART.
 - IRIS commonly **presents 2-8 weeks after starting ART** but can occur any time in the first 6 months, and in rare cases, later.
 - **Symptoms and signs of IRIS** overlap with those of the underlying opportunistic infection
 - IRIS can result in substantial morbidity, and increased complexity of management including changes in ART regimens when it is unclear if symptoms are as a result of ART toxicity. Whilst most IRIS is not fatal, there is some increased mortality particularly for cryptococcal meningitis.
 - **Tuberculosis** is the most common infection associated with IRIS. This is similar to ‘paradoxical reactions’ in non-HIV infected people being treated for TB. The most common symptoms include fever and an increase in the size or number of TB lesions, especially lymph node and/or pulmonary infiltrates, but also bronchial lesions, ureteric strictures, or CNS lesions.
The differential diagnosis of TB IRIS is treatment failure; due to poor adherence or drug-resistant TB (DR-TB).
 - IRIS may occur with many infectious and also non-infectious manifestations of HIV:
 - HBV and HCV → hepatitis
 - CMV → vitritis
 - Dermatological conditions – VZV, folliculitis.
 - CNS conditions – Cryptococcus, toxoplasmosis, TB, JCV, PML
 - Multi organ symptoms – MAC, TB, fungi
 - PCP, penicillium, histoplasmosis, etc.
 - Kaposi sarcoma (very rare in Cambodia)

9.2 Management of IRIS

- Continue ART, (except very occasionally in severe cryptococcal meningitis).
- Aggressively investigate for new OI or active OI that is failing treatment.
 - Test sputum m/c/s, blood cultures, chest x-ray, lumbar puncture if CNS symptoms, biopsy of new or worsening lymphadenopathy or skin lesions.
- Patients with worsening TB symptoms should have repeat sputum cultures and sensitivity testing to evaluate for treatment failure, DR TB or alternative Dx of MAC.
- Start/continue standard treatment for the OI.
- Recommence OI Rx for IRIS due to symptoms related to a previously treated infection, whilst establishing whether active infection is present. If there is any doubt, retreat the infection.
- Non-steroidal anti-inflammatory agents (NSAID) can be used to reduce symptoms related to inflammation, e.g. lymphadenitis and fever.
- A course of corticosteroids are occasionally required if symptoms become severe (e.g. dyspnoea, CNS symptoms, renal obstruction).
- **Notes about corticosteroid use:**
 1. If the patient is on rifampicin the interaction with steroids results in markedly reduced steroid concentration, therefore requiring higher dose of prednisolone than usual (e.g. start with prednisolone 1.5mg/kg).
 2. High dose/prolonged courses of steroids along with the immunodeficiency associated with HIV increases the risk of disseminated strongyloidiasis and septic shock.
 - If high dose prednisolone (>20mg) for more than 2 weeks is planned, treat empirically with albendazole 400mg orally with fatty food 12 hourly x 7 days¹⁴

¹⁴ Sanford Guide to Antimicrobial therapy. 45th Edition. 2015.

Chapter 10. Monitoring and substitutions for ART toxicity

- Patients should be informed about the key side effects of any medication prescribed.
- Monitoring for side effects is principally symptom directed, supported by some laboratory tests.
- At each clinic visit, the clinician should specifically ask about the medicine the patient is taking, and explore whether there are any side effects.
- Life – threatening and serious toxicities are outlined below and in the following table.¹⁵

10.1 Common side effects

Nausea and vomiting

- May be present with HIV anyway, and exacerbated with ART – particularly AZT, and PI.
- Often resolves after a few weeks, try taking at different times of the day, add metoclopramide 10mg three times daily if severe.
- If medication is vomited: take again 2 hours later.
- If intractable vomiting: assess for hypersensitivity syndrome (ABC), hepatitis, pancreatitis etc.
- If vomiting occurs > 6 months after commencement of ART, consider lactic acidosis.

10.2 Life threatening toxicities of ARV

10.2.1 Lactic acidosis

- Whilst most common with d4T, lactic acidosis can occur with any NRTI particularly AZT, although is very rare with TDF, ABC, 3TC.
- It occurs after more than 6 months on ART.
- Risk factors include female gender, obesity and pregnancy.
- **Monitoring for lactic acidosis:** Symptomatic monitoring. Asymptomatic elevations in lactate are common but not important.
- **Clinical presentation of lactic acidosis:** includes nausea and vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Lactic acidosis may be associated with the development of NRTI-induced peripheral neuropathy, or fatty liver (hepatic steatosis).
- **Differential diagnosis:** High lactate and acidosis are also present in sepsis or circulatory failure so a thorough clinical assessment is required.
- **Diagnosis:**
 - A raised lactate of > 5mmol/ litre + acidosis as measured by low serum bicarbonate (<20mmol/l).
 - However when lactate test is not available low serum bicarbonate (<20mmol/l) is adequate for the diagnosis provided the clinical context is compatible.

¹⁵ MSF HIV/TB Clinical Guide 2015, and WHO Consolidated guidelines 2013.

- Associated abnormalities include \uparrow ALT/AST and \uparrow creatinine kinase.
- **Management**
- If minor symptoms + bicarbonate < 20 mmol/ml \rightarrow switch NRTI from AZT to TDF or ABC.
- If severe symptoms +/- bicarbonate < 15 mmol/ml \rightarrow admit to hospital, stop all NRTI.
 - Look for sepsis and malaria, and add empiric IV antibiotics if any doubt.
 - Temporarily add ATV/r to the NNRTI until the patient improves and the bicarbonate normalizes. Then stop the ATV/r and change to TDF or ABC.
 - If the patient is already on LPV/r or ATZ/r, continue monotherapy until the patient improves and then add TDF or ABC.

10.2.2 Abacavir hypersensitivity

- A small % of patients on ABC will develop a hypersensitivity reaction, which most commonly occurs during the 1st 10 days on ABC, and usually within the first 6 weeks.
- **Clinical presentation** of abacavir hypersensitivity: fever (80% cases), rash (70% of cases but often mild), GIT and respiratory symptoms including cough and dyspnoea, and non-specific constitutional symptoms including malaise and myalgia. Symptoms continue to get worse after each dose.
- **Monitoring for abacavir hypersensitivity:** Symptomatic monitoring.
- **Differential diagnosis:** drug reaction e.g. to cotrimoxazole, or NNRTI. However ABC hypersensitivity tends to manifest more constitutional symptoms, and less severe /fewer rashes, compared to the other drug reactions.
- **Management**
- Stop ABC do not start again, as *re-challenge can be fatal*.
- Symptoms should settle within 48 hours, and substitute NRTI (TDF or AZT) can be commenced.

10.2.3 Pancreatitis

- Pancreatitis is more common with ddi and d4T (which should never be used in combination) however can also rarely be caused by 3TC.
- Gallstones, alcoholism and hypertriglyceridemia (associated with PI and EFV) also cause pancreatitis.
- **Monitoring for pancreatitis:** Symptomatic monitoring.
- **Clinical presentation:** abdominal pain.
- **Diagnosis:** Raised amylase or lipase, abdominal ultrasound.
- **Management:** If the amylase is < 1.5 x ULN and the symptoms are not severe, and the diagnosis is not clear \rightarrow review in 1 week with repeat the amylase. If unwell, or amylase > 1.5 x ULN +/- or US findings are suggestive, then cease the ART, give supportive care, and when recovered restart ART not containing ddi or d4T (use TDF, AZT or ABC).

10.3 Serious side effects of ARV

10.3.1 Tenofovir renal toxicity

- TDF kidney toxicity is due to proximal tubular cell dysfunction.
- It occurs in < 1% of patients on TDF.
- TDF toxicity usually occurs within weeks to months of starting TDF.
- For guidance on kidney impairment in general see Chapter 40. Kidney disease.
- **Risk factors** include older age, male sex, low body weight, advanced HIV infection, pre-existing impairment of kidney function, comorbidities (diabetes, HT, HCV co infection), concomitant use of nephrotoxic and renal excreted drugs, and following a ritonavir boosted protease regimen.

Baseline testing and monitoring for TDF toxicity¹⁶

- Prior to starting TDF baseline creatinine and estimation of eGFR should ideally be performed for all, and definitely in all high-risk PLHIV including older age, pre-existing decrease in kidney function, long term diabetes or HT, concomitant use of PI, nephrotoxic or renal excreted drugs.¹⁶
- Do not initiate TDF if eGFR < 50ml/min, or in long term diabetes, uncontrolled hypertension, or renal failure.
- Ongoing monitoring with serum creatinine and urine dipstick should ideally be routinely checked at M1, M3, and every 12 months after starting TDF.¹⁷
- If resources do not allow for routine serum creatinine, urine dipstick test for glycosuria (in non-diabetic) and proteinuria alone can be used to monitor for severe TDF toxicity → if positive serum creatinine must be performed.

Management of renal impairment occurring on TDF (Cr < 50ml/min):

- Assess and treat other causes of kidney injury (dehydration, BP etc.).
- Stop nephrotoxic drugs – esp. NSAIDs.
- Check HbsAg (if not already known).
- Switch TDF (if persistent, and no other treatable cause found):
 - If TDF is being used in 1st line → switch to AZT or ABC
 - If AZT previously used → switch to ABC or ddi.
- If HBsAg positive: there is a risk of a “flare” of hepatitis after stopping TDF, and of progression of HBV disease.
 - If borderline for TDF toxicity, continue TDF and monitor at 1 and 3 months.
 - If a switch from TDF is required, monitor for hepatitis flare (clinical + ALT), which may occur on ceasing TDF, and for ongoing progression of chronic HBV.
- Alter any drug doses of renally excreted drugs:

Monitor for changes in eGFR which may require further dose adjustments over time.

¹⁶ WHO Consolidated guidelines 2013.

¹⁷ MSF HIV/TB clinical guide 2015

- Table 47-1 Drug dose adjustments in patients with renal failure.
- Monitor the renal function for changes in eGFR which may require further dose adjustments.

10.3.2 Hematological toxicity

- PLHIV are often anaemic, due to chronic HIV infection and opportunistic infections, particularly TB, but also in advanced HIV due to bone marrow infiltration by fungal disease and MAC.
- In addition AZT and cotrimoxazole can cause anaemia, and neutropenia.

Baseline tests and monitoring for anaemia:

- Hb at baseline for all starting AZT (avoid if Hb <8g/dl) and check again at M1, M3 and every 6M

Management:

- For ↓Hb < 25% with mild anaemia (Hb≥80g/dL), and no severe symptoms, stop cotrimoxazole and investigate and treat for other causes; infections – including TB, GIT blood loss etc., and give folic acid. If the Hb improves, then continue AZT and monitor.
- If the ↓Hb > 25%, or Hb < 8 g/l, or symptoms of anaemia, stop both cotrimoxazole and AZT (switch to ABC or TDF), as well as investigating and treating other causes and giving folate. If a non – AZT related cause is identified, AZT can be reinstated at a later stage.

10.3.3 Hepatotoxicity

- Hepatitis reactions may occur with a wide range of medications including: TB drugs, ARV, other antimicrobials such as cotrimoxazole and fluconazole, lipid lowering agents, and NSAIDS etc.
- Some traditional medicines are also hepatotoxic.
- Chronic HBV, HCV and alcohol excess predispose to drug hepatotoxicity.
- IRIS due to HBV or HCV or other infection involving the liver may manifest as hepatitis in someone newly starting ART.
- **ATV/r not infrequently causes icterus (jaundice)** however this is not due to hepatitis. If the AST/ALT is normal and they are asymptomatic, there is no cause for concern.

Clinical presentation of hepatitis includes: nausea, vomiting, abdominal pain, liver tenderness, icterus, jaundice, and fever.

Baseline testing and ongoing monitoring:

- Baseline ALT/AST and at M1 and M3 after any new ART regimen.
- Symptomatic monitoring is the mainstay and symptoms should prompt testing.

Management

- If the ALT/AST is > 5 x ULN, +/- icterus (jaundice), +/- symptoms
 - Stop NNRTI, PI, cotrimoxazole, TB therapy, fluconazole and any other non-critical drugs that may cause hepatotoxicity.

- Check INR, ALP, bilirubin CBC, creatinine and electrolytes.
 - Consider admitting to hospital for IVI fluids and close monitoring.
 - The NRTI could be continued for another 7 days if the patient was on an NNRTI to protect against effective monotherapy, however if the patient is critically unwell then the NRTI should also be stopped.
 - Further investigation will depend on clinical and laboratory findings, but may include; abdominal ultrasound, investigation for TB and other infections.
 - If the patient is severely ill with TB, consider temporarily switching to TB drugs known to be less liver toxic (e.g. streptomycin, moxifloxacin) in consultation with CENAT.
- If the AST/ALT < 5 x ULN and asymptomatic, and no icterus (jaundice)
 - Continue ART and TB therapy but stop fluconazole, cotrimoxazole and other drugs.
 - Monitor the AST/ALT every 5 – 14 days.
- Depending on the severity, and the likely offending agent, discontinued agents can be reintroduced in a stepwise manner whilst monitoring liver function closely. If TB drugs are implicated this should be done together with CENAT.
 - Once AST/ALT has normalized
 - If NVP is implicated → introduce EFV and monitor weekly (never use NVP again).
 - If EFV is implicated → start PI (never use NNRTI again).
 - If PI is implicated and not NNRTI experienced → start EFV.
 - If PI is implicated →and NNRTI experienced consult an expert.
 - When reintroducing agents other than TB drugs or ART, restart (in order of necessity) at least 2 weeks apart, with AST/ALT monitoring weekly.

10.3.4 ARV drug rash

- Rash is typically associated with NNRTI drugs (more commonly NVP than EFV) and cotrimoxazole.
- For management of a rash clearly caused by cotrimoxazole see Table 5-2 Management of Cotrimoxazole hypersensitivity rash
- Rash is also a component of abacavir hypersensitivity however this reaction tends to be dominated by the systemic symptoms.

Assessment and Management

- With any rash check AST/ALT for concurrent drug induced hepatitis
- **Mild rash (grade 1 or 2):** diffuse or patchy erythema or macules and papules +/- pruritus, no mucosal involvement or fever, AST/ALT normal.
 - Continue NNRTI, add antihistamine, monitor.
 - If associated with lead in dose of NVP, the lead in dose can be continued for 1 more week.
- **Moderate rash (grade 3):** “wet” with vesicles, and some mucosal involvement, +/- raised ALT/AST, +/- fever.
 - Stop NNRTI and cotrimoxazole , continue NRTI for 7 more days.
 - Once the rash (+/-) hepatitis and systemic symptoms resolve;

- If the patient was on NVP, restart ART with EFV
- If the patient was on EFV, restart using ATV/r
- Once established back on ART, reintroduce cotrimoxazole using desensitization regimen Table 5-3 Cotrimoxazole Desensitization Protocol (adults + adolescents).
- **Severe rash (grade 4 + life-threatening):** Syndromes include:
 - **Drug hypersensitivity syndrome (DRESS):** Rash (morbilliform) involves > 90% skin, + fever, +/- lymphadenopathy, +/- eosinophilia, +/- nephritis (check BP, urine dipstick), +/- pneumonitis (check CXR).
 - **Stevens –Johnson syndrome and Toxic Epidermal Necrolysis:** Bullous skin reactions with epidermal necrosis, and involving at least 2 mucus membranes e.g. mouth, eyes, genitalia. Usually starts as abrupt onset of dusky purple macules with painful skin shedding in areas of pressure.
- **Stop all drugs,** refer for hospitalization, do not start any NNRTI nor cotrimoxazole again, for next ART regimen use ATV/r.

10.4 Long term complications of ART

Metabolic effects

- Protease inhibitors contribute to the risk for metabolic disease including hyperglycemia/ insulin resistance and diabetes, hyperlipidemia, and central adiposity.
- All these increase the risk of cardiovascular disease. However as HIV also increases the risk for cardiovascular disease, early introduction of ART has a net beneficial effect.
- Atazanavir/r has less adverse metabolic effects than lopinovir/r.
- Efavirenz also contributes to dyslipidemia.
- Tenofovir and PI's have been implicated in the development of osteoporosis.

Prevention and management:

- The focus should be on paying attention to modifiable risk factors, and appropriate management of hypertension, diabetes etc.

Table 10-1 ARV toxicity

ARV drug	Toxicity	Risk factors	Monitoring and Management	Switch options
AZT	Anaemia, neutropenia	Baseline anaemia or neutropenia	Avoid AZT if Hb <8g/dl Check Hb D0, M1, M3, + every 6M	Switch to TDF or ABC
	Myopathy		Symptomatic monitoring; if muscle pain or weakness check CK.	
	Lipoatrophy	Long term ART	Decrease fat in face, limbs, buttocks	
AZT, TDF, ddi	Lactic acidosis, or severe hepatomegaly and steatosis	Prolonged > 6 months NRTI High BMI, female	Symptomatic monitoring: if N + V, abdominal pain, dyspnoea, fatigue, check: bicarbonate, AST/ALT, CK, lactate	If on AZT Switch to TDF or ABC If on TDF or ABC consult an expert.
TDF	Renal tubular dysfunction.	Older age, male sex, low BMI, advanced HIV, pre-existing decrease in kidney function, comorbidities (diabetes, HT, HCV coinfection) use of nephrotoxic and renal excreted drugs or PI	Avoid TDF if eGFR < 50ml/min, or long term diabetes, or uncontrolled HT. Assess and treat other causes of kidney injury (dehydration, BP etc.) <i>Stop nephrotoxic drugs – esp. NSAIDS</i> Cr + dipstick D0, M1, M3, every M12	Switch TDF to AZT or ABC **Check HbsAg before switching**
	Decreased bone mineral density	Age > 40, female, low BMI, physical inactivity, smoking, IDU. Diabetes CLD Corticosteroid use.	Symptomatic. Fractures, loss of height Fracture risk assessment tool. (FRAX)	
ABC	Hypersensitivity reaction	Presence of HLA-B 5701 gene	Never retry ABC again.	Switch to TDF or AZT
3TC / FTC	V. rare NRTI class effects			

EFV	CNS – light headedness, abnormal dreams, mental confusion, depression, convulsion	History of depression or seizures	Typically resolve after 2 weeks on EFV, but may persist.	Change to NVP
	Male gynaecomastia			
NNRTI: EFV and NVP	Hepatotoxicity	Underlying hepatitis disease, hepatotoxic drug. For NVP women CD4 > 250 Men CD4 > 400	Symptomatic monitoring <i>and</i> AST/ALT DO, M1, M3.	Switch to the other NNRTI, however if can't tolerate either NNRTI switch to PI (or DTG when available)
	Rash and hypersensitivity syndrome (Stevens Johnson)			
ATV/r	Indirect hyperbilirubinaemia (clinical jaundice)		If asymptomatic and ALT/AST normal, no change.	
	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease. Hypokalemia	Avoid concomitant use of other drugs which may prolong PR interval.	
	Nephrolithiasis and risk of prematurity			LPV/r (or DRV/r when available)
Protease inhibitors	Hepatotoxicity	Underlying hepatitis disease, hepatotoxic drugs	Symptomatic monitoring <i>and</i> AST/ALT DO, M1, M3	Switch LPV/r or DRV/r to ATV/r
	Diarrhea and GIT (worst with LPV/r)			Switch LPV to ATV/r
	Metabolic syndrome	Heritable, and modifiable risk	BP every visit. Lifestyle advice.	Switch LPV/r to

	(LPV/r worst), diabetes, dyslipidaemia, pancreatitis	factors	Diabetes, and lipids test every 12M.	ATV/r
Darunavir /r (DRV/r)	Skin and hypersensitivity reactions	Sulfonamide allergy		
	CNS toxicity: insomnia, abnormal dreams, depression, confusion	Prior mental health issues	Daytime dosing	
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsade de points)	Pre-existing conduction disease. Hypokalaemia	Avoid concomitant use of other drugs which may prolong QT or PR interval	
	Skin and hypersensitivity reactions			ATV/r
Dolutegravir (DTG)	Insomnia and headache			
	Hepatotoxicity	Underlying hepatitis disease, hepatotoxic drugs	AST/ALT D0, M1, M3	
	Hypersensitivity reactions			

Chapter 11. Monitoring response to Antiretroviral Therapy

There are essentially three levels of monitoring ART.

See table 11-2 WHO definitions of clinical, immunological, and virological failure.

11.1 Virological monitoring

- The HIV Viral load is expected to be undetectable by the time of the first routine test at 6 months, and should stay undetectable whilst the patient is on ART. A sustained increase in the viral load whilst a patient is fully adherent on ART is considered as virological failure, and usually is as a result of the development of HIV drug resistant mutations, which enable virological escape.
- **Routine viral load monitoring** detects an increase in viral load, which should then trigger clinical review and enhanced adherence support.
- **Targeted viral load monitoring** can be used to confirm virological failure in the context of clinical or immunological failure.
- Routine VL testing is preferred however targeted VL testing may be employed if resources for routine VL testing are not available.
- See Viral load testing algorithm below.

11.2 Immunological monitoring

- A CD4 count should be performed prior to starting ART, however it is not required that the result be available prior to starting ART.
- Baseline CD4 count is important to determine the need for OI prophylaxis, and to know the degree of immunodeficiency and risk of developing OI +/- IRIS on ART.
- In stable patients CD4 monitoring can cease if the patient is:
 - On ART for at least 1 year, has CD4 > 350, and has no adverse drug reactions requiring regular monitoring, no current illness or pregnancy, has a good understanding of lifelong adherence, and evidence of treatment success (2 x undetectable VL).
- In the event of virological failure, the CD4 count should be checked.
- If routine VL monitoring is not available, 6 monthly CD4 tests should continue, and targeted VL performed if there is any drop in the CD4.
- See CD4 testing algorithm below.

11.3 Clinical monitoring

- PLHIV should be monitored for new or recurrent WHO stage 4 events that may indicate (late) failure of the ART regimen. Table 44-1 WHO staging system for adults and adolescents (≥ 15 years).

Figure 11-1 CD4 testing algorithm

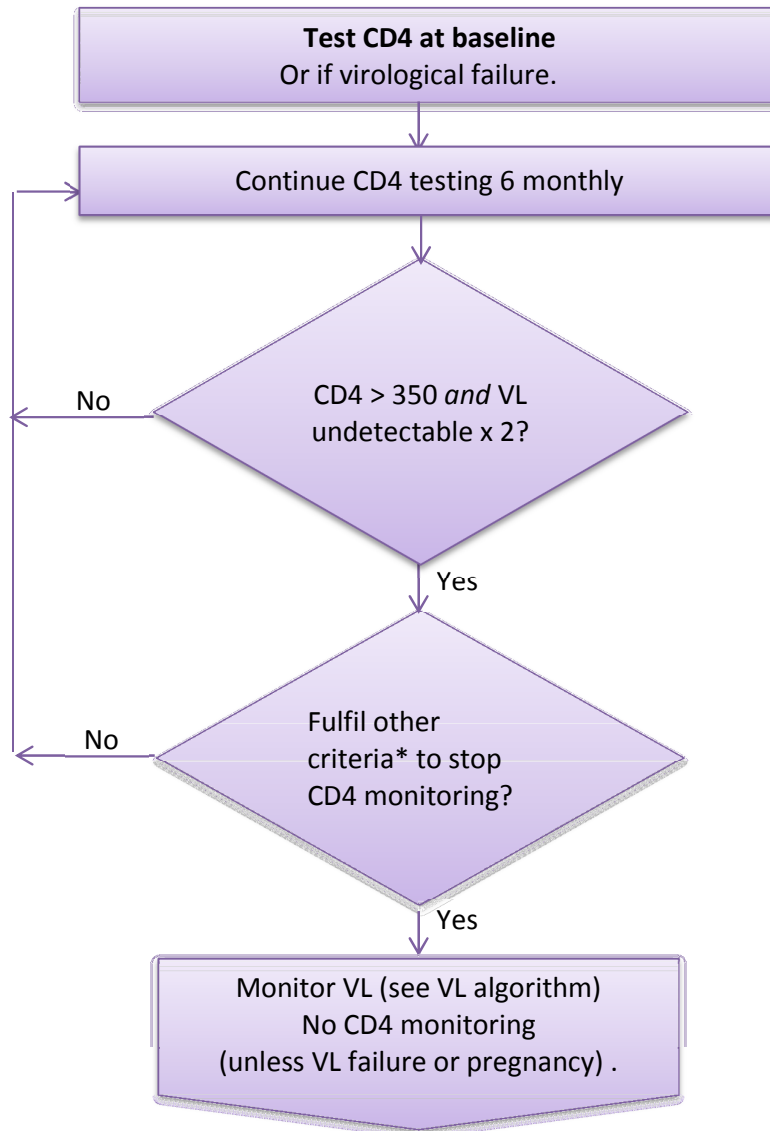


Table 11-1 When to start / continue and stop CD4 monitoring

Start / continue	Baseline CD4 then 6 monthly until stopping criteria are fulfilled
Criteria to Stop CD4 monitoring*	<p>On ART for at least 1 year <i>and all of the following:</i></p> <ul style="list-style-type: none"> • No adverse drug reactions requiring regular monitoring, • No current illness, and not on TB treatment • Not pregnant • Good understanding of lifelong adherence • 2 x CD4 > 350 cells/ mm³ • 2 x undetectable VL • Routine VL monitoring is available
Check CD4 again	<p>Virological failure → recommence CD4 algorithm</p> <p>Pregnancy → recommence algorithm if < 350 +/- or VL detectable.</p>

Figure 11-2 Viral load monitoring

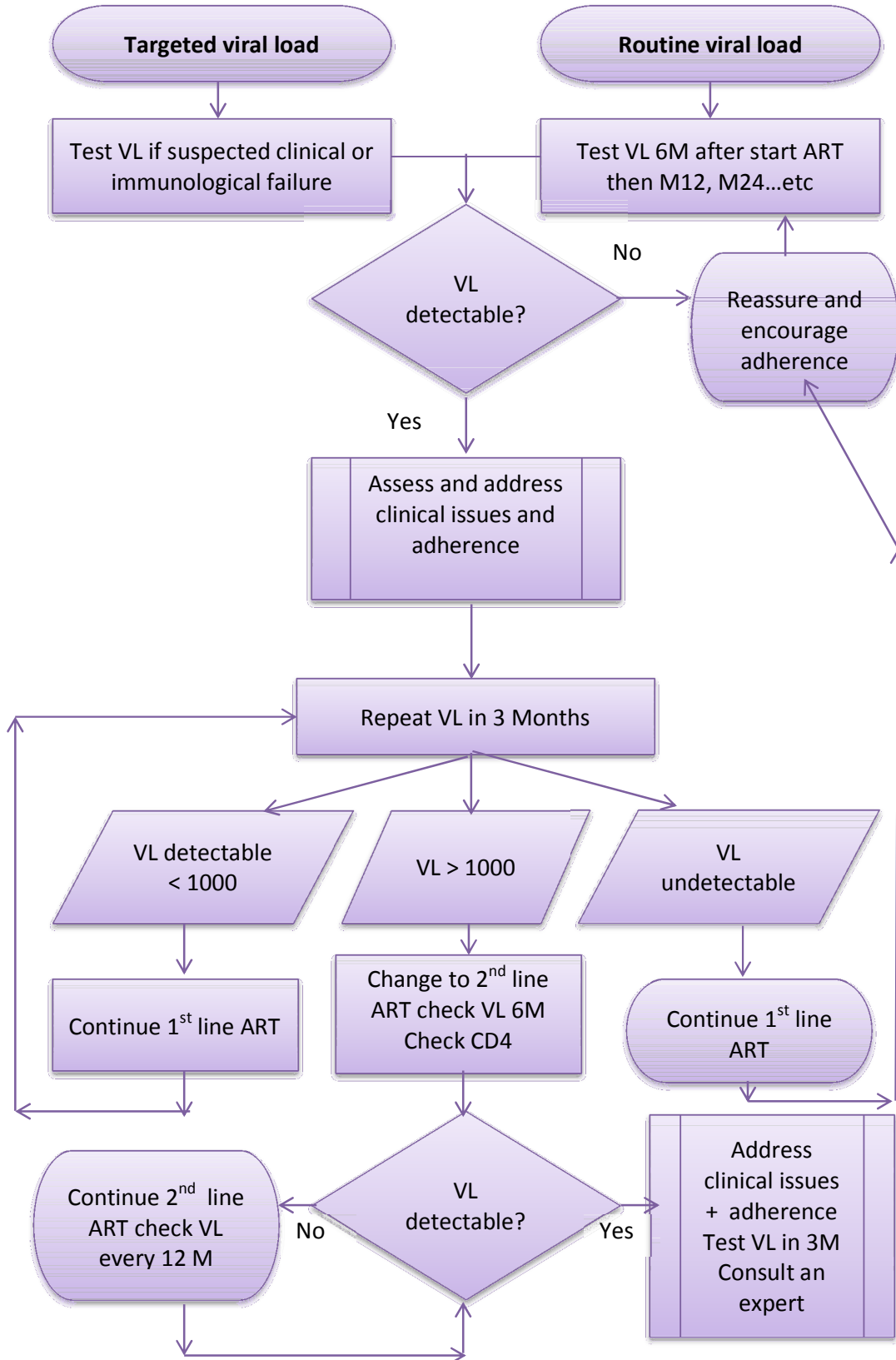


Table 11-2 WHO definitions of clinical, immunological, and virological failure¹⁸

Failure	Definition	Comments
Clinical failure	<p>Adults and adolescents</p> <p>New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)^a after 6 months of effective treatment</p>	<p>The condition must be differentiated from immune reconstitution inflammatory syndrome^b occurring after initiating ART</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure^a</p>
	<p>Children</p> <p>New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment</p>	
Immunological failure	<p>Adults and adolescents</p> <p>CD4 count falls to the baseline (or below)</p> <p>or</p> <p>Persistent CD4 levels below 100 cells/mm³</p>	<p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count</p> <p>A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (182). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure</p>
	<p>Children</p> <p>Younger than 5 years</p> <p>Persistent CD4 levels below 200 cells/mm³ or <10%</p> <p>Older than 5 years</p> <p>Persistent CD4 levels below 100 cells/mm³</p>	
Virological failure	<p>Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support</p>	<p>The optimal threshold for defining virological failure and the need for switching ARV regimen has not been determined</p> <p>An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed</p> <p>Assessment of viral load using DBS and point-of-care technologies should use a higher threshold</p>

¹⁸ WHO Consolidated Guidelines 2013

Chapter 12. Management Antiretroviral therapy failure

12.1 What to do when the viral load is detectable

Timely and focused management of any detectable VL in a PLHIV on ART is critically important for both the health of the individual and to reduce the risk of HIV transmission (including drug resistant HIV).

Viral load may be detectable due to:

1. ART drug resistance and viral escape.
2. Viral replication due to poor adherence.
3. A “blip”: sometimes the VL is detectable at a very low level < 1000 copies/mL (particularly < 500copies / mL), *and* it returns to undetectable without change in ART regimen).

Positive prevention:

- ART is highly effective at preventing sexual transmission from PLHIV to their HIV negative partner(s) *provided the viral load is undetectable*.
- If the VL becomes detectable on ART there is a risk of transmission of HIV with ARV resistant mutations.
 - PLHIV must be advised to use condoms to prevent HIV transmission to their partner(s), particularly until the VL returns to undetectable.

History:

- Check with the patient that they were truly ART naïve prior to starting ART – had they had any treatment before? Including PMTCT? Or mono/dual ARV in the private sector?

Clinical assessment:

- Assess and manage inter-current clinical issues that may be resulting in failure of viral suppression. Check for vomiting or diarrhoea that may result in short term malabsorption. And perform clinical assessment for TB and other OI.

Addressing adherence

- Most failure of ART is due to problems with adherence. In the event of any level of detectable VL it is very important to spend time with the patient to establish why there are adherence problems, and how they might be solved.
- Review the patients understanding of the ART regimen; check they know the correct dose and timing of the drug, and the necessity for full adherence.
- Review the food requirements for the drug, and check if the patient is taking correctly.
- Check drug – drug interactions.
- Explore the *degree* of adherence.
 - If adherence is very poor, and the VL is very high, then it is possible there is no HIV resistance to the ART regimen.
 - If the viral load is detectable but low, and there has just been a recent lapse in adherence, once full adherence is re-established, VL suppression may be achieved.
- Assess barriers to adherence including:

- Motivational barriers such as depressed mood (see Chapter 42 Mental health)
- Cognitive barriers including cognitive decline or dementia (see Chapter 20. HIV encephalopathy/dementia).
- Alcohol or other substance abuse.
- Drug tolerability, side effects of the regimen.
- Organizational barriers, such as busy schedule, travel, chaotic social situation etc.
- Work with the patient and their family to overcome adherence issues:
 - Provide information in a way that the patient can follow and understand.
 - Recruit a family member or treatment buddy to help.
 - If depression or dementia is suspected, manage or refer appropriately.
 - Advise the patient to make reminders - e.g. in their phone, or link taking medications to something that they do at the same time every day (e.g. wash, or clean teeth)
 - Enlist the help of the peer support workers, PLHIV volunteers, MMM groups or nurse counsellors.

Re check the VL in 3 months

- If VL undetectable: reassure the patient, and return to routine monitoring.
- If detectable VL < 1000 copies /ml : continue to work on adherence and repeat VL in 3M
- If VL > 1000 copies / mL: this is defined as *virological failure*

12.2 Virological failure on 1st line ART

- In the event of confirmed virological failure the regimen should be changed to 2nd line promptly, to avoid progressive accumulation of resistance mutations.
- On the other hand, only switch to 2nd line once all adherence issues have been addressed. With continued poor adherence they will fail 2nd line therapy, after which there are no further options.
- Check CD4 for immunological failure to assess the need for OI prophylaxis.
- If the patient is currently on treatment for active TB, consider deferring changing to 2nd line until after TB treatment is completed, to avoid issues with drug interactions requiring double dose LPV/r.
- Change to 2nd line if the VL is > 1000 copies / mL 2 times \geq 3 months apart, AND adherence issues are addressed.
- Select 2nd line according to the following:

12.3 Second line ART

As Cambodia has a public health approach to HIV treatment with standardised ART regimens, there are predictable resistance mutations that will develop after 1st line failure.

- See Table 12-1 Standard 2nd line ART regimens, which outlines the sequencing to 2nd line depending on the NRTI backbone used in 1st line ART. The preferred third drug is the protease inhibitor Atazanavir combined with low dose ritonavir as ATV/r 300/100mg once daily.

Check the following laboratory test results prior to switching to 2nd line regimen:

- HBV status. If HBsAg positive, TDF must be kept in the 2nd line regimen.
- CD4, CBC, Renal function, serum lipids.

Table 12-1 Standard 2nd line ART regimens

Failed 1 st line regimen	☑ Preferred second line
TDF + 3TC + NNRTI	AZT + 3TC + ATV/r (if HBsAg negative)
	TDF + 3TC + AZT + ATV/r (if HBsAg positive)
AZT (or d4T) + 3TC + NNRTI	TDF + 3TC + ATV/r
If on Rifampicin (TB treatment) ➤ Change back to ATV/r after TB treatment	2 nd line NRTI as above + combine with <i>either</i> <ul style="list-style-type: none"> · Double dose LPV/r 12 hourly <i>OR</i> · LPV/r + 3x100mg ritonavir 12 hourly Monitor closely for toxicity
If failed 1 st line included a PI	Consult an expert.

2nd line regimens include:

- ATV/r 300mg/100mg daily + (AZT 300mg + 3TC 150mg) 12 hourly
- ATV/r 300mg/100mg daily + (TDF 300mg + 3TC 150mg) daily
- ATV/r 300mg/100mg daily + TDF 300mg daily + (AZT 300mg + 3TC 150mg) 12 hourly
- Or if on rifampicin
 - 2 x LPV/r 400mg /100mg 12 hourly + NRTI backbone *OR*
 - LPV/r 400mg /100mg + ritonavir 3 x 100mg 12 hourly + NRTI backbone

Monitoring on 2nd Line ART

- Recheck VL after 6 months, and then 12 monthly.
- If the viral load is detectable, check clinical and adherence issues, and recheck VL in 3 months.
- Advise the patient of the increased risk of sexual transmission, and to use condoms.

Protease inhibitor in 2nd line ART regimen: ATV/r

- ATV/r is the preferred protease inhibitor for use in the standard 2nd line ART. It is equivalent efficacy to LPV/r, has less metabolic side effects.
- ATV/r 300mg/100mg is taken once daily with food in combination with 2NRTI drugs.
- ATV/r should not be used if the patient is taking rifampicin.
- Proton pump inhibitors and other gastric acid lowering drugs should be avoided as they decrease the absorption of ATV/r.
- ATV may increase the PR and QT intervals, so increasing risk of arrhythmia.
- Side effects include:
 - Rash, usually self-limiting within 2 weeks, however ATV/r should be stopped if the rash is severe.
 - Icterus (jaundice) which if asymptomatic, and ALT/AST are N is of no concern.
 - Headache, nausea, raised liver enzymes.
 - Long term metabolic complications: lipodystrophy, diabetes, hyperlipidemia.
- See Chapter 10. Monitoring and substitutions for ART toxicity
- For information on the NRTI drugs see above sections on 1st line ARV agents.

Protease inhibitor in 2nd line ART regimen: Lopinavir/ritonavir

- LPV/r is an alternative PI for 2nd line, however is advised only in the context of co-administration with rifampicin, in which a higher dose of LPV/r is recommended. Monitor closely for SE's including GIT upset and hepatotoxicity.
- Regular dose LPV/r = 400mg/100mg BD to be taken with food.

12.4 Second line ART failure

- In the event of confirmed 2nd line virological failure consult NCHADS AIDS Care Unit to discuss genotype analysis and 3rd lines options (depending on availability).
- All information on patients failing second line should be gathered using the NCHADS Data Collection tool and reviewed by AIDS Care, including a recent VL test.

Points to consider for management of patients failing second line ART: ¹⁹

Genotype analysis

- Genotype analysis is very important to determine *if* there are resistance mutations present. If there are no resistance mutations the virological failure is almost certainly related to adherence and the emphasis should be on addressing adherence and tolerability to the 2nd line ART (and not switching to 3rd line).
- Genotype analysis should be performed while the patient is taking the failing ART regimen, in order to detect ARV resistant mutations.
- If the genotype does confirm resistance mutations, this (along with the patients ARV treatment history) will then guide the construction of a new ART regimen, which should contain at least two, and preferably three, fully active drugs.

12.5. 3rd line (salvage) regimens

- Using a “new” drug that the patient hasn’t taken before does not ensure that the drug will be fully active, due to drug-class cross-resistance.
- However there are newer “second generation” agents in existing drug classes that have activity against HIV that are resistant to older drugs in the same classes; e.g. Etravirine (NNRTI). And depending on the specific drug resistance mutations, some PI will work in the context of resistance to another PI.
- In the presence of certain drug resistance mutations, the recommended doses of select ARVs, such as DRV/r (if major PI mutations) and DTG (if integrase inhibitor experienced) need to be given twice daily instead of once daily to achieve higher drug concentrations.
- Some ARV drugs retain partial activity (e.g. NRTIs and PIs) in a regime, but some (e.g. NNRTI) do not.
- Resistance mutations to 3TC/FTC confer an HIV “fitness” disadvantage, resulting in lower viral loads, and so it is usually advisable to continue this in a 3rd line regimen.
- Check HBV status. If HBsAg positive, TDF must be kept in the regimen, or if this is not possible due to toxicity, continue 3TC, and monitor closely for a hepatitis flare

¹⁹ WHO consolidated guidelines 2013, and Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>

(Etravirine is another HBV active agent (not active against HIV), which could be substituted however it is not yet available in Cambodia).

- Other ARV that could potentially be used to construct 3rd line regimens in Cambodia include -Darunavir/ritonavir (DRV/r), Etravirine (ETV), Raltegravir (RAL) and Dolutegravir (DTG).
- For some highly ARV-experienced patients, however many ARV options are available, maximal virologic suppression is not possible due to drug resistance, and toxicities. In this case, ART should be continued with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.

Tuberculosis

Chapter 13. Tuberculosis

13.1 Key points

- Cambodia has a high burden of TB infection in the general population.
- TB is the most common cause of morbidity and mortality in PLHIV.
- PLHIV with TB infection have a 30-50% lifetime risk of developing active TB.
- All PLHIV should be clinically screened for TB **at every clinic visit**.
- TB should be considered in all PLHIV with respiratory or constitutional symptoms.
- PLHIV with TB are more likely to have prolonged fever, minimal cough, AFB negative smears, and atypical CXR findings than non-HIV infected individuals.
- All PLHIV without active TB should be considered for Isoniazid Preventive Therapy (IPT).
- See Cambodian National guidelines for detailed background and management of TB/HIV and DR-TB.^{20,21}

13.2 Background

- Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis* (MTB).
- TB is **transmitted** via infectious respiratory droplets in the air originating from a person with active pulmonary TB (PTB).
- It is important to distinguish between **TB infection** alone (no symptoms or signs, not infectious, and only diagnosed by TST or Interferon test) and **TB active disease**.
- Isoniazid Preventive Therapy (IPT) can prevent TB infection developing into active disease
- **Active TB** manifests as
 - **Pulmonary (PTB)** either *smear positive* on microscopy (the most infectious), or *smear negative* (more difficult to diagnose) or
 - **Extra pulmonary TB (EPTB)** involving almost any organ in the body.

13.3 Drug resistant TB

- TB can be caused by either drug sensitive or drug resistant (DR-TB) strains of MTB.
- Transmission of DR-TB is airborne; the same as drug sensitive TB, so anyone can get primary DR-TB (particularly those exposed in health care / laboratory environments).
- DR-TB can also develop whilst a person is on treatment for previously DS – TB, due to an inadequate regimen or poor adherence.
- DR-TB is therefore more common after treatment failure, relapse, and return after default, and poor adherence or absorption of TB drugs.

²⁰ Kingdom of Cambodia, Ministry of Health. National Clinical Guideline for the Management of TB/HIV Co-infection. (English 2008 unofficial), Khmer 2013.

²¹ Programmatic Management of Drug-resistant TB in Cambodia Technical and Operational Guidelines 2013

13.3.1 Classification of DR- TB ²²

- Mono drug resistant: resistance to one of the first line TB drugs.
- Poly drug- resistant: resistant to ≥ 2 first line but not isoniazid (H) and rifampicin (R) together.
- Multi drug-resistant (MDR-TB): resistant to H and R, with or without resistance to other first-line drugs (FLD).
- Extensively drug resistant (XDR-TB): resistant to H and R and to any fluoroquinolone and to any of the anti-TB injectable drugs (amikacin, capreomycin, and kanamycin).

13.3.2 Diagnosis of DR TB

- Rapid DST testing: GeneXpert MTB/RIF test now used for TB diagnosis can detect rifampicin resistance. GeneXpert MTB/RIF is available in most provinces in Cambodia.
- Drug Susceptibility Testing (DST) using TB culture is required to confirm rifampicin resistance, and detect resistance to other drugs.

13.3.3 Management of DR TB

- If DR –TB: standard treatment it is likely to make the drug resistance worse.
- DR-TB needs prolonged multidrug therapy, and particular measures for contact tracing and infection control.²³

13.4 TB in Cambodia

- According to the WHO Cambodia TB profile in 2013²⁴
 - Cambodia is a country with a high burden of tuberculosis (TB) with 64% of population infected with TB (approximately 8 million), estimated 61,000 active cases.
 - The estimated prevalence of TB in Cambodia: 715 per 100,000 population.
 - Rates of MDR-TB were estimated as 1.4 % of new TB cases, and 11% of cases presenting for retreatment.
 - Over 1241 HIV patients were diagnosed with active TB.
- A Cambodian study in 2007-2009 of 236 PLHIV with TB found resistance to any 1st line TB drug in 34.7% of patients and 8.1% had MDR TB. The proportion of MDR TB amongst new patients was 3.7% and previously treated patients 28.9%.²⁵

13.5 TB and HIV co-infection

- Globally TB is the leading cause of death in PLHIV.
- PLHIV are more likely to have active TB, treatment failure, relapse, and die of TB.

²² Treatment of Tuberculosis guidelines 4th Edition, WHO 2010

²³ Programmatic Management of Drug-resistant TB in Cambodia Technical and Operational Guidelines 2013.

²⁴ WHO Cambodia TB Profile 2013 available at https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=KH&outtype=html

²⁵ Drug-resistant tuberculosis in HIV-infected patients in a national referral hospital, Phnom Penh, Cambodia Genevieve Walls et al Glob Health Action 2015, 8: 25964 <http://dx.doi.org/10.3402/gha.v8.25964>

- A non-HIV infected person infected with TB has a lifetime reactivation risk of 5-10%, while for PLHIV it is 30-50% or 5-8% every year.
- Early ART, at higher CD4 counts reduces the risk of reactivation of TB.
- See the **National Clinical Guideline for the Management of TB/HIV Co-infection**²⁶ for a comprehensive overview.

13.6. 3 Is Strategy in Cambodia

The 3 I's strategy in Cambodia²⁷ aims to reduce the impact of HIV/TB – coinfection by:

1. Intensified TB case finding (ICF) amongst PLHIV and their household contacts.
2. Isoniazid preventive therapy (IPT) for PLHIV who do not have active TB.
3. Strengthen TB infection control (IC) measures at Continuum of Care (CoC) settings.

Included in the Cambodian 3 I's strategy:

1. All patients with TB should have an HIV test, regardless of risk factors for HIV
 - All PLHIV should be clinically screened at every clinic visit for active TB for the following:
 - Fever, any time of any duration
 - Cough, any time of any duration
 - Drenching night sweats ≥ 2 weeks
 - Weight loss
 - All patients suspected of having either PTB or EPTB on clinical screening should be rapidly evaluated for TB (see below)
2. All PLHIV who clinically screen negative for active TB should be considered for IPT (see Chapter 6. Screening for TB and assessment for Isoniazid Preventive Therapy (IPT))
3. TB infection control includes:
 - Early diagnosis and treatment of active TB disease.
 - Separation of patients known or suspected TB.
 - Coughing patients to wear surgical masks.
 - Maximise ventilation, and natural light.

13.7 Clinical presentation of TB in PLHIV

- The clinical presentations of TB in PLHIV depend on the stage of HIV.
- Contact with a known case of PTB is a strong predictor of TB.

In PLHIV with high CD4 counts the clinical presentation with TB is similar to individuals who are HIV negative;

- Chronic cough unresponsive to antibiotics 2 – 3 weeks
- Weight loss (unintentional)
- Night sweats (drenching)

²⁶ Kingdom of Cambodia, Ministry of Health. National Clinical Guideline for the Management of TB/HIV Co-infection. English 2008, Khmer 2013 <http://www.cenat.gov.kh/km/documents/guidelines-and-sops>

²⁷ Kingdom of Cambodia, Ministry of Health Standard Operating Procedures (SOP) for Implementing the Three I's in Continuum of Care (CoC) Settings 2010.

- Fever
- Anorexia, weakness, tiredness
- Chest pains and haemoptysis.

As the CD4 reduces;

1. The presentation of PTB becomes less specific:
 - Predominance of general malaise and weakness
 - Greater weight loss (e.g. > 10% baseline body weight)
 - Less coughing, may be a dry cough, with shortness of breath
 - Anaemia
 - Microscopy is less sensitive
2. Rates of EPTB become relatively higher (although PTB is still more common).
See Table 13-1 Clinical features and diagnosis of common extra-pulmonary tuberculosis.

13.8 Diagnosis and management of PTB and EPTB in PLHIV

For more detail see the National Clinical Guideline for the management of HIV/TB Co-infection, also the algorithms from these guidelines are reproduced in the 46. Annex Tuberculosis: TB/HIV Algorithms.

13.8.1 Pulmonary Tuberculosis

Diagnostic work up:

PLHIV who are suspected to have TB, based on routine clinical screening require:

- Sputum testing *and*
- Chest x-ray (CXR)

Sputum

1. A sputum specimen should be examined by GeneXpert MTB/RIF. GeneXpert MTB/RIF is a rapid assay to diagnose PTB, and to evaluate sputum for rifampicin resistance. The GeneXpert MTB/RIF test sensitivity is higher than microscopy and overall is about 90% compared to culture.

GeneXpert MTB/RIF is available in most Provincial referral hospitals in Cambodia, and is expanding to other sites. At District level, the sample should be taken and transported immediately to a site where it can be tested within 12 – 24 hours from collection. The request form should include phone number for the laboratory to call for the result.

- If the GeneXpert MTB/RIF is positive, the patient should be recalled and commenced on 1st line TB treatment straight away.
 - If the GeneXpert MTB/RIF is positive, and indicates Rifampicin resistance, the patient should be recalled for 3 x sputum collections (1 for microscopy and 2 for culture) and started on 2nd line TB treatment straight away. Once the TB is growing on culture, it must be forwarded to CENAT for DST for confirmation of rifampicin resistance, and to look for any other drug resistance.
2. If GeneXpert MTB/RIF is not available, 3 specimens should be examined by microscopy.

Mycobacterial culture can be performed at CENAT in Phnom Penh, and laboratories in Battambang and Kampong Cham provinces. MTB culture results usually take 6-8 weeks.

- MTB culture must be performed in the event of rifampicin resistance identified on GeneXpert MTB/RIF.
- Culture is useful in GeneXpert MTB/RIF or sputum smear negative cases (pulmonary and extra pulmonary), especially in TB meningitis, for which definitive diagnosis is often difficult.
- **MTB positive cultures should be forwarded to CENAT for (DST)** in TB relapse, or treatment failure or other suspected cases of drug resistance including all GeneXpert MTB/RIF positive tests for rifampicin resistance.

CXR findings in PTB depend on the degree of immunosuppression.

- If CD4 >500 cells/mm³: typical cavitory TB or upper lobe consolidation.
- As CD4 progresses to < 200 cells/mm³: atypical radiographic presentations are more common including; near normal CXR, diffuse bilateral or lower lobar infiltrates, mediastinal lymphadenopathy, pleural effusion, interstitial nodules etc.

Differential diagnosis

See Table 14-1 differential diagnosis of respiratory presentations

If sputum test is negative for TB

- If the clinical picture and CXR are consistent with TB then refer/ treat empirically for TB and monitor closely (symptoms, Karnofsky score, weight, Hb).
- Or if bacterial infection is suspected give a trial of antibiotics (amoxycillin 1g 3 x daily or if allergic erythromycin 500mg 4 x daily with repeat clinical evaluation, +/- CXR and/or AFBs after completion of the antibiotic course.

13.8.2 Extra Pulmonary Tuberculosis

Extra pulmonary tuberculosis (EPTB) is more common in PLHIV than HIV uninfected individuals, regardless of CD4 counts. Approximately 50% of TB cases are EPTB in PLHIV with CD4<200 cells/mm³ compared with 20% of cases in PLHIV with CD4>200 cells/mm³.

Clinical presentation and diagnosis

Most often EPTB presents with unilateral lymphadenopathy. However, EPTB can be found in any organ and present in a many other ways including;

- CNS abscess or meningitis
- Spinal TB (Pott's disease), other joint or bone swelling or deformity
- Serositis (pleural, pericardial, and/or peritoneal)
- Abdominal mass or ascites
- Hepatitis or enteritis
- Renal TB; urinary obstruction or enlargement of kidneys
- Cutaneous lesions.
- Disseminated (military) TB

See Table 13-1 Clinical features and diagnosis of common extra-pulmonary tuberculosis.

Obtaining a definitive diagnosis of EPTB with positive smear, or culture for MTB is often difficult. Acid-fast stains of samples such as pleural fluid, CSF, and joint fluid are usually negative and require culture. GeneXpert MTB/RIF testing can be performed on all specimens except for blood, urine and stool

Table 13-1 Clinical features and diagnosis of common extra-pulmonary tuberculosis

(Adapted from the National Clinical Guideline for the management of HIV/TB Co-infection)

Extra pulmonary TB	Tuberculosis meningitis	Lymph Node (LN) TB (peripheral and abdominal)	Miliary TB (disseminated)	Bone and joint TB Spinal TB	Tuberculosis serous effusions
Symptoms and clinical signs	<ul style="list-style-type: none"> Fever, sweats, malaise ++ Gradual onset and progression of headache Confusion Decreased consciousness, convulsions, +/- Neck stiffness Focal neurological deficits e.g. Cranial nerve palsy 	<ul style="list-style-type: none"> ≥ 1 neck, axilla or inguinal LN enlarged (> 2 cm) painless, discrete firm or fluctuant nodes matted together +/- skin break down, abscesses, chronic draining fistula, +/- Fever, sweats, malaise 	<ul style="list-style-type: none"> Fever, sweats, malaise +++ Very unwell Hepato-splenomegaly Diffuse large LN Choroidal tubercles on fundoscopic examination 	<ul style="list-style-type: none"> Spine: Local pain, followed by deformity +/- neurological deficits Joint: swelling of hip /knee/elbow, pain usually not severe. +/- Fever, sweats, malaise 	<ul style="list-style-type: none"> Fever, sweats, malaise <i>Local features:</i> Pulmonary (chest pain, shortness of breath) Abdominal (pain, distention) Pericardial (chest pain and left (short of breath) and right ventricular failure (peripheral oedema)
Diagnosis	<ul style="list-style-type: none"> Lumbar puncture, If signs of ↑ intra-cranial pressure (papilledema, ↓ consciousness) LP dangerous, start treatment and LP when improves 	<ul style="list-style-type: none"> Needle aspirate of LN if node is fluctuant. Ultrasound (intra-abdominal lymph nodes) 	<ul style="list-style-type: none"> CXR Mycobacterial blood culture (if available) 	<ul style="list-style-type: none"> X-ray Tissue biopsy 	<ul style="list-style-type: none"> Physical examination CXR Ultrasound Echocardiogram Aspirate effusion
Results	<ul style="list-style-type: none"> CSF opening pressure ↑ CSF mild ↑ white blood cell count, predominantly lymphocytes Protein level ↑ Glucose ↓ AFB smear rarely positive. GeneXpert 	<ul style="list-style-type: none"> Caseation AFB may be seen. GeneXpert 	<ul style="list-style-type: none"> CXR diffuse, small miliary shadows CBC +/- pancytopenia Liver function tests +/- abnormal Sputum BK+, CSF or bone marrow aspirate may be +ve (GeneXpert cannot be used for blood) 	<ul style="list-style-type: none"> AFB may be seen Granulomatous reaction seen on histology 	<ul style="list-style-type: none"> CXR- pleural effusion, or large globular heart shadow Ultrasound: ascites and intra-abdominal LN Pleural biopsy: BK+ and/or granulomas Aspirate: Usually BK- TB culture (4-6 weeks) Exudate: Protein > 30 g/l (if aspirate clots exudate likely)

13.9 Management of PTB and ETPB

Drug treatment of TB

- All TB in PLHIV should be treated according to the Cambodian Standard guidelines.²⁸
- Check for any **potential drug interactions** with TB meds (esp. Rifampicin – e.g. warfarin (needs ↑ dose), contraceptives (↓ efficacy), fluconazole (↓ levels) and some ART.²⁹
- Add **pyridoxine** (vitamin B6) 50 mg daily to reduce the risk of peripheral neuropathy.
- TB meningitis: add Prednisolone 60mg / day x 4 weeks, then tapered over 2 weeks.
- High dose/prolonged courses of steroids plus immunodeficiency associated with HIV, increases the risk of disseminated strongyloidiasis and septic shock, so treat empirically with albendazole 400mg orally with fatty food 12 hourly x 7 days
- All patients with TB should commence **cotrimoxazole prophylaxis** regardless of CD4.

Review HIV: VL and CD4 count

- Patients on ART who are newly diagnosed with TB should have VL and CD4 count to investigate for immunological and virological failure.
- Adjust WHO stage accordingly (PTB in adults is WHO stage 3, EPTB WHO stage 4).

Commence ART

- All patients with TB should start ART regardless of CD4 count according to the schedule outlined in Table 8-3 Timing of ART initiation in setting of active OIs
- Check for drug interactions between ART and TB drugs according to Table 13-3 Drug interactions between ART and TB drugs

Monitor

- Symptoms –Cough, sweats, appetite, energy level, weight.
- Sputum smears (microscopy) at 2 and 5 months and at the end of treatment all (PTP)
- Monitor for side effects of the TB and ART regimens.

If not improving on TB treatment:

- Repeat microscopy (not GeneXpert MTB/RIF), perform culture and DST and consider:
 - Poor Adherence,
 - malabsorption
 - Drug resistant TB
 - Paradoxical IRIS (see Chapter9. Immune Reconstitution Inflammatory Syndrome)Other infections, cancers and cardiac failure see Table 14-1 differential diagnosis of respiratory presentations
 - Drug related adverse events.
- For EPTB, most forms except TB meningitis are treated with the same category 1 treatment as for pulmonary TB (2RHZE/4RH). TB meningitis requires a slightly different regimen. Please refer to National Tuberculosis guidelines.

²⁸ Kingdom of Cambodia, Ministry of Health, Standard tuberculosis treatment regimens. CENAT 2011, and Programmatic Management of Drug-resistant TB in Cambodia Technical and Operational Guidelines 2013, and National Clinical Guideline for the Management of TB/HIV Co-infection. Khmer 2013.

²⁹ www.hivdruginteractions.org/

13.9.1 Side effects of TB therapy combined with ART

Table 13-2 Side effects of TB therapy combined with ART

Side effect	ARV drug	TB drug
Nausea	AZT; PIs	Pyrazinamide
Hepatitis	NVP; EFV; PIs	Pyrazinamide, Rifampicin, INH
Peripheral neuropathy	d4T; ddl	INH
Rash	NVP; EFV	Rifampicin; INH; Pyrazinamide

13.9.2 TB – HIV drug interactions

Table 13-3 Drug interactions between ART and TB drugs³⁰

Drug	Interaction with ART and fluconazole
Anti – TB therapy: first and second line agents	
Ethambutol	No interaction
Isoniazid	No interaction
Pyrazinamide	DDI could ↑PYR level, no dose adjustment, monitor for SE
Rifampicin	AZT: ↓ concentration, avoid if alternative Dolutegravir: avoid, ↓↓ concentration Abacavir: slight ↓ in concentration Nevirapine : contraindicated as ↓↓ concentration Efavirenz : ↓conc, do not dose reduce EFV to 400mg Atazanavir /r: contraindicated as ↓↓concentration. Lopinavir/r : ↓↓ concentration, use higher dose LPV/r 400mg /400mg BD, or LPV/r 800mg/200mg BD but higher risk of toxicity Fluconazole: ↓ concentrations
Streptomycin	TDF: watch renal function closely
Capreomycin,	TDF: watch renal. DTV may ↑ Capreomycin concentration ddi and 3TC: Capreomycin and 3TC and DDI concentrations could ↑. PI and NNRTI ok
Ethionamide,	No interaction
Levofloxacin	Caution with ATZ + LPV as both can ↑ QT interval, 3TC concentration could ↑
Moxifloxacin	ATZ, LPV and Moxi all can ↑ QT interval levels
Cycloserine	No interaction
Kanamycin	Kanamycin and TDF both nephrotoxic. Monitor renal as 3TC dose may need to be adjusted.
Clarithromycin	AZT concentration ↓ so administer 2 hours apart, NNRTI: Clarithromycin levels ↓ PI: Dose alteration may be required depending on drug and renal function.

³⁰ <http://www.hiv-druginteractions.org/>

Respiratory conditions

Chapter14. Respiratory tract infections

- Both upper (e.g. sinusitis) and lower respiratory tract infections are common in PLHIV.
- Often multiple infections may be present at the one time.

Clinical assessment:

Clinical assessment requires a full history – including exposure, the period of onset, and time to develop symptoms, and full physical examination.

See also:

- Table 14-1 differential diagnosis of respiratory presentations for guidance as to clinical presentations and management of common respiratory infections.
- Figure 15-1 Algorithm: Respiratory presentation
- Chapter15. Pneumocystis pneumonia
- Chapter 13. Tuberculosis

1. Signs of severe respiratory distress:

It is important to recognize the severely ill patient with pneumonia, and refer to hospital:

- Respiratory rate > 30 breaths / min
- Breathless at rest or while talking
- Prominent use of respiratory muscles
- Cyanosis
- Agitation or confusion

2. TB clinical screening:

- If any of fever, cough, night sweats, or weight loss → Sputum for Gene/Xpert (or microscopy if not available) and CXR,
- Consider empiric treatment for TB if there is still a high suspicion for TB, even if the sputum is negative (GeneXpert will miss 10% of pulmonary TB)

3. Consider **Pneumocystis Pneumonia (see next section)**

- 4.** If bacterial infection is likely or the diagnosis is not clear, treat with antibiotics for bacterial infection and monitor for response:
 - Amoxicillin 1g 3 times daily *or* doxycycline 100mg 2 x daily *or* erythromycin 500mg 4 x daily, *or* cefixime 400mg daily for 1 week.

Table 14-1 Differential diagnosis of respiratory presentations

Diagnosis	Typical features	Typical CXR changes	Management
Infections			
1. Pulmonary TB (any CD4)	Sub-acute, cough +/- productive, night sweats, +/- pain	Lobar consolidation, Cavitation (upper zones) Pleural effusion, lymphadenopathy	See Chapter. 13
2. Bacterial pneumonia (any CD4)	Usually acute, febrile, cough +/- productive, +/- pain, responds to antibiotic.	Lobar consolidation with air/bronchogram or patchy interstitial change	Danger signs → admit to hospital. Outpatient: Amoxyl oral 1g 8 hourly or erythromycin 500mg oral 6 hourly, Hospital: IVI penicillin / ampicillin or IVI ceftriaxone
3. PCP (<i>Pneumocystis jiroveci</i> pneumonia) (CD4 < 200)	Usually subacute, Prominent dyspnoea dry, cough	Bilateral diffuse interstitial “ground glass” shadowing Pneumothorax No air bronchograms	See Chapter.15
4. Less common infections:	Fungal (e.g. Cryptococcus, penicilliosis), MAC, Nocardia	Variable	Guided by microbiology.
5. Lung abscess (any CD4)	Cough with large amounts of purulent sputum, fetid breath, consolidation with cavitation with fluid level on CXR	Focal change with air fluid level visible	Guided by microbiology or Amoxacillin /clavulanate 1x 2/ day, or clindamycin 450mg 3 x / day. Duration 3 – 4 weeks.
6. Bronchiectasis	Large amount of purulent sputum	Thickened bronchial tree, lower zones	Treat exacerbations, guide by microbiology.
Non-infectious differential diagnosis			
Bronchial carcinoma (lung cancer)		Risk factors (smoking, older age)	
Congestive cardiac failure		Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, epigastric discomfort from hepatic congestion O/E lung crackles, gallop rhythm, oedema	
Reactive airway disease (asthma)		Chronic, intermittent symptoms; expiratory wheezes; known triggers	
Chronic obstructive pulmonary disease (COPD)		Risk factor (smoking); chronic symptoms	

Chapter15. Pneumocystis pneumonia

Pneumocystis jiroveci (formally *Pneumocystis carinii* (PCP)) pneumonia is a common fungal infection in PLHIV with CD4 <200 cells/mm³. PJP is a WHO Stage 4 illness.

PCP infection may coexist with other respiratory infections, including TB.

Prevention: early ART, cotrimoxazole prophylaxis.

Clinical findings:

Symptoms: Subacute onset (1 – 2 weeks), dyspnoea (shortness of breath) initially with exertion but later at rest. Non-productive cough may develop, +/- Fever.

Examination: tachypnoea, chest may be clear or fine crepitation's, +/- cyanosis, low %O₂

Investigations and Diagnosis

CXR: Often non-specific, +/- widespread interstitial “ground glass” change, occasionally pneumothorax. Look for additional or alternative cause of respiratory presentation e.g. TB (cavity, adenopathy, and effusion), bacterial pneumonia (focal consolidation, effusion).

Other investigations – bronchoscopy and lavage, laboratory – PCR, silver stain.

Standard treatment

- Cotrimoxazole 15 - 20g/kg/ day divided into 3 – 4 doses daily for 21days
- Keep well hydrated (to avoid renal impairment on high dose cotrimoxazole)
- Add folic acid 5mg daily (cotrimoxazole depletes body of folic acid).

Table 15-1 Weight based cotrimoxazole dosing for treatment of PCP

Weight	Total dose TMP 15 – 20mg/kg / day ³¹	Dose in DS tablets (TMP160/SMX800mg) Divided into 3 or 4 x day
30-40 kg	450 – 800 mg/ day	2DS tablets 2 x day
40-50 kg	600 – 1000 mg /day	2DS morning, 1DS midi, 2 DS evening <i>or</i> 2 DS tablets 3 x day
50-60 kg	750– 1200 mg /day	2 DS tablets 3 x day
>60 kg	900 - 1200mg /day	2 DS tablets 3 - 4 x day

If hypoxemia with signs of respiratory distress or cyanosis add:

- **Prednisolone:** 40mg twice daily x 5 days, 40 mg daily x 5 days, the 20 mg daily x 11 days.
- High dose/prolonged courses of steroids along with the immunodeficiency associated with HIV increases the risk of disseminated strongyloidiasis and septic shock.
Treat empirically with albendazole 400mg orally with fatty food 12 hourly x 7 days.³²

Alternative treatment

- Trimethoprim 300mg/day + dapsone 100 mg/day orally for 21 days, or
- Clindamycin 600mg 4 x daily + primaquine 15 - 30 mg daily for 21 days

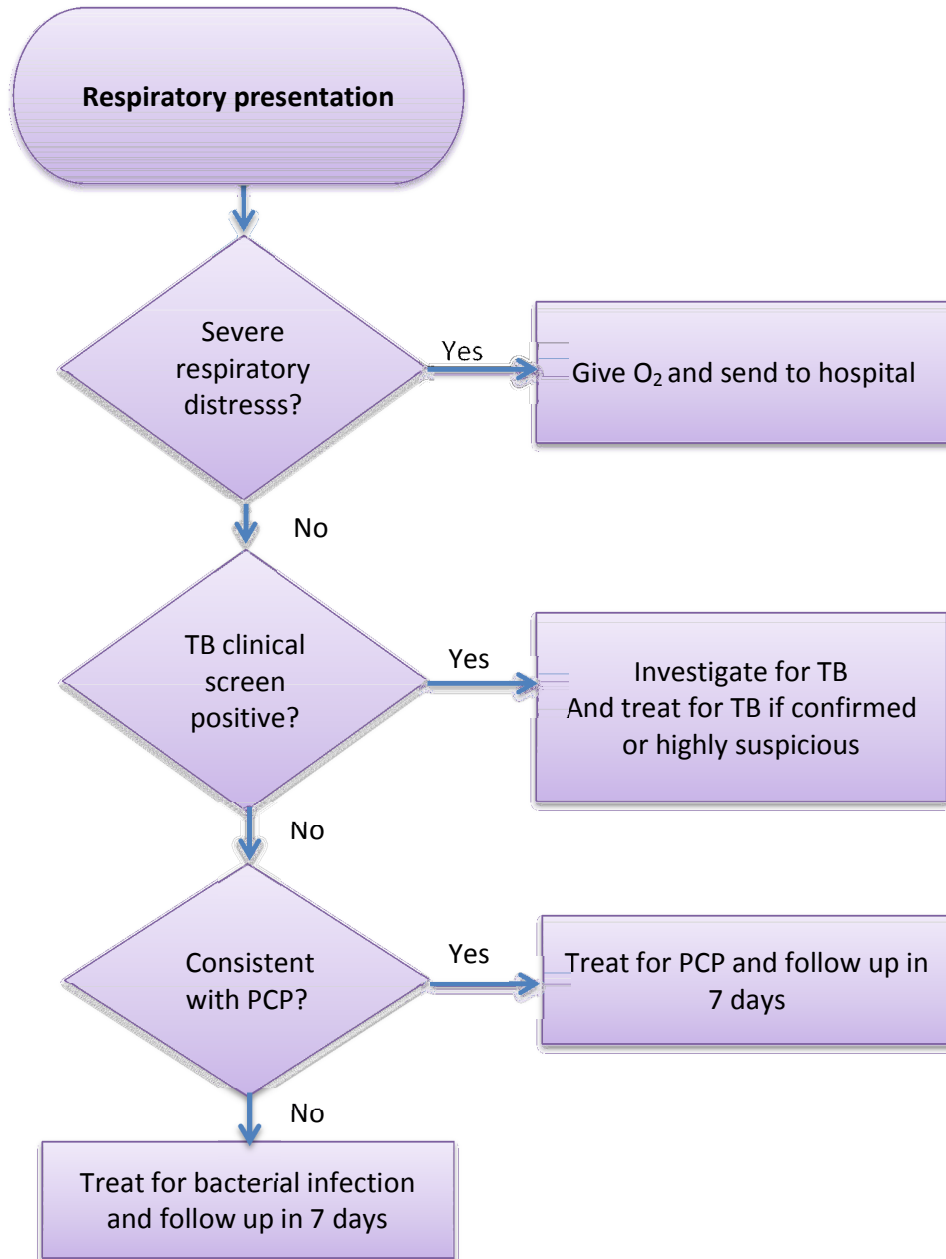
Monitor

- Clinical response: if not responding consider alternate or additional diagnosis.
- AE to cotrimoxazole – rash, anaemia, neutropenia, renal impairment.

³¹ Sanford guide. Antimicrobial therapy 2015

³² Sanford Guide to Antimicrobial therapy 2015

Figure 15-1 Algorithm: Respiratory presentation



If the patient does not improve with any treatments:

- Review history and progress, repeat clinical exam. CXR, CBC, sputum microscopy, culture + GeneXpert, blood culture, pleural analysis if effusion

Consider:

- Referring to higher level of care
- More than one infection may be present
- Empiric treatment for TB or PCP depending on the clinical picture
- Non – infectious causes (asthma, lung cancer etc.)

Neurological conditions

Chapter 16. Meningitis

Meningitis in PLHIV is most commonly due to: Cryptococcus, TB, or bacteria; *Streptococcus pneumoniae* (most common), *Neisseria meningitidis*, *H.influenza B*, viruses including HIV itself or HSV, or syphilis.

Prevention: early ART, TB screening and IPT, Cryptococcal Ag screening.

16.1 Clinical features

- Fever, nausea and vomiting
- Headache, not responding to analgesia, neck pain, photophobia, confusion, seizures
- Examination; fever, ↓consciousness, meningism (neck stiffness, positive Kernig's sign), papilledema (due to ↑ intracranial pressure).
- Petechial rash; associated mainly with *Neisseria meningitidis*, also *S. pneumoniae*.
- Focal neurological signs indicative of space occupying lesion (TB, stroke)

******Bacterial infection typically presents acutely and is a medical emergency. If suspected give ceftriaxone 2gm IVI as soon as LP performed, or prior to LP if a delay of more than 1 hour is expected.******

Differential diagnosis: consider also malaria, and non-infectious causes of headache (e.g.migraine).

16.2 Investigation and diagnosis of meningitis

- Lumbar puncture should be performed unless there is significant coagulopathy, or space occupying lesion (evidenced by focal neurological signs, seizures or CT scan appearance)
- Other Ix: consider CXR and sputum for GeneXpert/microscopy, CBC, malaria test, RPR.

16.2.1 Lumbar puncture (LP)

Table 16-1 Lumbar Puncture technique and CSF analysis

Lumbar Puncture technique and CSF analysis
<ul style="list-style-type: none">• 18 gauge needle• Measure the opening pressure (If no manometer is available, use IVI tubing and mark it with a tape measure, and attach to an IVI pole)• Normal OP is 10 – 20 cm H₂O• If pressure is elevated and the cause unknown – remove 5ml CSF initially• If pressure is elevated and Cryptococcal Meningitis is strongly suspected, remove 20 – 30 mls CSF.• Check CSF glucose and protein• CSF microscopy - leucocytes• Cryptococcus India (China) ink stain for microscopy, Cryptococcal antigen (CCAg)• Bacterial stain and culture• TB: microscopy, GeneXpert, TB culture

16.2.2 Differential diagnosis of meningitis

Table 16-2 Distinguishing between different causes of meningitis

	Cryptococcus	Tuberculosis	Bacterial	Viral
CD4 count	Low (< 100)	Any (commonly lower)	Any	Any
Onset and progression	Chronic	Sub-acute	Acute	Acute
LP opening pressure	High – very high	High or normal	High	Usually normal
CSF Appearance	Clear	Usually clear	Often Turbid	Usually clear
Cells (predominant)	Lymphocytes	Lymphocytes	Neutrophils ↑↑	Lymphocytes
Glucose	Normal /low	Low	Low	Normal
Protein	Mildly elevated.	Elevated.	Elevated.	Normal or slightly high.
Microscopy stains	India ink usually positive.	AFB usually not seen	Gram +ve cocci (<i>S. Pneumoniae</i>), Gram –ve (<i>N. meningitides</i>) etc.	Negative
Other investigations	CrAg positive	GeneXpert (moderate sensitivity in CSF) Request culture.	Request Grams stain and culture	Diagnosis of exclusion. HSV is only confirmed if PCR available.

CSF examination in neurosyphilis; ↑WBC predominantly mononuclear cells, and ↑protein, and normal glucose. VDRL should be positive.

16.3 Treatment of meningitis

- See Chapter17. Cryptococcal meningitis and for TB Meningitis see section on EPTB in Chapter13.Tuberculosis.

Bacterial meningitis treatment.

- Ceftriaxone 2gm IVI, 12 hourly x 10 days.
- Neurosyphilis
 - Benzypenicillin 1.8 g (= 3 million units), 4 hourly x 15 days.
- Herpes simplex encephalitis
 - Acyclovir 10mg/kg IVI, 8 hourly, x 10 days.

Chapter 17. Cryptococcal meningitis

17.1 Key points

- *Cryptococcus neoformans* is the most common life-threatening fungal infection in patients with AIDS. Mortality is high even with treatment.
- The risk of developing Cryptococcal meningitis (CM) is highest when $CD4 < 100$ cells / mm^3
- CM often has a sub -acute presentation; severe headache is the most common symptom.
- Early diagnosis and treatment are keys to improving mortality from CM, and so it is important to have a low threshold for suspecting CM and performing an LP.
- All patients with CM need to be hospitalized for treatment.
- Therapeutic lumbar puncture for the management of high intracranial pressure (ICP) is one of the most important treatments influencing mortality in CM.
- CSF opening pressure should be measured at the initial and all subsequent LP.
- IRIS is a particular concern in CM, and therefore ART commencement should be delayed until 4 – 6 weeks after commencement of treatment for CM.

17.2 Clinical presentation

Headache, fever +/- visual changes, confusion, cranial nerve palsy, meningismus (neck stiffness), seizures, and reduced consciousness.

Symptoms can be minimal, subacute, or even chronic (e.g. with headache and fever only). Meningeal signs (e.g. neck stiffness) are uncommon.

In disseminated infection patients may have cryptococcal skin lesions (which can look similar to molluscum contagiosum).

Differential diagnosis: bacterial meningitis, TB meningitis, bacterial sinusitis (see Table 16-2 Distinguishing between different causes of meningitis).

17.3 Diagnosis

- **Diagnostic lumbar puncture** is essential for diagnosis of CM. An LP must be performed if *Cryptococcus* is found at any site by culture, or if serum CRAG is positive, and the patient is symptomatic (see Table 16-1 Lumbar Puncture technique and CSF analysis, and Figure 7-1 Cryptococcal Antigen screening)
- If your facility does not perform lumbar puncture or CSF studies, and CM is suspected;
 - Start fluconazole 1200mg / day *AND*
 - Transfer the patient to a higher level of care.
- Lumbar puncture should not be performed if there is significant coagulopathy, or space occupying lesion (evidenced by focal neurological signs, seizures or CT scan appearance).

- If the patient has focal neurological signs, do a serum CRAG test, which if positive, and the clinical picture is consistent with CM, start empirical treatment for CM. Remember a patient could have toxoplasmosis, and still have a positive CRAG so in some cases it would be best to treat both for toxoplasmosis and CM.
- If microscopy for cryptococcus and CRAG are negative – perform microscopy and culture for bacteria.
- **Diagnosis of a 2nd episode of CM:** both India ink microscopy and CRAG may remain positive for many months after successful treatment, so the only way to be make a definitive diagnosis of current infection in the context of possible relapse or recurrence is to do fungal culture.

17.4 Treatment of cryptococcal meningitis

- Patients with CM need to be managed in hospital, where there is access to LP, and capacity to deliver IV hydration, monitor electrolytes and creatinine, and manage electrolyte disturbance, and renal impairment.

Induction phase:

- **Amphotericin B** 0.7 - 1 mg/kg daily for 2 weeks PLUS Fluconazole 800 mg daily.
- See Table 17-1 Amphotericin: Administration, toxicity prevention, monitoring and management
- If there is any delay in transferring the patient: start fluconazole 1200mg / day until transferred.
- It is strongly recommended that the patient be treated in hospital; however if this is absolutely not possible, complete 2 weeks induction with fluconazole 1200mg daily.

Therapeutic Lumbar Puncture

- High intracranial pressures due to CM should be aggressively managed with repeated therapeutic LPs, as this can improve patient outcomes and will alleviate headaches better than most analgesics.
- Measure the opening pressure during each LP
- Patients with an opening pressure >25 cm H₂O: remove 20–30 ml of CSF, the goal being to reduce the opening pressure to <20 cm H₂O or > 50% reduction if the opening pressure is extremely high.
- Repeat LP daily until the opening pressure has stabilized in the normal range for three consecutive days.
- If once daily LP is not adequate to control severe symptoms (severe headache, visual symptoms, and cranial nerve abnormalities), twice daily (even 3 – 4 x daily) LP can be performed.

Monitoring response to treatment:

- Clinical monitoring of symptoms and clinical signs.
- There is no need for routine LP at the end of treatment, unless the patient is still symptomatic after 14 days when repeat LP for opening pressure can be performed, and CSF sent for fungal culture +/- sensitivity testing (if available).

- CSF India Ink, and CSF or serum CRAG are not useful to monitor for treatment response as they may stay positive for months even with successful therapy.

In the absence of clinical improvement, consider IRIS (see below) and it will be necessary to try to exclude cryptococcal antimicrobial resistance and investigate for the presence of other causes (including additional infectious causes).

Consolidation phase therapy

- Fluconazole 400mg daily x 8 weeks

Maintenance treatment (secondary prophylaxis)

- Fluconazole 200mg daily.

Discontinuation of Maintenance treatment:

- Patients may cease after ≥ 12 months provided they are
 1. Stable and adherent to fluconazole and ART, *AND*
 2. CD4 > 100 for two measurements at least 6 months apart and undetectable VL (Or if VL not available CD4 > 200 for two measurements at least 6 months apart).

17.4.1 Treatment of isolated CRAG +ve (IPCA)

Ensure active CM is excluded by clinical screening or LP:

Induction phase: Fluconazole 800mg daily for 2 weeks, followed by

Consolidation and maintenance phase: the same as for CM.

Table 17-1 Amphotericin: Administration, toxicity prevention, monitoring and management

Administration of Amphotericin – toxicity prevention, monitoring and management³³
<p>Pre-emptive hydration and electrolyte supplementation</p> <ul style="list-style-type: none"> • One litre of normal saline solution with one ampoule (20 mmol) of KCL over 2-4 hours before each infusion of amphotericin B (with one litre of 5% dextrose) • One to two 8mEq KCL tablets orally 2 x daily. • An additional one 8mEq KCL tablet 2 x daily may be added during the second week. • If available, add two 250mg tablets of magnesium trisilicate 2 x daily. • Potassium replacement should be withheld if renal impairment or hyperkalaemia. • A test dose for amphotericin B is not recommended
<p>Administration of Amphotericin B</p> <ul style="list-style-type: none"> • Amphotericin powder (50mg vials); refrigerate 2 – 8⁰C and protect from light. Reconstitute each 50mg vial into 10ml sterile water and inject into 1liter bag of 5% dextrose and mix well. (Never use saline) • Use within 24 hours of reconstitution • Infuse through a peripheral IV cannula over ≥ 4 hours. After infusion remove the infusion bag and flush the line with normal saline. Monitor the IV cannula for phlebitis and change as necessary.

³³ Rapid Advice Diagnosis, Prevention and Management of Cryptococcal Disease in HIV –infected Adults, Adolescents and Children. WHO .December 2011.

<p>Monitoring during the infusion</p> <ul style="list-style-type: none"> · Pulse, BP, temperature; every 30 mins during the first 2 hours then every hour. · In case of fever and shivers - give hydrocortisone 50mg IVI · If BP < 70mmHg cease the infusion and give IVI fluids, and clinical assessment.
<p>Monitoring for toxicities</p> <ul style="list-style-type: none"> · Serum potassium and creatinine (baseline and twice weekly), especially in the second week of amphotericin B administration. · Haemoglobin (baseline and weekly) · Careful attention to fluid monitoring of intake and output, and <i>daily weight</i>
<p>Management of toxicities</p> <ul style="list-style-type: none"> · If K < 3.3mmol/l, increase potassium supplementation to two KCL ampoules (40 mmol), or one or two 8mEq KCL tablets 3 x daily. Monitor potassium daily. · If hypokalaemia remains uncorrected, double magnesium oral supplementation. · Renal impairment at baseline is not a contraindication to standard dose of amphotericin B. Ensure well hydrated and if creatinine increases by >2 x from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one litre 8 hourly. Once improved, restart at 0.7 mg/kg/day. May need to consider alternate day amphotericin B. · If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200mg/day (see notes on fluconazole below). Monitor creatinine daily.

17.4.2 Antifungal drug interactions with ARV

Table 17-2 Drug interactions between antifungal drugs and ARV

Antifungal therapy	Interaction with ARV
Amphotericin B	PI and NNRTI no interactions Amphotericin is nephrotoxic, monitor renal function closely as may need to adjust NRTI dose.
Fluconazole	AZT and NVP: ↑concentration, no dose adjustment but monitor for side effects

17.4.3 Fluconazole; renal impairment and liver toxicity³⁴

- **Fluconazole with renal impairment:** Fluconazole is excreted unchanged in the urine, so consider dose reduction after the first 3 days of treatment if creatinine clearance is < 50 mL/min;
 - Cr Clearance 21 – 50 mL/min give ½ planned dose daily,
 - Cr Clearance 11 – 20mL/min give ¼ planned dose daily

³⁴ MIMS Fluconazole . 2015. <http://www.mims.com.au>

- **Fluconazole and the liver:** Few patients need to cease fluconazole due to adverse events, however fluconazole can cause mild elevations in ALT/AST, and rarely clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. The risk is higher in patients also taking: rifampicin, phenytoin, isoniazid, valproic acid or oral sulfonylurea hypoglycaemic agents.
- If a patient develops abnormal liver function tests during fluconazole therapy:
 - Monitor closely for the development of more severe liver injury (↑Bilirubin and liver tenderness on examination are signs of severity).
 - Review medications for drug interactions.
 - Advise to stop drinking alcohol, and stop taking herbal medicines.
 - Check renal function – as dose reduction may be required.
 - Consider dose reduction, particularly if on a high dose fluconazole (800mg or 1200mg)
 - Management will depend on a risk: benefit assessment - seek expert advice.

17.4.4 Antifungal treatment of Cryptococcal Meningitis pregnant/breast feeding women³⁵

- **Fluconazole** is in pregnancy risk Category D: There have been reports of congenital abnormalities in infants whose mothers were being treated for 3 – 4 months with high dose fluconazole therapy although the relationship between fluconazole use and these events is unclear. The risk: benefit ratio would be in favour of using fluconazole in the context of cryptococcal meningitis (consolidation and maintenance phases). Non-pregnant women should use effective contraception (in addition to condoms) until they have completed the full course of fluconazole.
- Whilst fluconazole is excreted into the breast milk, no drug-induced toxicity has been demonstrated in infants, so likelihood of toxicity is low.
- **Amphotericin B** is safe to use in pregnancy (pregnancy risk Category B), so consider using this as monotherapy in a pregnant woman for the induction phase.

17.4.5 Cryptococcal IRIS

- Cryptococcal IRIS may occur either as “unmasking IRIS” where it becomes symptomatic after starting ART, or may occur whilst on treatment, or after treatment for CM.
- Differential diagnosis is non-adherence to fluconazole treatment, other CNS infection (e.g. TB, toxoplasmosis), or resistance to fluconazole (which is rare).
- Treatment of intracranial hypertension in cryptococcal IRIS is identical to the above.
- If the diagnosis of IRIS is unclear, restart or escalate antifungal therapy (e.g. recommence amphotericin, or increase dose of fluconazole).
- ART should not be stopped unless very severe.
- If major severe complications consider prednisolone 0.5 – 1mg / kg daily 2 – 6 weeks with taper.
- High dose/prolonged courses of steroids along with the immunodeficiency associated with HIV, increases the risk of disseminated strongyloidiasis and septic shock. If high dose prednisolone (>20mg) for more than 2 weeks is planned, treat empirically with albendazole 400mg orally with fatty food 12 hourly x 7 days³⁶

³⁵ Johns Hopkins ABX Guide. 200 – 2015. The Johns Hopkins University.

³⁶ Sanford Guide to Antimicrobial therapy 2015

Chapter 18. Cerebral toxoplasmosis

- Cerebral toxoplasmosis is caused by reactivation of the protozoa *Toxoplasma gondi* cysts lying dormant in the brain following past (usually asymptomatic) infection.
- Cerebral toxoplasmosis occurs in PLHIV with advanced immunodeficiency CD4 < 100.
- Cerebral toxoplasmosis is a WHO Stage 4 illness.

Prevention: Cotrimoxazole prophylaxis, early ART.

18.1 Clinical features

- Headache, +/- fevers.
- Focal neurological symptoms and signs (hemiplegia, ataxia etc.)
- Encephalitis – like symptoms: reduced consciousness and confusion
- Fundoscopy: +/- retinochoroiditis, + / or papilledema (due to ↑ intracranial pressure).

18.2 Investigation and diagnosis

- Lumbar puncture is contraindicated if there are focal neurological signs.
- Unless there is access to CT scan → treat empirically and observe the response to treatment to confirm the diagnosis.
- If CT scan available: lesions are typically multiple “ring enhancing”.
- Toxoplasmosis IgG serology is positive in past *or* present infection with toxoplasmosis, therefore is only useful if negative, as a “rule out test”.

18.3 Differential diagnosis

- Tuberculoma: Check CXR and sputum for GeneXpert for TB as this is the main treatable disease in the differential diagnosis.
- Cerebral lymphoma, bacterial brain abscess, stroke.
- If taking cotrimoxazole prophylaxis the diagnosis is less likely to be toxoplasmosis.

18.4 Standard treatment

- High dose cotrimoxazole: 10/50mg/kg daily in 2 divided doses for 6 weeks.
 - Adults > 50kg: 2x DS tablets twice daily
 - Adults < 50kg: 3x SS tablets twice daily
- Add folic acid 5mg daily as high dose cotrimoxazole inhibits folate synthesis.
- Advise to drink fluids ++ as high dose cotrimoxazole can affect kidney function.
- If cotrimoxazole hypersensitivity develops – give outpatient or inpatient desensitization (see Table 5-3 Cotrimoxazole Desensitization Protocol (adults + adolescents))

18.5 Monitoring for response

- Clinical and radiological response is expected within 2 – 3 weeks. If not, then look for another diagnosis, and consider empiric TB treatment.
Start ART: within 2 weeks of diagnosis.

18.6 Secondary prophylaxis

Cotrimoxazole 1 DS daily until CD4 > 350 x 6 months and undetectable VL.

Chapter19. Cytomegalovirus

- Cytomegalovirus (CMV) is a common virus, which reactivates to cause disseminated or local disease in PLHIV with advanced immunodeficiency; CD4 < 100 cells/mm³, (particularly CD4 < 50).
- CMV most commonly causes retinitis but also frequently GIT (esophagitis, colitis), and pneumonitis, and occasionally encephalitis, hepatitis, adrenalitis, pancreatitis and/or epididymitis.
- CMV is a WHO stage 4 clinical illness.

Prevention: early ART

19.1 Clinical features of CMV retinitis

- PLHIV may present with ocular symptoms in late stage HIV, or develop symptoms soon after starting ART when it can become “unmasked” as CMV IRIS.
- Symptoms: Visual “floaters,” photophobia (light sensitivity), and visual field defects. Pain and redness of the eye are absent.
- Ophthalmoscopic examination: white perivascular exudates with or without associated haemorrhage

19.2 Management

- Refer for intravitreal ganciclovir injections.
- Continue /start ART.

Chapter20. HIV encephalopathy/dementia

- The term *HIV-associated neurocognitive disorder* (HAND) encompasses a spectrum from mild cognitive impairment (minor neurocognitive disorder, MND) to HIV associated dementia (HAD).
- Risk factors for HAND: advanced HIV, a low nadir CD4 prior to starting ART, older age, vascular and metabolic disease such as diabetes and HT.
- Severe forms of HAND are much less common in the era of effective ART.
- Mild forms of HAND are common and often go undiagnosed, however they may contribute to poor adherence to care and treatments including ART, mood disturbance, and reduced ability to function well within the family, work and community.
- HIV associated dementia is a WHO clinical stage 4 condition.

Table 20-1 Clinical features of HIV associated dementia

1. Cognitive impairment; Progressive memory loss, loss of concentration, confusion and slowing of thought.
2. Motor symptoms; Loss of balance, clumsiness, change in handwriting, tremor, unsteady gait, incontinence
3. Behavioural changes; Apathy, social withdrawal, loss of interest in what is going on, and their own well-being.

20.1 Diagnosis: HAND is a diagnosis of exclusion

Differential diagnosis:

- CNS infections; CMV encephalitis, TB, toxoplasmosis.
- CNS malignancy; lymphoma
- Thyroid dysfunction
- Depression or other psychiatric conditions.
- Substance use disorders – e.g. alcoholic dementia
- Delirium (characterized by fluctuating consciousness)
- Nutritional deficiency: B12
- Other dementia syndromes including vascular (multi – infarct dementia associated with hypertension), Alzheimer diseases, Parkinson disease etc.

20.2 Clinical evaluation:

- Screen for depression, as severe depression may mimic dementia (see Chapter 42.Mental Health)

Useful screening questions for HAND:

- Do you frequently forget things?
- Do you feel that you are slower when planning activities or solving problems?
- Do you have difficulty paying attention (e.g., to a conversation, or task)?
- Ask the partner / family if they have noticed any of the above.

A full neurological examination and cardiovascular examination are required.

Examination findings in HAND:

- Slowing of affect involving speech, facial motility and general movements
- Slowed fine motor movements
- Hyper-reflexia
- Mild leg weakness
- Impaired tandem gait (heel – toe)
- Tremor
- Tools have been developed, known as HIV dementia scales (HDS) to aid in diagnosis of HIV-associated dementia. However they are limited in their sensitivity and specificity.

Table 20-2 The International HIV dementia scale (IHDS)³⁷

Memory-Registration	Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat the words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later	
1. Motor Speed:	Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.	4 = 15 in 5 seconds 3 = 11-14 in 5 seconds 2 = 7-10 in 5 seconds 1 = 3-6 in 5 seconds 0 = 0-2 in 5 seconds
2. Psychomotor Speed	Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put perpendicular to flat surface on the side of the 5th digit. Demonstrate and have the patient perform twice for practice	4 = 4 sequences in 10 seconds 3 = 3 sequences in 10 seconds 2 = 2 sequences in 10 seconds 1 = 1 sequence in 10 seconds 0 = unable to perform
3. Memory-Recall	Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).	1 point for each word spontaneously recalled Give 0.5 point for each correct answer after prompting Maximum – 4 points
Total International HIV Dementia Scale Score: This is the sum of the scores on items 1-3. The maximum possible score is 12. A patient with a score of ≤10 should be evaluated further for possible dementia		

³⁷ Reprinted from Sacktor NC, Wong M, Nakasujja N, et al. The International HIV Dementia Scale: A new rapid screening test for HIV dementia. AIDS 2005;19:1367-1374

20.3 Investigations:

- Syphilis test – RPR,
- Diabetes check - BSL.
- Thyroid function tests, Vitamin B12,
- Consider LP, and CT scan (if available) to exclude other CNS pathology.

20.4 Management

- Commence ART as soon as possible (response to ART is often quite good);
 - Consider commencing or changing EFV to NVP if there is any suggestion that the CNS effects of EFV are causing problems. In addition NVP has good CNS penetration.
- Ensure optimal management of comorbidities – hypertension, diabetes.
- Enlist the patient’s family for support to provide;
 - Adherence to medication including ART,
 - Adequate nutrition
 - A safe environment (consider fire, electrical, traffic)
- Advise the patient to minimize alcohol consumption.

Chapter 21. Peripheral Neuropathy

Peripheral neuropathy (PN) frequently affects PLHA particularly if CD4 <200 cells/mm³.

21.1 Causes of PN include:

- HIV infection itself,
- Vitamin deficiencies (B6, B12, thiamine, etc.)
- Side effects of different drugs, including ARVs (d4T or ddi) and TB drugs (INH).
- Diabetes.
- Alcohol abuse.

21.2 Prevention of PN

- Ensure pyridoxine is always prescribed simultaneously with INH.
- Try to avoid d4T containing ART
- Diabetes: screen, and treat aiming for good glycemic control.
- Advise re good nutrition and safe levels of alcohol consumption.

21.3 Clinical presentation

- Decreased +/- altered sensation in a symmetrical 'glove and stocking distribution' (feet and occasionally hands).
- "Pins and needles", burning sensation, "cold feet" cramps.
- Absent ankle reflexes, and ankle / leg weakness may develop.

21.4 Management

- Ensure accurate diagnosis (examine for symmetry)
- Review medications, alcohol consumption and screen for diabetes (see "prevention of PN" above), and manage accordingly.
- Prescribe analgesia
 - Paracetamol; 500mg – 1000mg 4 times a day.
 - Ibuprofen; (take care if abnormal renal, liver, GIT or HT).
 - Amitriptyline; start with 25 at night, may increase to 50mg. (Warn the patient regarding symptoms of postural hypotension).

Viral hepatitis and chronic liver disease

Chapter 22 Hepatitis B

Hepatitis B is a DNA virus that belongs to the hepadnavirus family.

Hepatitis B virus (HBV) is one of the most common infectious diseases in the world and Cambodia is considered a high prevalence country with > 8% of the population HBV infected.

22.1 HIV HBV relationship

- HIV and HBV have common modes of transmission.
- HIV co-infection results in higher rates of progression of HBV to cirrhosis and hepatocellular carcinoma (HCC), and there is some evidence to suggest that there is increase progression to HIV outcomes and all-cause mortality.
- HBV results in higher risk of liver toxicity with ART and other drugs.
- ART includes some drugs with anti HBV activity, and this influences the management of co infected patients
- Immune reconstitution on ART may result in “flare” of hepatitis

22.2 HBV Transmission and prevention

HBV is transmitted through infected blood or body fluids (semen, vaginal fluids); the virus can enter the bloodstream through mucous membranes or a break in the skin.

Table22-1 HBV transmission and prevention

Transmission of Hepatitis B	Prevention of Hepatitis B transmission
<ul style="list-style-type: none"> • Perinatal (30 – 90% transmission risk) • Parenteral <ul style="list-style-type: none"> – Injecting drug use (IDU): very high risk – Health care setting: <ul style="list-style-type: none"> • Transfusion • Medical procedures • Needle stick injury (~ 30% risk) – Household: <ul style="list-style-type: none"> • Child to child • Toothbrush, razors, etc. • Piercing, tattoos • Sexual (including oral) 	<ul style="list-style-type: none"> • Vaccination <ul style="list-style-type: none"> – Newborn (↓ by 70%) – HCW – Spouse • Universal precautions • Blood screening • Condoms • Household precautions

22.3 Diagnosis of HBV

Serology:

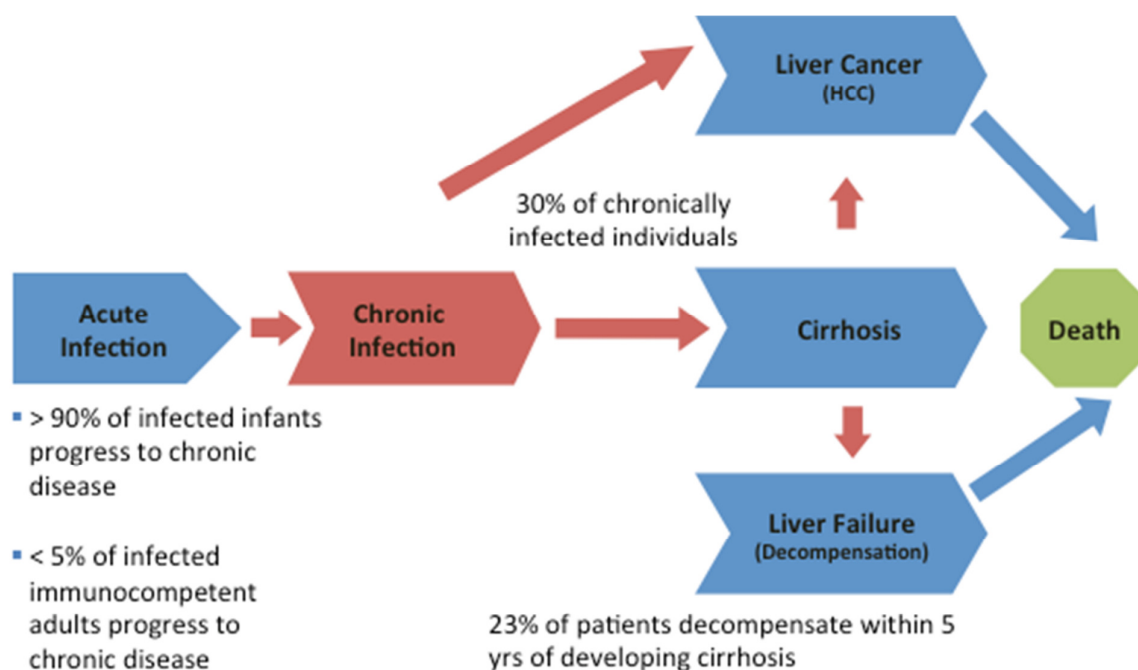
- HBsAg positivity indicates current HBV infection
- If the HBsAg is negative but the HBsAb positive this indicates immunity to HBV due to vaccine or past infection.

- HBcAb is positive either due to previous exposure, or with a positive HBsAg due to persistent infection
- Further testing not readily available in Cambodia includes HBeAg (active replication and high infectivity), HBeAb, and HBV DNA Viral Load. These assist in assessing the phase of the disease, which is important for determining when to initiate HBV antiviral therapy in HBV mono infected patients.

22.4 HBV clinical disease and natural history of chronic infection

Incubation period: 10 weeks (range 4 – 26 weeks)

Figure 22-1 Natural History of untreated HBV mono infection



The four phases of chronic HBV infection³⁸

1. **Immune tolerance:** Little immune activation /response to the virus
 - Lasts decades when infected in infancy but mostly brief or absent in adults
 - Normal ALT, HBeAg positive, high viral load (HBV DNA)
2. **Immune clearance:**
 - Fluctuating ALT and HBV DNA levels
 - 5% - 10%/yr seroconvert from HBeAg → HBe Ab which is associated with ↓↓ HBV VL.
3. **Immune control:** Non-replicative (latent) infection.
 - HBeAg negative, low or undetectable HBV DNA, normal ALT levels
 - Previously called “carrier” however this may be misleading as may reactivate.

³⁸ See Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection WHO.March 2015.

4. **Immune escape:** Reactivation

- Spontaneous reactivation occurs in 20% of people in the immune control phase
- HBeAg negative, positive HBcAb, VL detectable (often high).

Extra hepatic manifestations of HBV are associated with deposition of circulating Ag-Ab immune complexes → inflammation:

- Arthralgia and arthritis
- Purpuric cutaneous lesions (leukocytoclastic vasculitis)
- Glomerulonephritis
- Polyarteritis nodosa (small/medium vessel vasculitis: skin, eyes, kidney, heart, CNS, etc.).

22.5 Pregnancy and HBV

- Mother to child transmission: rate 10% - 90% (dependent on DNA VL)
 - HBV vaccine to infant within 24 hours of birth reduces transmission by 70%
 - Further reduction in transmission is expected if the woman is on antiviral therapy
 - There is no indication for caesarean section.
 - There is no evidence of transmission from breast milk (although HBsAg and HBV DNA are detectable in breast milk)
- Pregnant woman with chronic hepatitis should be monitored closely for deterioration in liver disease.
- Monitor for a hepatitis flare up to 6 weeks after delivery (esp. if not on antiviral therapy)

22.6 Management of HBV HIV co infection

Management of HBV HIV co infection

In mono-infected HBV patients antiviral medication is only indicated in the immune clearance, and immune escape phases of HBV infection, when there is a risk of progression to cirrhosis and HCC. Patients not in either of these phases should be monitored 6 – 12 monthly with HBV VL and liver function tests.

This assessment is difficult as these tests are not readily available in Cambodia.

However in the HIV infected patient some ARV used to treat HIV are also effective for HBV (TDF and 3TC). Now all HIV patients will be commenced on TDF + 3TC containing ART, this will automatically include treatment for HBV co-infection.

It is important that all patients with HIV HBV co infection commenced TDF + 3TC containing ART must continue both drugs even if they change to 2nd line ART.

If just one of these drugs (particularly 3TC) is used, drug resistance will develop.

Standard 2nd line ART for HBV HIV co-infected patients will therefore include: AZT + 3TC + TDF+ ATV/r.

HBsAg is ideally measured prior to starting ART, however it is not necessary for this to be routinely performed whilst the preferred 1st line ART contains TDF.

However a HBsAg test is essential if there is consideration to change to 2nd line ART, and is clinically indicated if there are any abnormalities in the liver function tests.

See also Chapter24. Chronic liver disease

Chapter 23. Hepatitis C

Hepatitis C (HCV) is a single stranded RNA virus belonging to the flavivirus family. HCV genotypes 1 – 6 differ in their clinical courses and responses to treatment.

23.1 HIV HCV relationship

- Hepatitis C is mostly transmitted via the parenteral route and is common in IVDU.
- However the risk of sexual and perinatal transmission is higher in PLHIV than in non-PLHIV.
- HIV co-infection results in higher rates of progression of HCV to cirrhosis and hepatocellular carcinoma (HCC).
- HCV increases the risk of liver toxicity with ART and other drugs.

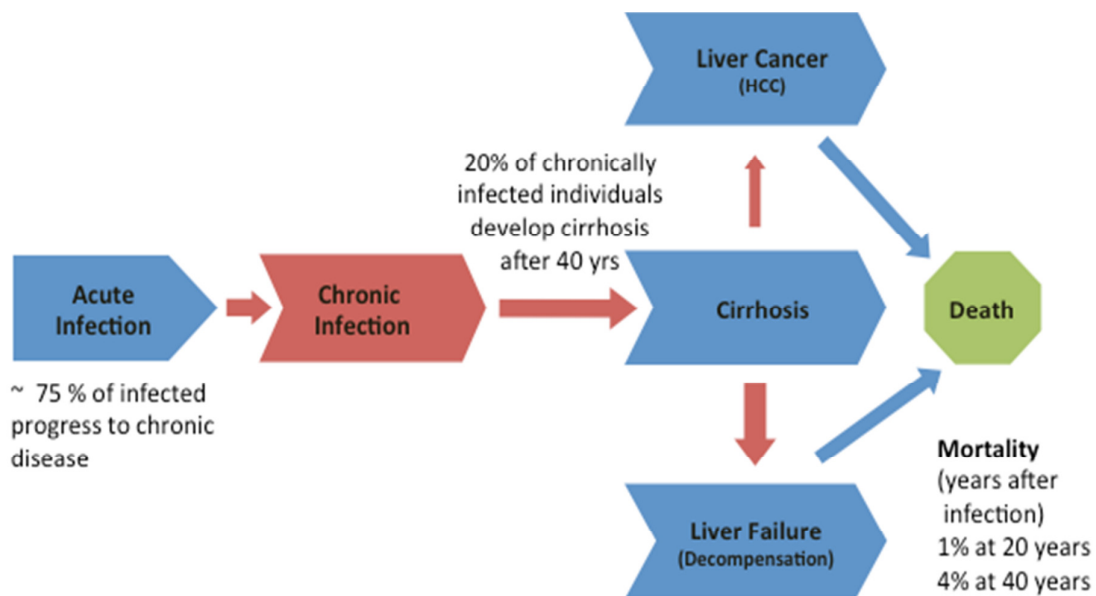
23.2 HCV Transmission and prevention

- There is no vaccination for HCV, and prevention relies on universal precautions, blood screening in the health care setting, harm reduction strategies with IVDU such as needle and syringe exchange, and household measures such as not sharing razorblades or toothbrushes.
- Sexual transmission is rare, but more likely with HIV co-infection and blood contact. Condoms may be advised.
- Perinatal transmission is ~5% in non-PLHIV.

23.3 HCV clinical disease and Natural history

HCV incubation period: 7 weeks (range 2 – 21).

Figure 23-1 Natural History of untreated HCV mono infection



Acute HCV infection is often asymptomatic, and chronic HCV often remains asymptomatic for many years. After many years chronic infection may progress to cirrhosis, liver cancer, and hepatic failure.

Extra hepatic manifestations of chronic HCV infection include dermatological conditions such as porphyria cutanea tarda, and vasculitic rashes associated with cryoglobulinaemia. Also rheumatological conditions, and haematological abnormalities, and thyroid disorders.

23.4 Diagnosis of HCV

- Hepatitis C Ab remains detectable in all infected with HCV, even if the virus has been cleared spontaneously or with treatment.
- HCV RNA testing is required to diagnose current chronic HCV infection, and to monitor therapy.

23.5 Management of HCV HIV co infection

Management of HCV HIV co infection

- Management of HCV has been traditionally with interferon-based regimens, which are very difficult to tolerate, and have limited efficacy.
- Emerging as standard treatment are new HCV antiviral agent known as Direct Acting Antiviral Agents (DAA) which are highly effective and well tolerated, include combination oral regimens requiring 8 – 24 weeks therapy.
- The DAA variably target specific genotypes, or are pan genotypic, and are becoming available in fixed dose combinations.
- The newer regimens are also highly effective and well tolerated in HCV HIV co-infection.
- Many DAA are becoming available globally, including protease inhibitors Simeprevir, and Paritaprevir NS5A inhibitors Ledipasvir, Ombitasvir, Daclatasvir, and NS5B inhibitors Sofosbuvir, and dasabuvir.
- A pilot project of HCV diagnosis and treatment among co-infected HIV patients will start in June 2016 in Cambodia. It is expected that access DAA and viral load testing for HCV treatment will improve rapidly in Cambodia.
- An algorithm for the diagnosis and assessment of HCV is included in Chapter 51. ANNEX HCV diagnostic algorithm.
- Some guidance for the clinical management of HIV-HCV co-infection using DAA in Cambodia will be issued soon as an addendum of the current guidelines.
- See also Chapter 24. Chronic liver disease

Chapter 24. Chronic liver disease

The assessment and management of chronic liver disease is similar regardless of whether the disease is caused by HBV, HCV or alcohol.

24.1 Clinical assessment

- History: symptoms of acute and chronic liver disease, and extra hepatic manifestation.
- Examination: signs of chronic liver disease + liver failure.

24.2 Laboratory assessment

Markers of severity of chronic liver disease

- ALT:
 - Some correlation with inflammation,
 - Poor correlation with fibrosis,
- An inverted AST/ALT ratio (AST > ALT)
- Low platelets (portal hypertension + hypersplenism)
- Low albumin (synthetic function)
- Raised prothrombin time (PT) (synthetic function)
- Elevated direct bilirubin (secretory function)
- Severe liver injury may be indicated if ALT falls and bilirubin rises.
- Whilst biopsy has traditionally been used to assess the degree of hepatic fibrosis, non-invasive tests including Elastography (Fibro-scan) are increasingly taking this role.

24.3 Management of chronic liver disease

Table 24-1 Management of complications of chronic liver disease

General management of complications of chronic liver disease due to any cause (including HBV, HCV and alcohol)
• Avoid hepatotoxic drugs (e.g. NSAIDs, and traditional medicines)
• Stop or minimize drinking alcohol.
• Healthy diet: low in salt + saturated fat, adequate protein (1 – 1.5 g/kg body weight/day), fruit, vegetables see Table 2-5 Recommendations for prevention and management of NCD
• Treat the underlying cause (HBV, HCV)
Management of Ascites
• Restrict dietary salt and water (e.g. 1 - 1.5 litre) intake
• Bed rest if significant fluid overload
• Diuretic: spironolactone preferred, dose: 25–200 mg /day
• +/- low dose furosemide (K ⁺ supplements may be required)
• Monitor carefully: <ul style="list-style-type: none"> • Clinical: BP (lying + standing), HR, weight, peripheral oedema, CVS, ascites • Laboratory: K⁺, Na⁺, Creatinine, albumin
• Drainage of ascites may be necessary.
• There is often ↑ extravascular volume but with ↓ intravascular volume, so there is a risk of renal failure, esp. with diuresis, and large volume drainage of ascites.

<p>Management o Spontaneous bacterial peritonitis (SBP)</p> <ul style="list-style-type: none"> • Usually associated with severe hepatic dysfunction • Suspect if ascites ↑, fever, abdominal pain and tenderness, encephalopathy. • Ix: ascitic tap - WCC > 500/mm³ +/- neutrophil >250/mm³ • Causative organisms mostly enteric Gram-negative bacilli eg E coli, + if on prophylaxis; streptococcal or enterococcus. • Rx: ceftriaxone 1g IVI daily, + if on antibiotic prophylaxis add amoxicillin/ ampicillin 1 g IV, 6-hourly. • Prophylaxis - cotrimoxazole 1 DS daily if: <ul style="list-style-type: none"> • GIT bleeding • Low ascitic protein (<10g /l) • Previous episode of SBP
<p>Management of portal hypertension</p> <ul style="list-style-type: none"> • Ideally all patients with cirrhosis should have endoscopy to determine if varices are present, and if they are identified: • Treatment of oesophageal varices (e.g. banding, sclerosis) • Non selective beta-blocking agents to lower portal pressure (propranolol)
<p>Management of portal systemic encephalopathy</p> <ul style="list-style-type: none"> • Look for underlying cause: HCC, SBP, renal failure etc. • If severe (grade 3 or 4) <ul style="list-style-type: none"> • Withhold protein for 24 – 28 hours then gradually increase to normal. • Empirically treat for sepsis with ceftriaxone 1 gm. IVI /daily • Maintain optimal fluid and electrolyte balance • Lactulose to both clear the colon and alter ammonia metabolism and diffusion. • Use doses to ensure two soft stools per day and continue long term.

Gastro- intestinal conditions

Chapter25. Oral disease

- Oral health is important to enable adequate nutritional intake, quality of life, and adherence to medication regimens.
- The mouth is frequent site of pathology in PLHIV, including WHO stage 3 conditions: oral candidiasis, and oral hairy leukoplakia (OHL), and WHO stage 4 conditions including esophageal candidiasis, HSV >1 month and oral KS.

PLHIV should be advised regarding oral hygiene:

- Regular teeth brushing (don't share toothbrushes), and flossing.
- Mouthwashes (1 teaspoon baking soda, 1 teaspoon salt, 250cc warm water) can be used for symptomatic relief and hygiene.
- Dental checkup when gum disease or cavities is present.

Oral disease in PLHIV

Gingivitis and tooth infections:

Inflammation of the gums may lead to tooth loss, and severe pain.

Examination reveals foul smelling breath, erythema and necrosis of the gums.

Management: Mouthwash + oral metronidazole 500mg 3 x / day, or clindamycin 450mg 3 x / day for 7 days, or amoxicillin – clavulanate 875/125mg 12 hourly. Tooth abscess should be drained, and severe necrotizing infections (Vincent's Angina, Norma, Cancrum oris), require urgent surgical debridement of necrotic tissue.

Oral candidiasis:

Persistent oral candidiasis = WHO stage 3

Clinical features

Symptoms: pain, difficulty eating.

Examination: White patches anywhere in the mouth some of which can be scraped off (may bleed). White coated tongue alone is often not candida so look on the upper palate and around the gums. Also "atrophic" thrush with erythema but little plaque, also angular stomatitis.

Diagnosis: usually on clinical history and appearance.

If available, fungal microscopy, culture, and sensitivity testing could be considered if clinical manifestations are atypical or treatment is ineffective.

Standard treatment (7 days)

Local application of gentian violet, 1 % aqueous solution twice daily, or

Miconazole 2% gel or gum patch 1x /day or

Nystatin pessary, 100 000 IU, oral 4 x / day or

Nystatin oral solution 1 – 2 ml swirl around mouth 5x /day or

Nystatin tablets or amphotericin lozenges sucked 4 x/day.

Alternative treatment

Fluconazole 100mg daily for seven days (if severe /not responding to topical therapy).

Oral hairy Leukoplakia (OHL):

Caused by Epstein –Barr Virus, occurs with advancing immunodeficiency. It manifests with a very typical appearance of white raised vertical lines on the sides of the tongue. No treatment is necessary and it usually resolves once established on ART.

Kaposi's sarcoma (rare in Cambodia):

Purple swellings on the upper palate or gums. May be indicative of pulmonary or GIT involvement as well. Management includes promptly starting ART, and referral to an expert for consideration of chemo/radiotherapy.

Angular stomatitis:

Caused by candida or bacteria, presents as painful cracking of the corners of the mouth. Management: antifungal cream or gel 2 x /day for 10 days, +/- topical antibacterial.

Oral ulcers: HSV

Shallow painful ulcers, often multiple.

If extensive / recurrent treat with acyclovir 400mg 3 x / day

Syphilis chancre:

Often not painful. Check RPR but may take time to rise, so if consistent clinical presentation treat empirically with Benzathine Penicillin 2.4 million units IMI x 1 (Alternate doxycycline 100mg BID x 14 days)

Syphilis mucous patches :

May be seen in the mouth in secondary syphilis. RPR high, treat as for primary syphilis.

Oral ulcers: Aphthous ulcers:

Often very painful, cause unknown.

Management: Mouthwash and topical steroid (Prednisolone 5mg crushed, apply a small amount to affected area). Occasionally oral steroids if very severe and esophageal involvement.

Chapter 26. Odynophagia

Odynophagia (painful swallowing): Pain in the throat and retrosternal space on swallowing food.

Dysphagia : difficulty swallowing.

Odynophagia and dysphagia both impact on the PLHIV's ability to maintain adequate nutritional intake and adhere to medications.

Oesophageal candida, and CMV esophagitis are WHO stage 4 conditions.

26.1 Clinical presentations and diagnosis

Candida esophagitis is the most common cause of odynophagia and dysphagia. Diagnosis is made on the basis of a history of odynophagia and dysphagia, CD4 <200, and almost all will have visible oral candidiasis.

Herpes esophagitis is often associated with herpetic mouth lesions (painful crops of vesicles) that invade the gingiva or herpetic skin lesions at the mouth border.

CMV patients have more systemic symptoms including fever, nausea, vomiting, abdominal pain, hepatomegaly, or bloody stools, occurs with very advanced immunodeficiency (CD4 < 50 cells/mm³).

Reflux-esophagitis is common, and in patients with higher CD4 counts this may be the most likely diagnosis: symptoms include intermittent retrosternal burning pain, +/- regurgitation, although constant pain or difficulty swallowing are uncommon.

Other causes: Aphthous ulcers, Kaposi sarcoma. Neurological problems e.g. due to stroke or HIV encephalopathy, may also cause difficulties (but not pain) with swallowing.

26.2 Drug treatment for esophagitis

- Candida: Fluconazole 200 mg, daily for 14 days.
- HSV: Acyclovir 800mg 3 x /day for 14 days.

26.3 Management

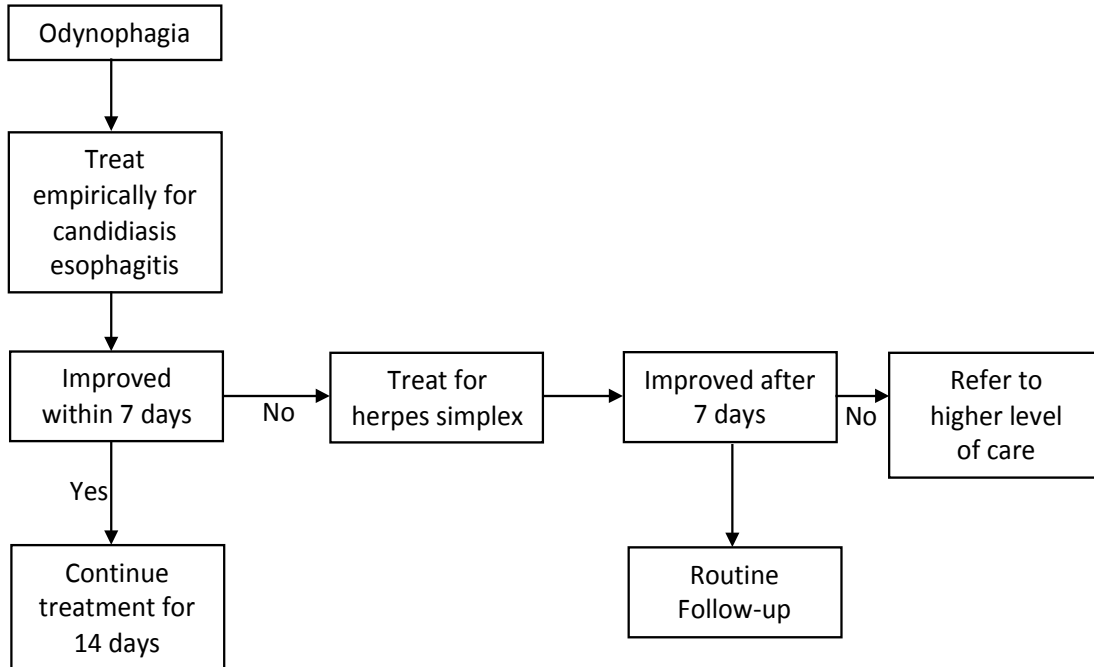
- For patients with likely diagnosis of candidiasis (based on typical symptoms, CD4 > 200 cells / mm³ and oral candidiasis): treat empirically for candidiasis and follow up in 7 days.
- If no response, treatment for HSV can be trialed.
- If the patient has herpetic mouth lesions, treat for HSV first, then for candida if they don't respond adequately (both infections may be present concurrently).
- Reflux esophagitis: try proton pump inhibitor or ranitidine
- However, check for drug interactions:³⁹ omeprazole is contraindicated with ATV/r and cimetidine or ranitidine should be avoided if possible, as the absorption of ATV/r is

³⁹ <http://www.hiv-druginteractions.org/>

reduced. If unavoidable use the lowest possible dose of ranitidine / cimetidine, and space as far apart from the ATZ/r dose as possible.

- If no response, refer for endoscopy if available.

Figure 26-1 Algorithm for Syndromic management of odynophagia



26.4 Antifungal agents and pregnancy/breast-feeding⁴⁰

Fluconazole should generally be avoided in first trimester of pregnancy however the overall risk benefit needs to be assessed. (See Chapter 17. section on 17.4.4 Antifungal treatment of Cryptococcal Meningitis pregnant/breast feeding women).

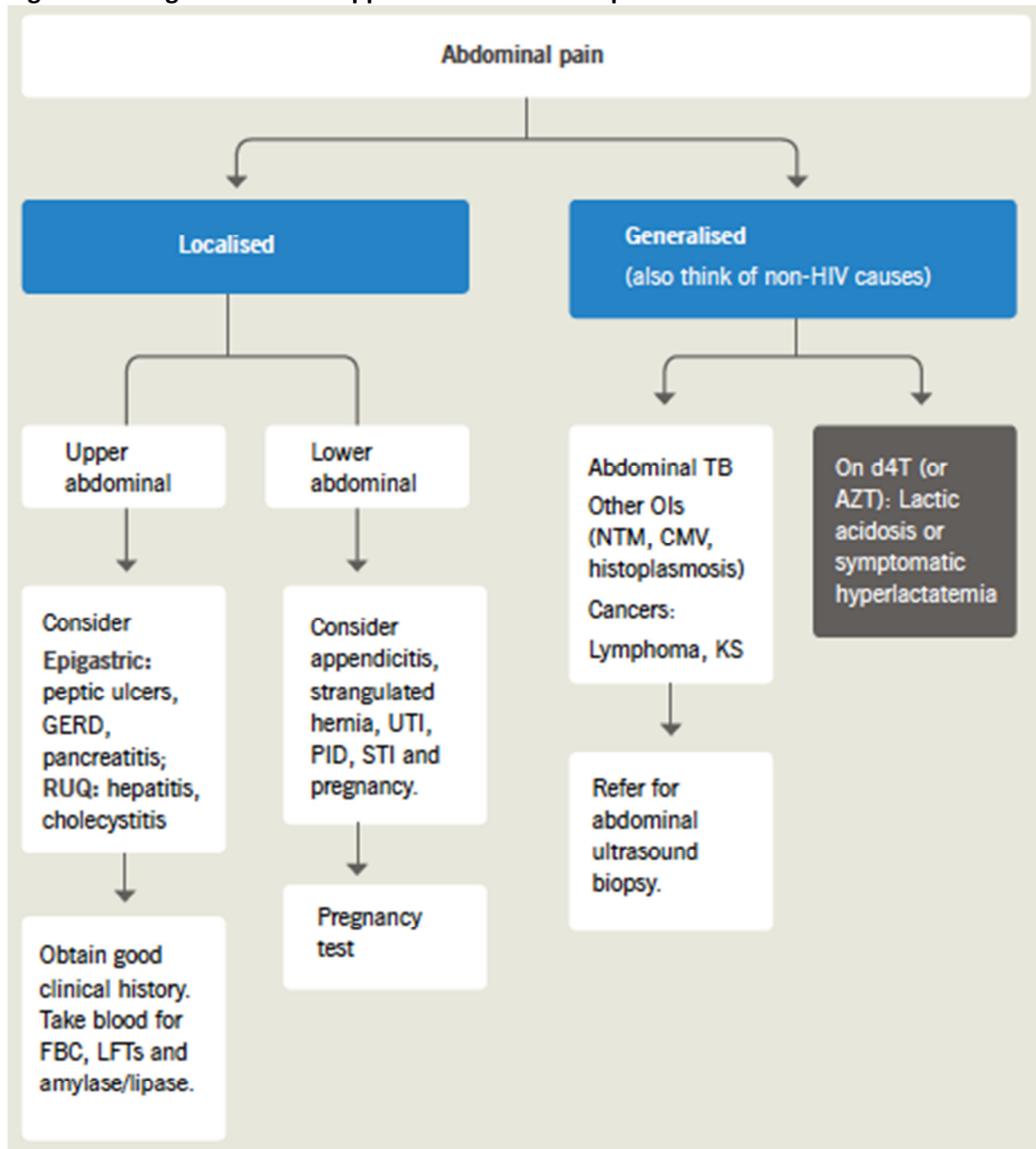
⁴⁰ Sanford Guide Antimicrobial Therapy 2015.

Chapter 27. Abdominal pain

An approach to abdominal pain is provided in the algorithm below.

Urgently refer for surgical review if evidence of peritonitis (rigidity on abdominal exam).

Figure 27-1 Algorithm for an approach to abdominal pain⁴¹



⁴¹ Copied directly from MSF HIV/TB clinical guide 2015 p 214

Chapter 28. Diarrhea

PLHIV are vulnerable to both acute and chronic diarrhea, including illness caused from common infections, and opportunistic infections with unusual organisms.

Prevention: Food and water sanitation and safety, and prompt establishment on ART.

28.1 Definitions

- **Diarrhea:** the passage of loose or watery stools, typically > 3 stools per day.
- **Acute diarrhea:** ≤14 days duration
- **Persistent diarrhea:** >14 days and ≤30 days duration
- **Chronic diarrhea:** > 30 days duration

28.2 Acute diarrhea

Acute diarrhea presents as either **simple gastroenteritis** with watery diarrhea, or as **invasive diarrhoea / dysentery**; diarrhea with visible blood, commonly associated with fever, abdominal pain and rectal symptoms.

28.2.1 Causes

Include viruses (norovirus), and bacterial (e.g. *E.coli*, *Salmonella spp.*, *Shigella spp.*, *Campylobacter spp.*) and parasites (e.g. *Entamoeba histolytica*).

Non-infectious causes include side effects to medications (e.g. Lopinavir/r).

28.2.2 Management of acute diarrhea

- The mainstay of treatment of acute diarrhea is the assessment and management of dehydration according to Table 28-1 Assessment and management of dehydration in patients with diarrhea.
- **Antimicrobial management**
If acute diarrhea doesn't improve within one week, and the person has frequent stools (>6 per day), together with a high temperature and/or bad cramps, then give:
 - Cotrimoxazole DS 1 tablet 2x /day AND metronidazole 500 mg 3 x / day for 5 days.
 - If there is blood in the stools, together with the above symptoms, or the diarrhea is not improved with the above treatment, then give:
 - Ciprofloxacin 500 mg 2x /day x 5 days.

Table 28-1 Assessment and management of dehydration in patients with diarrhea⁴²

Signs	Severe dehydration (2 of the following signs)	Some dehydration (2 of the following signs)	No visible dehydration
Level of consciousness	Lethargic or unconscious	Restless and irritable	Alert
Eyes	Sunken	Sunken	Not sunken
Ability to drink	Poor or unable	Eager, thirstily	Normal, not thirstily
Skin pinch (turgor)	Very slow return >2 seconds	Returns slowly <2 seconds	Returns immediately
Treatment	<ul style="list-style-type: none"> • Rehydrate with IV (or nasogastric tube). • Consider causes and treat. • Report cases. 	<ul style="list-style-type: none"> • Give fluid and food. • Immediately advise when to return. • Follow up in 5 days if not improving. 	<ul style="list-style-type: none"> • Treat at home. • Advise when to return. • Follow up in 5 days if not improving.

Rehydration:

- Drink as much fluid as possible, as often as possible, e.g. 1 cup of fluid every 15 – 30 minutes.
- If unable to drink and/or severe vomiting → arrange for rehydration with intravenous fluid.
- Oral rehydration fluids:
 - Oral rehydration salts (ORS) are best; one sachet into one liter of clean or boiled water
 - Sugar salt solution (SSS) = One liter of clean boiled water + half a teaspoon of salt + 8 teaspoons of sugar. If available add some potassium (for example, add orange juice).
 - Rice soup = boil 1 cup of rice in 5 cups of clean water with a bit of salt for one hour.
- Make new batch of rehydration solution daily and keep clean and cool.
- Continue to eat as tolerated; do not just have rice soup /ORS. Bananas are a good source of potassium (which is lost in the stool).

28.3 Chronic diarrhea

Advanced HIV itself can cause chronic diarrhea, also PLHIV with low CD4 counts are vulnerable to chronic infections with Protozoa (*Microsporidia*, *Cryptosporidium spp.*, *Isospora belli*, *Giardia lamblia*, *Entamoeba histolytica*) Bacteria (*Salmonella spp.*, *Mycobacterium avium* complex, MTB) and viruses including CMV.

Non-infectious causes of chronic diarrhea include gut neoplasms including lymphoma and Kaposi’s sarcoma, pancreatic insufficiency, or drug side effects (eg. LPV/r).

⁴² WHO. 2011. IMAI District Clinician Manual: Hospital Care for Adolescents and Adults, copied from MSF HIV/TB Clinical guide 2015

28.3.1 Diagnosis

It is critical to look for TB: clinical assessment, sputum examination, CXR.

Stool microscopy: for WBC, RBC, parasites (increased sensitivity with 3 specimens).

Abdominal ultrasound: examine for enlarged LN and hepatosplenomegaly (TB, MAC).

28.3.2 Management ⁴³

- Assess and manage dehydration and nutritional status according to Table 28-1 Assessment and management of dehydration in patients with diarrhea, and Chapter 33. Nutrition and weight management in HIV infected Adults and Adolescents
- **Treat any identified and treatable infections**
 - Isosporiasis: cotrimoxazole 1 DS 4 x /day for 10 days, then 2 x / day for 3 weeks
 - Strongyloidiasis: Albendazole 400mg 2 x / day (with fatty food) x 7 days
 - Giardiasis: Metronidazole 500mg 3 x /day x 7 days
 - TB: refer to CENAT for standard treatment
- Otherwise trial empiric antimicrobial therapy (although ensure TB is excluded prior to prescribing ciprofloxacin).
- Cotrimoxazole DS 1 tablet 2 x /day, AND metronidazole 500 mg 3 x day x 5 days.
- If fails: try albendazole 400mg 2 x /day (with fatty food) x 7 days
- **Antidiarrheal drugs** may be used cautiously in the event of poor response to above treatments, and only if diarrhea is watery, with no blood or abdominal pain.
 - Loperamide 2mg tablet after each episode of diarrhea, or regular regimen up to maximum of 6 - 8 tablets per day
 - Codeine phosphate 30 – 60 mg up to 4 x per day.
- **Ensure the patient is established on ART as soon as possible.**

⁴³ Antimicrobial doses are taken from MSF HIV/TB clinical guide 2015, and The Sanford Guide, Antimicrobial therapy 2015

Chapter29. Enteric Fevers

Enteric fevers (including Salmonella) are caused by *Salmonella typhi*, non typhoidal *Salmonella spp.* and other gram negative bacteria including *Campylobacter* and toxin producing *Shigella* and *E.coli*,

Recurrent septicaemia (specifically including non typhoidal Salmonella) is classified as WHO stage 4.

Prevention: Early ART, cotrimoxazole prophylaxis (partially protective), food / drinking water hygiene (see Chapter33. Nutrition and weight management in HIV infected Adults and Adolescents section on Food handling Safety).

29.1 Clinical features of enteric fever

Symptoms: fever, rigors, nausea, abdominal pain, GIT may include profuse bloody or non-bloody diarrhoea, or constipation (typhoid).

29.2 Investigation and Diagnosis

Stool microscopy: leucocytes and red blood cells, and parasites.

Stool culture and blood culture (if available) may isolate the causative organism.

Malaria testing.

Differential diagnosis: parasitic GIT infection, e.g. amoebiasis.

29.3 Standard treatment⁴⁴

Initial management:

- Aggressive IVI fluid replacement + broad antibiotic cover with IVI ceftriaxone (or oral ciprofloxacin 500mg) and metronidazole 500mg (IV or oral) twice daily.

Once the diagnosis is established, and if no extra-intestinal infection is suspected:

- Ciprofloxacin 500 mg tablet 12 hourly x 7 - 14 days or
- Ceftriaxone 2gm IVI daily or
- Azithromycin 1gm stat followed by 500mg daily 5 days

If bacteraemia is confirmed, or highly suspected, ensure at least 2 weeks antibiotic therapy.

If extra –intestinal infection is suspected or confirmed (e.g. osteomyelitis or mycotic aneurism) OR severe immunodeficiency (<200 cells/mm³) treatment with ciprofloxacin can be extended 2 – 6 weeks

29.4 Secondary prophylaxis

- Cotrimoxazole prophylaxis according to standard regimen.

⁴⁴ Sanford Guide Antimicrobial Therapy 2015, and Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.2015.

Skin conditions and STI

Chapter30. Skin disease

30.1 Key points

- Skin lesions are common and are often present early in the course of HIV infection.
- Skin lesions may be a manifestation of any of the following:
 - Primary dermatologic disorder (e.g. psoriasis)
 - Infection: superficial (e.g. folliculitis), or deep (cellulitis) or disseminated (Cryptococcus)
 - Allergy (drug rash)
 - Disordered inflammatory response to antigens (e.g. PPE)
 - Malignancy (e.g. Kaposi's sarcoma)
- Prompt diagnosis and treatment of cutaneous manifestations is important for symptom relief and also to treat potentially life-threatening disease (e.g. systemic infection, or severe drug reaction).

30.2 Adverse drug reactions

- Adverse cutaneous reactions are common and range from mild to life threatening.
- If a patient presents with rash, + / - fever and constitutional symptoms always consider drug reactions.
- Classic drug reaction patterns include; drug induced exanthems (most common), urticarial/angioedema, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity vasculitis, exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruption, and photosensitivity reactions. There are many other less common patterns of drug induced skin disease.
- The following drugs are commonly implicated:
 - ARVs: nevirapine, efavirenz, abacavir (as part of abacavir hypersensitivity syndrome), and less commonly 3TC, or AZT.
 - Cotrimoxazole
 - TB drugs
 - Others: anti-epileptics (e.g. carbamazepine, phenobarbitone), NSAIDs, allopurinol, etc.

30.3 Clinical presentation⁴⁵

Key syndromes:

1. **Maculopapular (also morbilliform, or exanthematous) drug eruptions** are the most common type of adverse drug reaction. They are diffuse symmetrical eruptions of macules +/- papules occurring approximately one week after the initiation of the drug (earlier if the patient has already sensitized to the drug). Other symptoms may include itching, low-grade fever, and mild eosinophilia.

⁴⁵ Source: Samel A.D, Drug eruptions In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA

Cotrimoxazole causes this reaction, which is more common in PLHIV. Other drugs include antiepileptic drugs, some NSAIDs, penicillins, and TB drugs.

2. Drug hypersensitivity syndrome/DRESS

Erythroderma or diffuse morbilliform eruption involving 90% or more of skin, fever and multi organ failure including liver, kidneys, heart, lungs (check BP, urine dipstick, CXR). Eosinophilia is common but not always present. Usually starts ~3 weeks after the causative medication has commenced. Abacavir and nevirapine hypersensitivity are examples of DRESS, and other drugs include antiepileptic drugs, dapsone, and allopurinol.

3. Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN):

SJS/TEN occur within the first 8 weeks of treatment, and the most commonly implicated drugs include allopurinol, anticonvulsants, sulphonamides, nevirapine and some NSAIDs. Muco-cutaneous reactions are severe and characterized by extensive necrosis and detachment of the epidermis. SJS includes skin detachment of < 10% of the body surface, TEN involves > 30% of the body surface area, and SJS / TEN overlap syndrome 10 – 30%. Mucous membranes are effected in > 90%, usually at two or more sites (ocular, oral and genital). Fever is common. The skin lesions typically begin with ill-defined, coalescing erythematous macules with purpuric centers, or may present with diffuse erythema. The skin is often painful and tender. Lesions often start on the face and throat, and as the disease progresses vesicles and bullae form and then begin to slough. In severe cases acute complications include sepsis, massive fluid loss through the skin, and multi organ failure. Long-term sequelae include cutaneous, mucosal, ocular and pulmonary complications.

30.4 Management

- For any severe drug rash, particularly with extensive skin involvement +/-or systemic symptoms, and DRESS or Stevens – Johnson / TEN is suspected.
- STOP all drugs, and refer to hospital for supportive management and expert consultation.
- Where it is not clear which drug is causing the rash – stop all, and stepwise reintroduction can be considered after the rash has resolved.
- For more information regarding management of specific drug reactions see:
 - Abacavir hypersensitivity and other ARV drug rashes in Chapter10. Monitoring and substitutions for ART toxicity
 - Cotrimoxazole rash in Chapter5. Primary Prophylaxis for Opportunistic Infections.

30.5 Disseminated infections with dermatological manifestations

- Bacterial infections: *Staphylococcus aureus*, *Bacillary angiomatosis*, *Neisseria gonorrhoea*, Syphilis
- Mycobacterial infections: TB, non TB
- Acute viral exanthemas infections
- Herpes simplex and varicella zoster acute / recurrent infections

- Fungal infections: Cryptococcus (about 10% of cryptococcal infection), Histoplasmosis Sporotrichosis, Penicillium.

30.5.1 Invasive fungal diseases with dermatological manifestations

Invasive fungal disease with Cryptococcus, Penicillium or Histoplasmosis can present with skin lesions and severe systemic symptoms. All present late in HIV, and have a high mortality. They are WHO stage 4 conditions.

30.5.2 Penicilliosis

Penicilliosis is caused by infection with *Talaromyces* (formally *Penicillium*) *marneffe*, which is endemic in Southeast Asia, including Cambodia. Transmission is suspected to be mostly airborne. The organism proliferates in macrophages and is disseminated throughout the body, especially in the reticulo-endothelial system.

Clinical Presentation

- Abrupt onset, fever, anemia, weight loss, skin lesions, +/- lymphadenopathy and hepato splenomegaly +/- respiratory complaints (cough, shortness of breath).
- CBC cytopenias, ALP raised with liver involvement.
- Skin lesions present as one or multiple papular lesions, often with central umbilication or ulceration, resembling molluscum contagiosum or cryptococcus. The lesions are typically on the face, scalp and upper trunk but may also be found in the genital area.

Diagnosis

- Difficult to diagnose if no skin lesions, and if there are, it is difficult to distinguish from Cryptococcus. It is recommended to consult an expert regarding investigation and management if this diagnosis is being considered.
- Fungal identification from blood culture, microscopy of skin lesions with Wright's stain, lymph node, or bone marrow aspirate is definitive.

Standard treatment

- Amphotericin B 0.7 mg/kg daily IV for 2 weeks, followed by itraconazole 400 mg / day for 10 weeks, followed by itraconazole 200mg / day until CD4>100 for 6 months.⁴⁶
- Fluconazole is minimally active against Penicillium, so use IVI amphotericin B until itraconazole can be procured.
- If itraconazole is unavailable, use ketaconazole 200 mg twice daily or fluconazole 400 mg twice daily for 10 weeks.
- For less severe cases, itraconazole 400mg /day for 12 weeks then 200mg / day until CD4>100 for 6 months.

Secondary Prophylaxis

Long-term suppressive therapy with itraconazole 200 mg daily should be given to prevent relapse until the patient's CD4 is above 100 cells/mm³

⁴⁶ Sanford Guide to Antimicrobial therapy 2015

30.5.3 Histoplasmosis

Histoplasma capsulatum is a dimorphic fungus inhabits soil enriched by bird and bat droppings. Inhaled small spores of *H. capsulatum* reach the person's alveoli and with time an intense granulomatous reaction occurs. Caseous necrosis or calcification may mimic tuberculosis. Severity of illness depends on the intensity of exposure and the immunity of the host. Acute and rapidly fatal disseminated infection can occur among immunosuppressed PLHIV. Some patients may present with reactivation disease as their immunity decreases with HIV. Histoplasmosis has been rarely reported in Cambodia.

Clinical manifestations

- Acute pulmonary histoplasmosis presents with cough, fever, weight loss, malaise, chills, myalgia, anorexia and chest pain. It is difficult to distinguish from PCP. CXR shows pneumonitis with hilar lymphadenopathy or miliary pattern.
- CXR in chronic pulmonary histoplasmosis shows retraction and cavitation of upper lobes with spread to lower lobes and other area of the lung, with emphysema and bulla.
- Disseminated histoplasmosis is characterized by prolonged fever, weight loss, hepatosplenomegaly, lymphadenopathy, large oral ulcerations, or discrete erythematous fungating skin papules or masses.

Diagnosis and treatment

- In most cases a diagnosis will not be able to be established. Consult an expert if this diagnosis is being considered for advice re investigation and management.
- A definitive diagnosis can be made by histopathologic identification of yeast forms in white blood cells and macrophages in Giemsa stained smears from blood, bone marrow or BAL, however these investigations are rarely available.
- Treatment: Amphotericin B 0.7 mg/kg/day IV for 2 weeks, then itraconazole 200 mg twice daily for at least 12 months.

30.5.4 Bacterial skin and soft tissue infections

Table 30-1 Bacterial skin and soft tissue infections

Bacterial skin infection	Causative organism	Description	Treatment
Folliculitis	<i>Staphylococcus aureus</i>	Inflammation, infection of the hair follicles	Warm compress Cleansing Topical gentian violet Cloxacillin in severe cases
Cellulitis	<i>Streptococcus spp.</i> <i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i>	Inflammation of skin and subcutaneous tissues, characterized by oedema, erythema, and pain +/- fever	Cloxacillin 500 mg 4 x daily for 10 days. Severe cases require IV antibiotic (cloxacillin or ceftriaxone)
Boils, soft tissue abscess	<i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i>	Localized collection of pus in a cavity; may complicate untreated cellulitis	Surgical drainage is most important. Warm compress if mild. Systemic antibiotics if surrounding cellulitis

Impetigo	<i>Staphylococcus aureus</i> , <i>Streptococcus spp.</i>	Yellow colored crusting or irritating blisters	Soak crusts with warm water. Topical antibiotic or antibiotic/salicylic acid preparation Cloxacillin for disseminated lesions
Paronychia	<i>Staphylococcus aureus</i>	Infection involving the folds of tissue surrounding the fingernail or toenail	Surgical drainage if pus under nail. Cloxacillin for 5-7 days
Pyomyositis	<i>Staphylococcus aureus</i>	Deep abscess formation within muscle. Likely systemically unwell, fever, pain.	Surgical drainage most important. Cloxacillin 1-2 grams IV 4 x daily or ceftriaxone 2 grams daily x 10 days
Bacillary angiomatosis "cat scratch disease"	<i>Bartonella henselae</i>	Disseminated vascular lesions that may mimic Kaposi's sarcoma	Consult expert Erythromycin 500 mg 4 x daily or doxycycline 100 mg 2 x daily for two months
Necrotising soft tissue infections including necrotizing fasciitis	<i>Streptococcus pyogenes</i> , <i>Clostridium perfringens (gas gangrene)</i> , of <i>Vibrio spp.</i> or <i>polymicrobial mixed aerobic and anaerobic bacteria</i>	Severe pain, even if skin inflammation is limited. Bullae, skin necrosis, firm oedema, gas in the soft tissues, rapidly spreading, Systemically severely unwell	Surgical EMERGENCY Debridement. IV antibiotic as broad cover as available. E.g. ceftriaxone + metronidazole/ clindamycin, or meropenem + metronidazole/ clindamycin. Narrow antibiotic spectrum if culture results available
Staphylococcal Scalded Skin Syndrome	<i>Staphylococcus aureus</i>	Diffuse bullous lesions starting on face, most common in infants; may mimic Stevens Johnson Syndrome but without precipitating exposure and NO mucosal involvement	Cloxacillin 200 mg/kg/day IV divided in every 6 hours Surgical consultation Aggressive wound care and attention to hydration status
Syphilis	<i>Treponema pallidum</i>	1 ^o Painless, indurated ulcer (chancre) at site of inoculation Dx clinical (RPR takes 4 – 6 weeks to become positive)	Benzathene penicillin 2.4 M IU x 1 2 nd line doxycycline 100mg 2 x daily x 14 days, 3 rd line erythromycin 500mg 4 x daily x 4 weeks
Syphilis	<i>Treponema pallidum</i>	Maculo-papular rash, condylomata lata, fever, lymphadenopathy, oral mucus patches. Dx high RPR	Benzathene penicillin 2.4 M IU x 1 2 nd line doxycycline 100mg 2 x daily x 14 days, 3 rd line erythromycin 500mg 4 x daily x 4 weeks

30.5.5 Viral skin infections

Table 30-2 Viral skin infections

Viral skin infection
<p>Herpes simplex 1, 2. Orolabial lesions, Genital lesions Vesicles with an erythematous base on lips, nose, tongue, oropharynx, gingival and genital areas. Dx clinical and Tzank test Management: Acyclovir 400mg 5 x /day for 7 days. Gentian violet can help reduce bacterial super-infection.</p>
<p>Herpes Zoster, shingles Herpes Zoster virus (reactivation) Common in HIV. Dermatomal distribution of painful vesicles – then crusting, rarely crosses midline. May cause ocular damage. Dx clinical + Tzank Management: Acyclovir 800mg 5 x /day for 7 – 10 days Gentian violet can help reduce super-infection. Calamine lotion for skin lesions</p>
<p>Herpes Zoster, chicken pox Herpes Zoster virus (primary infection) Prodrome 3 days, Generalised vesicular rash in “crops” may be complicated by pneumonitis, hepatitis, encephalitis Management: Acyclovir 800mg 5 x /day for 7 – 10 days Gentian violet can help reduce superinfection. Calamine lotion</p>
<p>Molluscum contagiosum Caused by <i>Molluscum contagiosum virus</i>. Umbilicated papules, patient not unwell. Must be differentiated from Cryptococcus or Penicillium or Histoplasmosis (usually systemically unwell). Management: Self-limiting. Or open lesion with sterile needle and express contents, curettage, or liquid nitrogen cryotherapy.</p>
<p>Warts Human papilloma virus Cauliflower-like lesions in genital and peri-anal area, may also occur elsewhere, and flat lesions on plantar surface. Management: Non-mucosal affected areas: podophyllotoxin 0.5% solution twice daily for 3 consecutive days per week for up to 4 weeks (maximum). Protect unaffected skin with vaseline or zinc ointment, then wash with water and soap after 1-4 hours. DO NOT ADMINISTER DURING PREGNANCY. Cryotherapy if available.</p>

30.5.6 Fungal skin infections

Table 30-3 Fungal skin infections

Fungal skin infection
<p>Tinea (ringworm) Tinea corporis, Tinea capitis, Tinea pedis. Trunk, face, limbs, annular lesions with red scaly edge and central healing Diagnosis: predominantly clinical. Management: Keep moist areas dry. Whitfield's ointment (benzoic acid with salicylic acid) 2 times daily for 2 to 5 weeks on body lesions. Or 2% miconazole, or 1% clotrimazole cream for two to four weeks. Extensive disease and <i>tinea capitis</i> treat with systemic fluconazole 150mg weekly for four weeks.</p>
<p>Tinea onychomycosis Tinea unguium Hyperkeratosis of undersurface of the nail plate. Diagnosis: fungal microscopy and culture. Management: Treat onychomycosis only if severe. Itraconazole 200 2 x daily for first seven days of 4 consecutive months. Or Terbenafine if available. Check for interaction with ARV</p>
<p>Cutaneous candidiasis Candida species (usually albicans) Moist areas – skin folds, erythematous rash with well demarcated borders. Also on genitals, or paronychia. Management: Topical 1% aqueous gentian violet solution, Topical nystatin or miconazole 3 x per day until 48 hours after rash resolves.</p>

30.5.7 Scabies

Table 30-4 Scabies

Scabies infestation
<p>Scabies Sarcoptes scabiei var. hominis Pruritic papular lesions esp. webs of the fingers and toes, folds of the wrist, antecubital area, and axilla. Management: Benzyl Benzoate 25% lotion or Permethrin 5% cream: apply over the body except head/face, leave in place 12 hours, then wash off, repeat in 7 days.</p>
<p>Crusted (Norwegian) scabies Sarcoptes scabiei var. hominis Hyperinfestation with millions of mites, and very contagious. Thick scaly crusting, esp. on elbows, back of neck and ears, buttocks. Not always pruritic, secondary bacterial infection common. Management: Family members often have regular scabies – treat all household members, and wash all clothes and bed linen Systemic treatment with Ivermectin 200mg/kg single dose, repeated on day 0, 7, 14. If not available use topical therapy 2nd daily with topical keratolytics on alternate days (e.g. salicylic acid 5 – 10% in sorbolene, or lactic acid 5% + urea 10% in sorbolene) Consult an expert.</p>

30.5.8 Non infective skin lesions

Table 30-5 Non infective skin lesions

Non infective skin lesions
<p><i>Seborrheic Dermatitis</i> Seborrheic dermatitis is characterized by dry, flaky, or scaly skin occurring on the scalp; it also may be seen on the face nasolabial folds, the skin behind the ears, and the eyebrows. Management: Selenium sulfide or ketoconazole shampoo for scalp lesions Topical steroids can be applied to the affected areas three times per day. Only use 1% hydrocortisone cream on the face as skin atrophy can occur. Stronger (betamethasone 10%) can be used elsewhere.</p>
<p><i>Pruritic Papular Eruption (PPE)</i> Most common in patients with CD4 < 200 cells/mm³ Chronic eruption of papular lesions on the skin, usually evenly distributed on the trunk and extremities May be related to disordered inflammatory response to common antigens such as those due to repeated mosquito bites. Very pruritic. Management: Generally refractory to treatments other than ART. Oral antihistamines may help.</p>
<p><i>Eosinophilic folliculitis</i> Oedematous, red, skin-coloured papules and pustules On the face, scalp, neck and chest. Pruritic. Management: May fluctuate and improve with initiation of ART. Oral antihistamines may help.</p>
<p><i>Psoriasis</i> Extensive Psoriasis can be observed in severely immunosuppressed patients. Presents with thick plaques with silvery scale, mostly on extensor surfaces. Finger and toenails may have pitting and irregular thickening (onychodystrophy). Management: includes exposure to sunlight, coal tar 5-10% ointment in salicylate ointment 2 x daily with coal tar shampoo (if scalp is involved), and potent topical steroids (betamethasone 0.1% or Diprosalic cream applied to lesions 1-2 x daily for 14 days. Generally psoriasis is refractory to treatment other than ART.</p>
<p><i>Kaposi Sarcoma (very rare in Asia)</i> Cancer due to HHV8 virus, WHO stage 4 illnesses. Single or multiple purple macules, papules or nodules, often smooth, but may be scaly or ulcerated. Located anywhere on the skin, often on the upper palate. On the legs +/- firm oedema. Internal KS includes, chest – pleural effusion, abdominal organs, GIT (blood in stools). Management: start ART, discuss with an expert re need for radio /chemotherapy.</p>

Figure 30-1 Algorithm for rash with pain

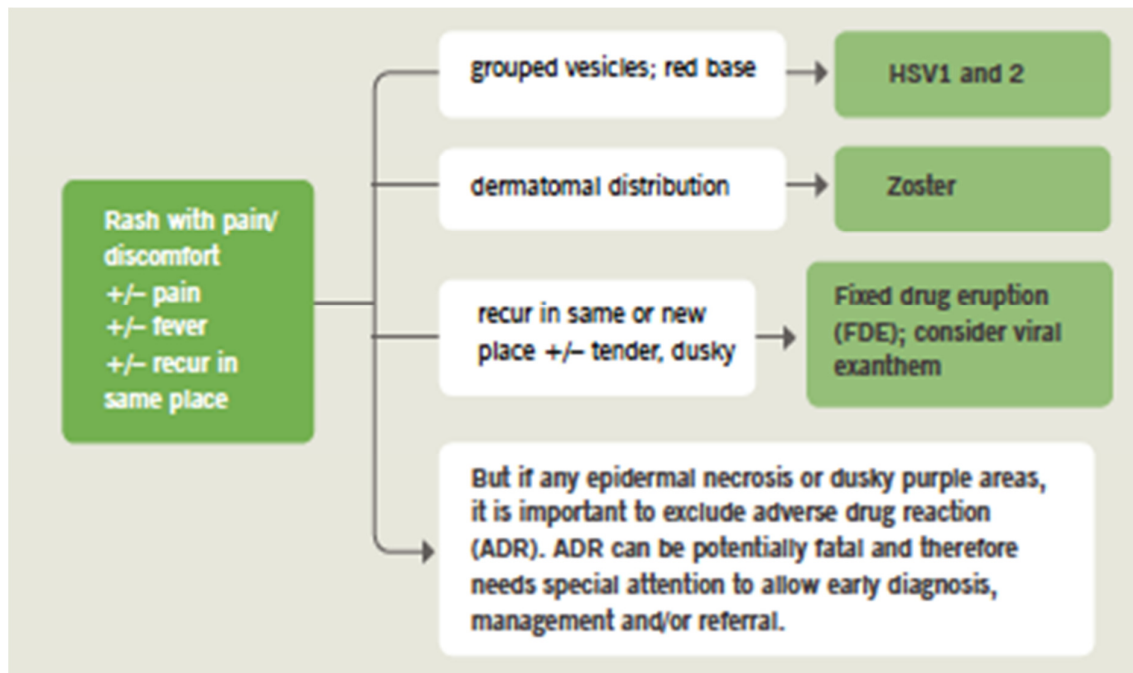


Figure 30-2 Algorithm for rash with no pain/itch

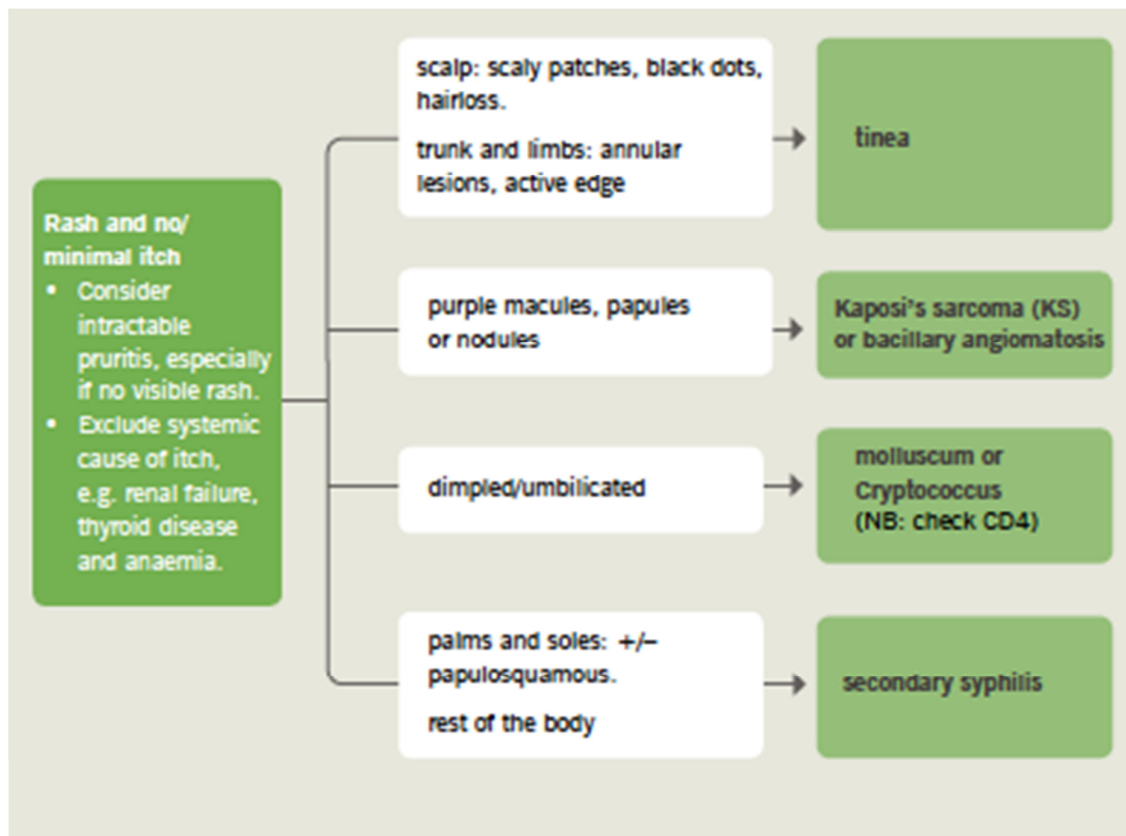


Figure 30-3 Algorithm for rash with itching

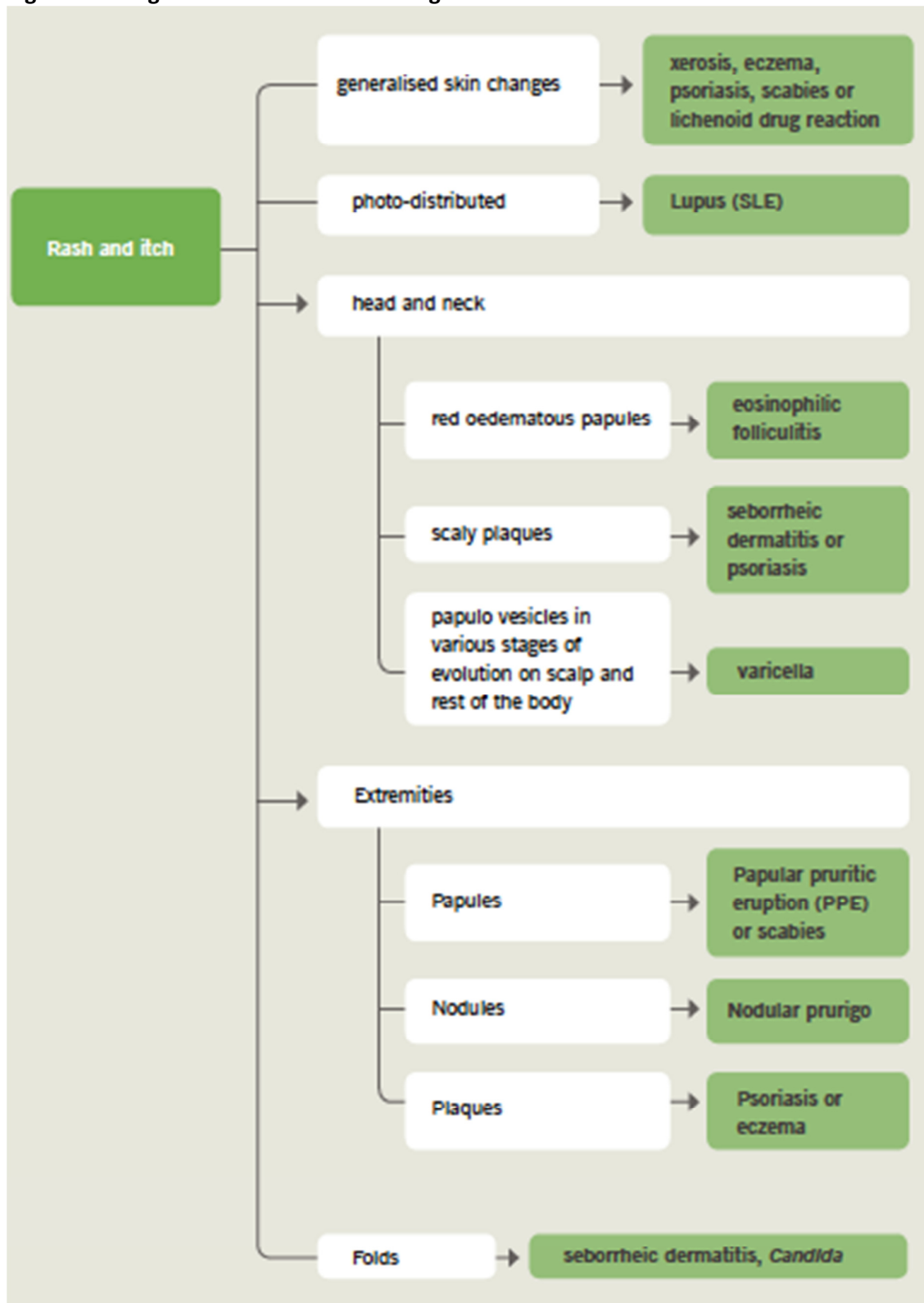
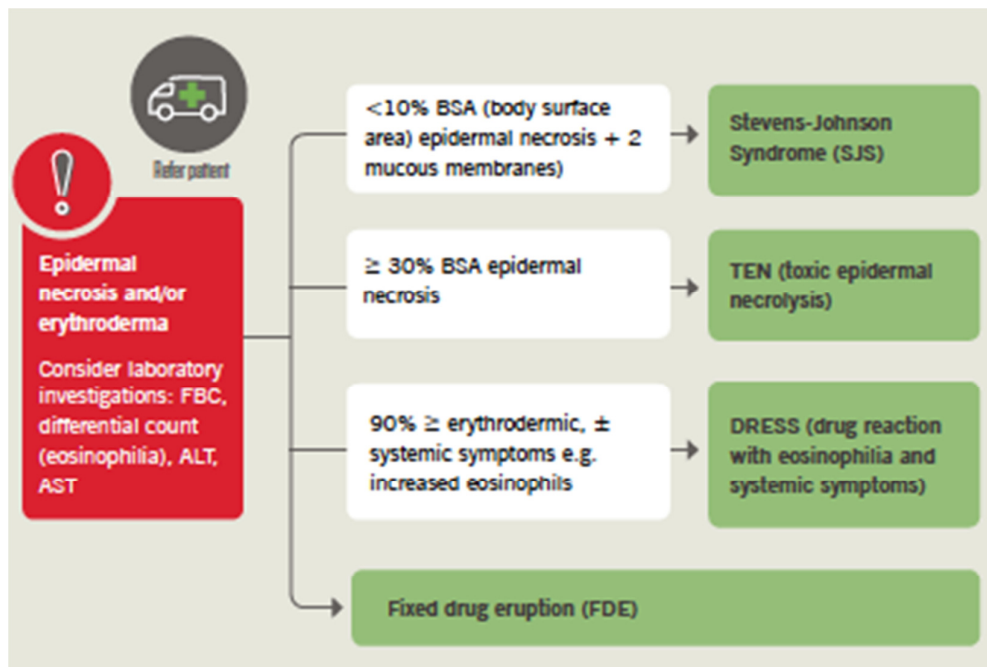


Figure 30-4 Algorithm for severe rash



Chapter31. Reproductive and Sexually transmitted infections

- It is important that PLHIV and their partners are treated for STIs 1) in order to care for the health of the individuals, and 2) as STIs increase the risk of transmission of HIV.
- Generally evaluation and treatment for STI are the same as for non-HIV infected individuals.
- See NCHADS STI management guidelines, in particular Module 5 Chapter. 6 STI/RTI care and treatment for people living with HIV/AIDS⁴⁷
- See section in this guideline in Chapter3. Women of child bearing age, regarding family planning and contraception.

31.1 Vaginal candidiasis

Vaginal candidiasis is a very common and troublesome problem for some women with HIV.

31.2 Clinical findings

Symptoms: itching or burning sensation and a white vaginal discharge.

Examination: White adherent vaginal discharge with cheese-like plaques, vulvo- vaginal area is erythematous, swollen and tender.

31.3 Diagnosis

Clinical, on the basis of symptoms and examination findings.

Consider also other causes of vaginal discharge including bacterial vaginosis and cervicitis due gonorrhoea, chlamydia, and trichomonas. Particularly if clinical features are atypical or treatment is ineffective.

31.4 Standard treatment

(any of the following)

- Clotrimazole vaginal cream 5 g/day or clotrimazole vaginal suppository 100 mg once daily for 3-7 days, or clotrimazole 500 mg suppository x 1 one time.
- Miconazole cream 5 g/day or 100 mg vaginal suppository daily for 7 days.
- Nystatin 100,000 units vaginal suppository daily for 14 days.

31.5 Treatment of persistent or recurrent vaginal candida

- Fluconazole 150-200 mg one time (longer duration maybe considered in a difficult case).

⁴⁷ Kingdom of Cambodia, Ministry of Health. National guidelines on sexually transmitted infections (STI) and reproductive tract infections (RTI) case management. 2010 module 6 Ch. 6 p 217 – 222

HIV associated malignancy

Chapter 32. HIV associated malignancies

Primary CNS and B cell variant Non-Hodgkin's Lymphomas (associated with EBV), invasive cervical carcinoma (linked to HPV), and Kaposi's sarcoma (HHV-8) are WHO clinical Stage 4 AIDS defining cancers. PLHIV also have higher rates of non – AIDS defining cancers, e.g. lung cancer.

Diagnostic and treatment options are very limited for cancers in Cambodia. The most important focus should be on prevention of malignancy by early diagnosis of HIV, and prompt establishment on ART. In addition other preventative measures should be promoted, in particular smoking cessation (see Figure 35-1 WHO Counselling tool to assist individuals to quit smoking.)

32.1 Non-Hodgkin's lymphoma (NHL)

NHL is usually associated with very advanced HIV (CD4 < 50 cells/ mm³), and manifests as;

- Systemic NHL (>80 %)
- Primary central nervous system (CNS) lymphoma (15 %)
- Primary effusion (or body cavity) lymphoma (<5 %)

Clinical presentation

Similar presentation to TB, and should be considered if it fails to improve with TB treatment, including fever, lymphadenopathy, fatigue, weight loss, night sweats, splenomegaly, hepatomegaly, evidence of focal infiltrates, and cytopenias on CBC.

Table 32-1 Site dependent clinical presentations of NHL

Mediastinal or Pharyngeal tumor	Abdominal tumor
Dyspnea, Tachypnea, Stridor, Cough Localized decrease in breath sounds,	Abdominal distension, Ascites, Abdominal mass, Jaundice, Pain
Central nervous system disease	Maxillofacial tumor
Headache, Vomiting, Visual disturbances Gait instability, Cranial nerve palsies Hemiparesis, Seizures	Jaw mass, Numbness of the chin (peripheral facial nerve compression) Asymmetric facial expression

Diagnosis

Diagnosis is difficult, in most instances the patient should be started on empiric TB treatment, and if there is no improvement should be referred for further assessment and management. Definitive diagnosis requires tissue biopsy for histopathology.

Treatment

Options for any malignancy are very limited in Cambodia, if feasible refer to The Khmer Soviet Hospital for assessment.

32.2. Cervical Cancer

Cervical cancer is one of the most common cancers worldwide. It is caused by cervical infection with strains of HPV which if not cleared spontaneously progress over time to

develop cervical intraepithelial dysplasia (CIN) and on to invasive cervical carcinoma. PLHIV are less likely to clear the HPV infection, and have a higher incidence of CIN, and are more likely to progress to invasive carcinoma compared to HIV negative women. Other contributing risk factors for cervical cancer include smoking, and other sexually transmitted infections.

Prevention

- HPV vaccine (not routinely available in Cambodia) targets cancer-causing strains of HPV, should ideally be administered to adolescents prior to the onset of sexual activity.
- Address other risk factors: cease smoking, avoidance of and early treatment for STIs
- Early diagnosis of HIV and prompt initiation of ART.
- Screening: there is a long screen-detectable preclinical phase of several years prior to the development of invasive cancer. Screening methods include cytology (Papanicolou or “pap” smear, or Liquid based cytology) +/- HPV PCR testing, which identify lesions which may be simply treated. In some resource limited settings visual inspection methods (acetic acid (VIA) or Lugol’s Iodine) followed by cryotherapy are available, as one stop screen and treat services. If this is available, refer all women over 35 years old.

Clinical presentation

Cervical dysplasia and cancer are usually asymptomatic until late stage, but can present with intermittent vaginal bleeding and discharge, bleeding after sexual activity, vaginal discharge. Women with advanced invasive carcinoma may present with fever, weight loss, abdominal pelvic or lower back pain, renal or bowel obstruction, vaginal stool discharge, or blood in either stool or urine. It is important that pelvic examination including visual inspection, and palpation be performed if there is any such presentation.

Treatment

Treatment options are limited in Cambodia, however if feasible refer to the Khmer – Soviet Hospital for further investigation and treatment for cervical dysplasia with loop electrical excision cauterization, or cone excision procedures. Treatment for cervical cancer includes more invasive surgery, radiation, and chemotherapy.

Nutrition and chronic non- communicable diseases

Chapter 33. Nutrition and weight management in HIV infected Adults and Adolescents

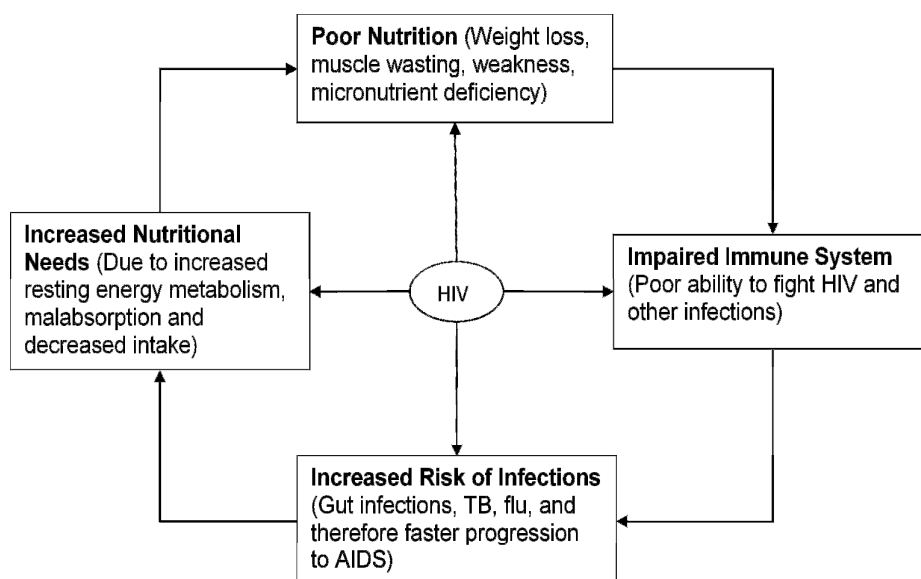
33.1 Key points

- Symptomatic PLHIV (particularly pre ART) have increased metabolic rate and nutritional requirements because of recurrent infections and HIV infection itself.
- Malnutrition associated with HIV/AIDS itself leads to increased vulnerability to infections and increased risk of mortality.
- Symptomatic PLHIV require an increased in caloric intake of 10 – 30%.
- Inadequate intake may be due to lack of access to appropriate food, poor appetite, physical symptoms, or GIT malabsorption.
- On the other hand, PLHIV well controlled on ART may become overweight and risk diabetes, hypertension and cardiovascular disease.
- It is important to regularly monitor all patients' weight, body mass index (BMI) and nutritional status for optimal health.

33.2 Definition of Malnutrition

A simple definition of malnutrition is “a condition resulting from the inadequate or inappropriate consumption basic foods and nutrients that can impair physical and mental health and contribute to increased risk infectious diseases.”

Figure 33-1 Cycle of malnutrition and infection in HIV⁴⁸



⁴⁸ Adapted from RCQHC and FANTA Project 2003, *Nutrition and HIV/AIDS: A Training Manual*

33.3 Nutrition Screening and weight management

33.3.1 Initial evaluation

1. Ask the patient if they know what their baseline body weight (BBW) was before they became unwell.
 - Assess change in weight as a % relative to their BBW
Change in weight % = $(BBW - \text{current weight})/BBW \times 100$
 - WHO stage weight loss according to change in weight relative to BBW
< 10% = WHO stage 2, > 10% = WHO stage 3, HIV wasting syndrome = stage 4
2. Calculate body mass index (BMI) – measure height and weight.
 - BMI = weight (kg) divided by the square of the height in metres = (kg/m^2) .
 - Classify BMI according to Table 33-1 WHO BMI Classification of adult underweight, overweight and obesity and Figure 33-2 WHO BMI Classification of child /adolescent.
3. Check waist circumference
 - Method: Stand, arms loose, feet together. Use non – stretch measure, do not compress the skin. Measure the narrowest section between the lower ribs and iliac crest.
 - Overweight = men ≥ 85 cm, women ≥ 80 cm
4. See the following sections according to if the patient is **under, normal** or **overweight**.

33.3.2 Weight evaluation at every visit

- Check weight, monitor according to management plan
 - If weight changed – calculate BMI, % change in weight, + waist circumference.
 - If weight reduced – calculate % weight loss from BBW and advance WHO stage accordingly.

At initial and follow up visits – see the following sections (in this chapter) relevant to the patient's needs:

- *Underweight* (WHO and BMI criteria): section 33.4 underweight or loss of weight.
- *Overweight* (BMI or waist circumference criteria): section 33.5 Overweight.
- *Normal weight* : section 33.6 Normal weight at initial or follow up visits

Table 33-1 WHO BMI Classification of adult underweight, overweight and obesity⁴⁹

Classification	WHO Principal cut-off points	Cambodian cut-off points*
Underweight	<18.5	<18.5
Severe thinness	<16.0	<16.0
Moderate thinness	16.0 - 16.9	16.0 - 16.9
Mild thinness	17.0 - 18.4	17.0 - 18.4
Normal range	18.5 - 24.9	18.5 - 22.9
Overweight	≥25.0	23.0- 24.9
Pre-obese	25.0 - 29.9	
Obese	≥30.0	≥25

*Health risks related to being overweight may increase below the WHO principle ranges in Asian populations. WHO has added these alternative cut off points, which have been adopted in Cambodia.⁵⁰

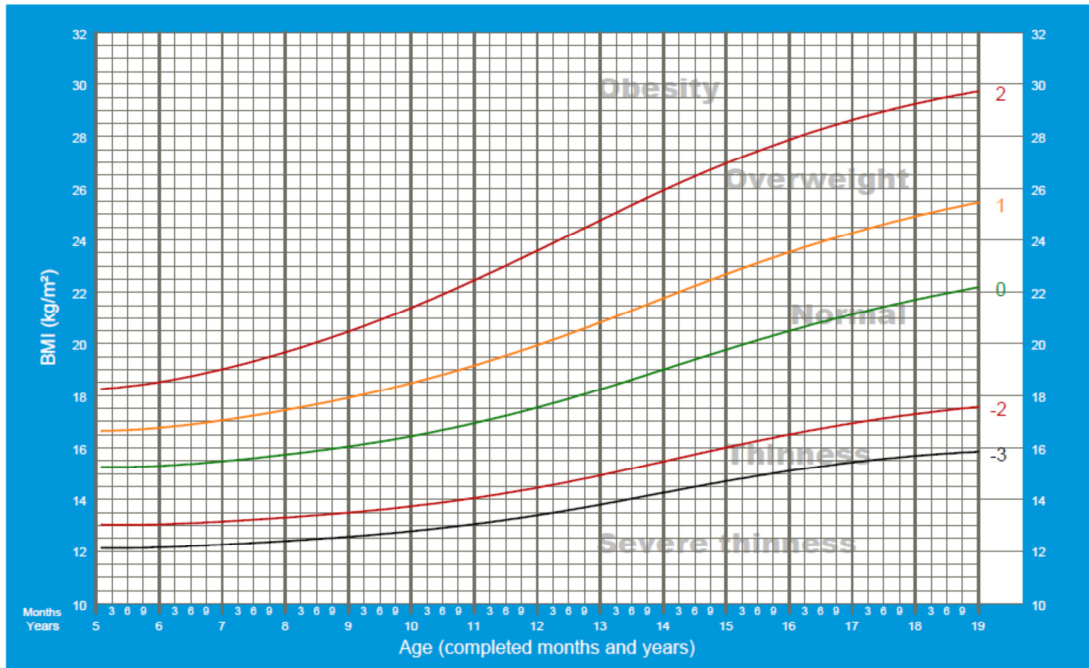
⁴⁹ Adapted from WHO classification: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html

⁵⁰ These cut off points are consistent with the CAMBODIAN MINISTRY OF HEALTH CLINICAL PRACTICE GUIDELINES. TYPE 2 DIABETES. A continuum of care for diabetes patients both with and without complications at NCD clinics/RHs Bureau for NCD Prevention & Control DEPARTMENT OF PREVENTIVE MEDICINE 2015.

Figure 33-2 WHO BMI Classification of child/adolescent

BMI-for-age BOYS

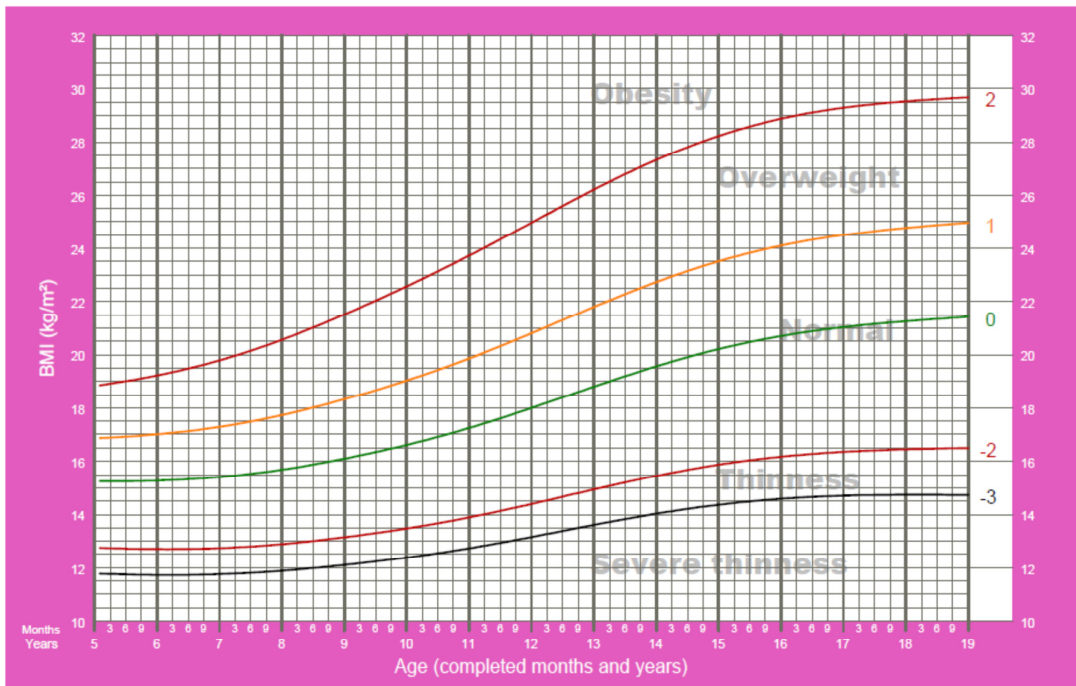
5 to 19 years (z-scores)



2007 WHO Reference

BMI-for-age GIRLS

5 to 19 years (z-scores)



2007 WHO Reference

33.4 Underweight or loss of weight: assessment and management

Assessment:

If the patient is underweight, or has lost >5% weight → perform further history and examination to assess:

- Overall food intake
- Knowledge about nutrition
- Knowledge about water and food safety
- Access to food – economic issues related to food security
- Appetite
- Drug side effects - e.g. nausea
- Eating
 - Altered taste
 - Mouth ulcers, gingivitis, oral candidiasis
 - Painful or difficulty swallowing
 - Neurological swallowing problems
 - Abdominal cramps or pain.
- Diarrhoea (including evidence of malabsorption in stool – fat / food)

Management:

- Treat any treatable conditions – e.g. oral thrush, mouth ulcers, gingivitis etc.
- Ensure that the patient and the family understand that they need to *increase* their food intake to get healthy, (and that rice porridge alone is inadequate).
- Patients who are underweight should maintain a balanced diet (detailed in Table 34-1 Recommendations for prevention and management of NCD) but may eat more fat and sugar until they achieve a normal weight.
- If they have loss of appetite, they need to make an extra effort to eat enough.
- Refer to food security programs for support if required.
- Symptom targeted suggestions; see the following table.
- Monitor weight, clinical findings and discuss nutrition at each visit.

Table 33-2 Symptom targeted management of poor food intake

Symptoms	Management ⁵¹
Loss of appetite	<ul style="list-style-type: none"> · Eat small, frequent meals (5–6 meals/day) · Eat nutritious snacks · Drink plenty of liquids · Take light exercise including walks before meals to stimulate appetite · Have family or friends assist with the preparation of food · Add flavour to drinks and food
Mouth ulcer	<ul style="list-style-type: none"> · Avoid citrus fruits, and acidic and spicy foods · Eat food at room temperature · Eat soft and moist food · Avoid caffeine and alcohol
Dry mouth and Sore Throat	<ul style="list-style-type: none"> · Rinse with slightly salty warm water: use clean boiled water. · Clean mouth frequently · Use cinnamon tea as a mouthwash (1/4 teaspoon of cinnamon to one cup of boiling water; cover and allow to cool).
Nausea and vomiting	<ul style="list-style-type: none"> · Eat small, frequent meals · Avoid being on an empty stomach as this makes the nausea worse · Eat bland food · Avoid food with strong or unpleasant odours · Drink plenty of liquids · Rest and relax after meals · Avoid lying down immediately after eating · Avoid coffee and alcohol
Diarrhea	<ul style="list-style-type: none"> · Continue to eat food, as much as tolerated. · Drink lots of fluids: more than 8 cups a day to prevent dehydration · Drink clean boiled water, +/- Oral Rehydration Solution (ORS) · Eat ripe yellow bananas, cooked fruit; avoid unripe fruits. · Peel and cook vegetables rather than eating them raw. · Make Rice soup: (boil 1 cup of rice in 5 cups of clean water with a bit of salt for one hour), at both the rice and the rice water, but also continue to eat food as well. · Avoid milk products, for a day, and then put it back in gradually to about two cups in the day.
Constipation	<ul style="list-style-type: none"> · Eat fibre-rich food · Take light exercise and activity · Drink plenty of water

⁵¹ Adapted from *Management of HIV infection and antiretroviral therapy in adults and adolescents*. WHO/SEARO, 2007.

33.5 Overweight: assessment and management

- Patients are more likely to become overweight once OI are successfully treated and HIV infection is controlled on ART.
- Overweight and particularly obese patients are at higher risk of diabetes, hypertension and cardiovascular disease (CVD) including ischemic heart and periphero-vascular disease, cerebrovascular disease and chronic kidney disease.

Assessment:

If the patient is overweight → perform a further history and examination to assess:

- Other risk factors for chronic disease
 - Past history of gestational diabetes, family history of diabetes or CVD,
 - Smoking, alcohol
- Blood pressure, cardiovascular / respiratory examination
- Investigations:
 - Diabetes check, serum cholesterol and triglyceride.

Management:

- Ensure that the patient understands that they will need to *reduce* their caloric intake, and pay attention to other risk factors, to stay healthy.
- Stop smoking (see Figure 35-1 WHO Counselling tool to assist individuals to quit smoking)
- Reduce alcohol (has a high calorie content)
- Reduce food - caloric intake, particularly oils/fats and sugars (eliminate soft drinks), but otherwise a healthy balanced diet with protein and vegetables. (see Table 34-1)
- Undertake daily exercise – e.g. brisk walking at least 30 min /day
- If *hypertension* (>140/80) – see Chapter 36. Hypertension
- If *diabetes or glucose intolerant* – see Chapter 37. Type 2 Diabetes
- Monitor weight, BMI, waist circumference, and discuss nutrition at each visit.

33.6 Normal weight – at initial or follow up visits

- Ensure that the patient and the family understand that they need to maintain their food intake to get healthy, and that rice porridge alone is inadequate.
- Check the patient understands about food and water safety.
- The diet should include regular healthy foods with a normal balance of fats, protein and carbohydrates (see Table 34-1)
- Monitor weight at each visit
- If undesired weight loss, refer to section in this chapter on 33.4: Underweight or loss of weight: assessment and management.
- If undesired weight gains refer to section in this chapter on: 33.5 Overweight: assessment and management

33.7 Food and medications

Always check whether there are any requirements regarding the timing of food with each medication prescribed. (eg TDF should be given with food, cotrimoxazole is best with food).

33.8 Nutrition and Pregnancy

Birth weight is one of the most important determinants of a child's survival and is highly influenced by the mother's nutritional status before and during pregnancy. Low pre-pregnancy weight and inadequate weight gain during pregnancy are the most significant predictors of intrauterine growth retardation (IUGR) and low birth weight (LBW).

Women who begin their pregnancy with a BMI < 18.5 must increase their daily energy intake to gain at least 12.5 kg during pregnancy. Refer to the MCH for nutrition services for pregnant women including provision of iron and micronutrient supplements.

33.9 Food handling and safety

- Wash your hands thoroughly before and after cooking.
- Use clean or boiled water.
- Keep kitchen surfaces clean.
- Cook food thoroughly.
- Eat cooked food immediately.
- Store food in a clean, cool place.
- Re-heat cooked food thoroughly.
- Avoid contact between raw and cooked food.
- Protect food from rodents, insects and animals.
- Do not eat raw eggs.
- Do not eat food that has not been thoroughly cooked, especially meat and chicken.
- Do not drink unboiled water or juices made with unboiled water.

Chapter34. Chronic non- communicable diseases in PLHIV

34.1 Key points

- With effective ART, PLHIV live longer, and uncontrolled VL, immunodeficiency and opportunistic infections are less of a problem.
- However HIV itself, long term ARV, and advancing age puts PLHIV at increased risk of NCDs.
- PLHIV are at increased risk of developing a range of metabolic and non-communicable diseases (NCDs), including cardiovascular disease, diabetes, chronic lung disease and cancers.
- It is important that the HIV clinician is aware of NCD, and regularly addresses issues of 1st and 2nd prevention with PLHIV during consultations.
- In addition PLHIV on long-term ART should be screened for NCD (according to this guideline) and referred for appropriate care.
- The HIV clinician needs to check for any drug interactions with ART and medications prescribed either within or outside the HIV clinic, and to monitor for toxicity on an ongoing basis.

34.2 NCD prevention: Healthy diet and lifestyle

- All patients should be advised to pay attention to healthy diet and lifestyle to reduce their risk of metabolic and non-communicable diseases.⁵²

Table 34-1 Recommendations for prevention and management of NCD

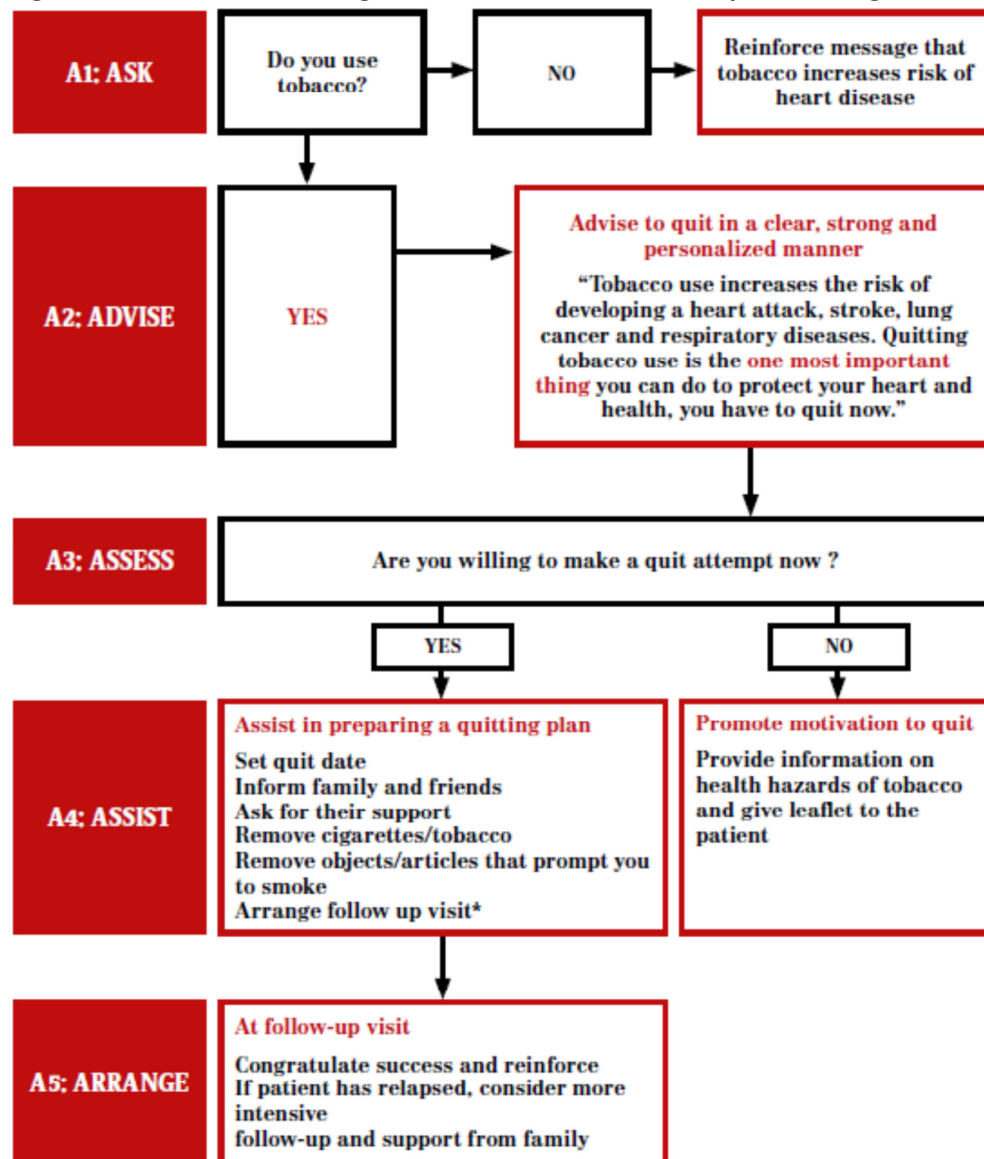
The emphasis on diet and lifestyle modification will vary depending on whether the patient is under/over/normal weight and other risk factors, HT, diabetes etc.
<p>Diet: most people need to pay attention to eat</p> <ul style="list-style-type: none"> • More protein (tofu, beans, chicken, fish) • More vegetables (5 x 400 – 500gm servings vegetables and fruit per day) • Less fat (avoid deep fried foods, cut/ skin the fat of meats e.g. pork /chicken) • Less sugar (soft drinks, sweets, condensed milk). • Less salt (prohok, MSG, fish sauce, soy sauce and salted meat or fish) instead use other flavours (e.g. lemon juice, pepper) and herbs. • Minimize processed foods (usually high in salt, fat, sugar)
Weight: Maintain BMI between 18.5 – 22.9
Alcohol: maximum of 2 standard drinks per day, ≥ 2 alcohol free days.
No smoking
Exercise 30 minutes per day (e.g. brisk walking) (more if need to lose weight)

⁵² Prevention and Control of Noncommunicable Diseases: Guidelines for primary health care in low-resource settings. WHO. 2012.

Chapter35. Smoking cessation

- Clinicians should encourage, and provide practical advice to patients to quit smoking.
- The following tool can assist clinicians to help patients give up smoking.

Figure 35-1 WHO Counselling tool to assist individuals to quit smoking⁵³



* Ideally second follow-up visit is recommended within the same month and every month thereafter for 4 months and evaluation after 1 year. If not feasible, reinforce counseling whenever the patient is seen for blood pressure monitoring.

⁵³ Implementation tools: package of essential non-communicable (PEN) disease interventions for primary health care in low-resource settings. WHO. 2013.

Chapter 36. Hypertension

36.1 Screening, and diagnosis hypertension in PLHIV

All patients should have blood pressure taken at each visit.

- If BP > 140/90 on more than one occasion = hypertension.

36.2 Management of hypertension

The Cambodian Clinical Practice Guidelines detail the management of hypertension.⁵⁴

Hypertension requires both pharmacological and non-pharmacological management.

1. Patients should be advised how to reduce BP and risk of CVD:
 - Weight loss if overweight
 - Healthy diet and lifestyle as detailed in Table 34-1, with an emphasis on reduced sodium intake.
 - If mild hypertension e.g. up to SBP 159 + / or DBP 99 try non – pharmacological measures for 3 – 6 months prior to considering antihypertensive therapy.
- Evaluate for other conditions associated with HT:
 - Cardiovascular disease (history, examination, ECG if available)
 - Cerebrovascular disease – stroke, dementia
 - Perform the following laboratory tests:
 - Diabetes – fasting glucose
 - Serum lipids – total cholesterol, HDL cholesterol, triglycerides
 - Renal disease – serum creatinine, potassium, sodium. Urinalysis.
2. Pharmacological management

Table 36-1 Cambodian guidelines for commencement of antihypertensive medicine

Hypertensive Patient	Initiate pharmacologic treatment	BP goal
≥ 60 years*	SBP ≥ 150 mm Hg or DBP ≥ 90 mm Hg	SBP < 150 mm Hg and DBP < 90 mm Hg
< 60 years		
18-59 years	SBP ≥ 140 mm Hg DBP ≥ 90 mm Hg	SBP < 140 mm Hg DBP < 90 mm Hg
≥ 18 years with		
CKD or/and Diabetes	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	SBP < 140 mm Hg and DBP < 90 mm Hg

⁵⁴ MINISTRY OF HEALTH CLINICAL PRACTICE GUIDELINES Arterial Hypertension in adult. A continuum of care for Hypertensive Patients both with and without complications at NCD clinics/RHs Bureau for NCD Prevention & Control DEPARTMENT OF PREVENTIVE MEDICINE 2015

- The Cambodian Clinical Practice Guidelines recommend the following initial regimens:
 - Patients > 55 years old - Thiazide diuretic
 - Patients < 55 years old – Angiotensin converting enzyme inhibitor (ACE I)
 - Diabetic or kidney disease (any age) - ACE I
- If the BP is not controlled to the target level a second agent should be added. Acceptable combinations are:
 - Thiazide diuretic + ACE I
 - Thiazide diuretic + calcium channel blocker
 - ACE I + calcium channel blocker
- Examples of drug doses:
 - ACE I; Enalapril – start 5mg OD - increase up to max 20mg OD
 - ACE I; Captopril – start 12.5mg BID – increase to max 150mg TID
 - Thiazide; Hydrochlorothiazide - start 12.5mg – increase to max 50mg
 - Thiazide; Indapamide - start 1.25mg – increase to max 2.5mg
 - B blocker; Atenolol – start 25mg OD - increase to max 50mg OD
 - B blocker; Metoprolol – start 25mg BID – increase to max 100mg BID
 - Calcium channel blocker; - Amlodipine start 2.5mg OD – increase to max 10mg
- Follow up after starting antihypertensive medication every 2 weeks, until stable.

Drug interactions with antihypertensive medicines and ART ⁵⁵

Table 36-2 Antihypertensive drug interactions with ARV

Drug	Interaction with ARV
ACEI : enalapril, captopril, ramipril;	No described interactions with NNRTI, NRTI or PI.
Calcium channel blockers: including amlodipine, nifedipine;	Levels of CCB are potentially <i>decreased</i> by NNRTI, and <i>increased</i> by PI → careful monitoring of BP and dose adjust.
Beta blockers: atenolol, metoprolol, propranolol;	Potential interaction as both may prolong PR interval→ careful monitoring of BP, and dose adjust, consider ECG.
ARB (angiotensin 2 receptor blockers)	Losartan levels potentially <i>decreased</i> by NNRTI, and <i>increased</i> by PI → careful monitoring of BP and dose adjust

⁵⁵ <http://www.hiv-druginteractions.org/>

Chapter 37. Type 2 Diabetes

The Cambodian Clinical Practice Guidelines detail diagnosis and management of diabetes.⁵⁶

37.1 Screening for Diabetes in PLHIV

Individuals who are at higher risk and should be screened for type 2 diabetes include;

- Overweight (BMI > 23, +/- or waist circumference in men \geq 85cm and in women \geq 80cm)
- Family history of diabetes
- Hypertension (BP > 140/90)
- Dyslipidaemia
- History of stroke or ischaemic heart disease
- Women with history of gestational diabetes or have given birth to a large baby (> 3.5 kg)
- Age over 35
- Chronic renal impairment
- Glycosuria on urine dipstick.

PLHIV commencing Protease Inhibitor containing ART

PLHIV should be screened for diabetes prior to starting a PI, as these can cause insulin resistance. Follow up screening at 3 months after commencing PI and every 12 months.

37.2 Diagnosis of Type 2 Diabetes and impaired glucose tolerance

Table 37-1 Diagnostic criteria for Diabetes and impaired glucose tolerance

WHO diagnostic criteria for diabetes

	Glucose concentration, mmol/l (mg/dl)		
	Venous	Whole blood Capillary	Plasma venous
Diabetes mellitus			
Fasting	\geq 6.1 (110)	\geq 6.1 (110)	\geq 7.0 (126)
or			
2-hour post glucose load or both	\geq 10.0 (180)	\geq 11.1 (200)	\geq 11.1 (200)
Impaired glucose tolerance			
Fasting concentration (if measured) and	\leq 6.1 (110)	\leq 6.1 (110)	\leq 7.1 (126)
2 hours after glucose load	6.7-9.9 (120-179)	7.8-11.0 (140-199)	7.8-11.0 (140-199)
Fasting hyperglycaemia			
Fasting	5.6-6.0 (100-109)	5.6-6.0 (100-109)	6.1-6.9 (110-125)
2 hours (if measured)	\leq 6.7 (120)	\leq 7.8 (140)	\leq 7.8 (140)

Notes about testing for diabetes: Venous plasma is the preferred test however the blood must be tested within the hour, or collect in sodium fluoride tube to inhibit glycolysis and place the tube in ice-water until analysis. Corresponding capillary values are similar for fasting samples and differ only for the 2 hours.

⁵⁶ CAMBODIAN MINISTRY OF HEALTH CLINICAL PRACTICE GUIDELINES. TYPE 2 DIABETES. A continuum of care for diabetes patients both with and without complications at NCD clinics/RHs Bureau for NCD Prevention & Control DEPARTMENT OF PREVENTIVE MEDICINE 2015

37.3 Management of impaired glucose tolerance

- Weight loss if overweight
- Healthy diet and lifestyle as detailed in Table 34-1 .
- Follow up testing in 12 months.

37.4 Management of Type 2 Diabetes

- See the Cambodian National guidelines for comprehensive guidance on management of diabetes⁵⁷
- If available the patient should be referred to a diabetes clinic.

Diabetes requires both pharmacological and non-pharmacological management:

1. Non- pharmacological measures to reduce risk of complications of diabetes:

- Healthy diet and lifestyle as detailed in Table 34-1 .
- Modification of the diet → diabetic diet. Most importantly reduce the portion size of carbohydrate, including rice. (see Figure 48-1 Food pyramid for Diabetes Type 2).

Patients should be evaluated for other conditions associated with diabetes:

- Weight, BMI, (see
- Table 33-1 WHO BMI Classification of adult underweight, overweight and obesity) *and* Waist circumference (overweight = men ≥85 cm, women ≥ 80cm)
- Hypertension > 140/90 or > 130/80 if accompanied by proteinuria
- Cardiovascular disease (history, examination, ECG if available)
- Cerebrovascular disease – stroke, dementia.
- Renal disease - serum creatinine, potassium, sodium. Urinalysis.
- Hyperlipidemia -serum lipids
- Detailed foot examination :
 - Vascular supply; pulses, capillary return
 - Neurological; sensation, ankle reflexes
- Visual acuity and fundoscopy for cataracts and diabetic retinopathy.

2. Pharmacological management of diabetes as recommended by the NCD includes

- First line: Metformin 500 – 2000mg divided into 2 doses with meals
- Alternative first line: Gliclazide 40 – 320mg divided into 2 doses with meals
- Second line: Metformin + sulfonylurea
- Third line: basal or premix insulin + oral agent, or basal + meal time insulin

Drug interactions between diabetes medication and ART ⁵⁸

Table 37-2 Diabetes drug interactions with ARV

Drug	Interaction with ARV
Gliclazide and Glimepiride;	Levels potentially <i>decreased</i> by PI, and <i>increased</i> by EVF. Careful monitoring and dose adjustment of the gliclazide may be required.
Glibenclamide	Levels potentially <i>decreased</i> by EFV and NVP and <i>increased</i> by PI.
Metformin and insulin	Not known to interact with NNRTI, NRTI PI, ART, however dolutegravir could potentially increase metformin concentrations.

⁵⁷ CAMBODIAN MINISTRY OF HEALTH CLINICAL PRACTICE GUIDELINES. TYPE 2 DIABETES. A continuum of care for diabetes patients both with and without complications at NCD clinics/RHs Bureau for NCD Prevention & Control DEPARTMENT OF PREVENTIVE MEDICINE 2015

⁵⁸ <http://www.hiv-druginteractions.org/>

Chapter38. Hyperlipidaemia

38.1 Screening for hyperlipidemia in PLHIV

- The risk of cardiovascular disease is increased with elevated low – density lipoprotein cholesterol (LDL – C) and /or hypertriglyceridemia, especially if associated with reduced high-density lipoprotein levels (HDL-C).
- Lipid related risk for CVD is not reflected in the Total Cholesterol (TC) measurement alone, as this is comprised of LDL-C and HDL – C, (high HDL-C is cardio protective).
- Triglyceride levels > 10 mmol/l increase the risk of pancreatitis
- PLHIV who are taking PI based ART regimens are at risk of hyperlipidaemia, although less so with ATV/r compared to LPV/r.
- Indications for testing serum lipids, and thresholds for treatment with lipid lowering drugs depend on the patients overall cardiovascular risk. In high risk situations statins are recommended regardless of serum lipid measurements. Eg *all* patients who have a myocardial infarct or stroke benefit if commenced on a statin, unless contraindicated.

PLHIV commencing PI containing ART

- All PLHIV should have fasting serum lipids checked prior to starting a PI containing ART regimen (usually 2nd line) and monitored after 3 months and then 12 monthly, as PI drugs can cause hyperlipidaemia.
- PLHIV may have other indications for serum lipid levels – eg diabetes.

38.2 Management of hyperlipidaemia

Hyperlipidaemia requires both pharmacological and non-pharmacological management.

1. Non pharmacological management

- Follow Table 34-1 which all impact on lipid levels directly or associated risk factors for NCD
- Reduce saturated fats (animal fats), replace with mono /polyunsaturated fats.
- Optimize diabetic control.

2. Pharmacological management

- Change from LPV/r to ATV/r (unless contraindicated)
 - If predominantly raised LDL-C
 - Statin
 - Predominantly raised TG (>10mmol/l), especially if with a low HDL-C
 - Fibrate +/- fish oil
- **Target levels on therapy** (increase drugs within max safe doses to achieve the following)
 - Total Cholesterol < 4.0 mmol/L
 - HDL –C ≥ 1.0 mmol/L
 - LDL-C < 2mmol/L
 - TG < 2mmol/L

38.2.1 Drug interactions between lipid lowering medications and ART

Table 38-1 Lipid lowering drugs interactions with each other and ARV

<p>Statins</p> <ul style="list-style-type: none">• Simvastatin and lovastatin are <i>contraindicated</i> with PI containing ART as there is a high risk of rhabdomyolysis.• Other statins may be used with PI containing ART but at lower doses:<ul style="list-style-type: none">• Atorvastatin start 10mg → max dose with PI ART = 40mg• Pravastatin start 20mg → max dose with PI ART = 40mg• Rosuvastatin start 5mg → max dose with PI ART = 20mg
<ul style="list-style-type: none">• Fibrates<ul style="list-style-type: none">• Gemfibrozil :<ul style="list-style-type: none">• Drug levels may be lowered by PI ART• Do not use in combination with a statin due to the risk of myositis• Fenofibrate<ul style="list-style-type: none">• Monitor ALT/CK if in combination with statins due to increased risk of side effects
<ul style="list-style-type: none">• Fish oils are not known to have interaction with ART

38.2.2 Monitoring for adverse effects

Lipid lowering drugs can cause liver dysfunction and myopathy

- Patients should be warned of the symptoms of myopathy (pain, stiffness, weakness) and liver inflammation (abdominal pain, vomiting)
 - Check ALT and creatinine kinase (CK) at baseline
 - Check CK and ALT again if any symptoms
 - Stop drug if persistent muscle pain or weakness, esp. if CK > 500 U/L
 - Stop drug if CK > 1000 U/L with no symptoms.
 - Stop drug if ALT increases to > 3 x ULN.

Chapter 39 Osteoporosis

- Osteoporosis is characterized by reduced bone strength, which predisposes to an increased risk of fracture.
- Osteopenia is characterized by or “bone loss” and is a precursor to osteoporosis.

39.1 Risk factors for osteoporosis

- Age>40, female, low BMO, physical inactive, smoking, IDU.
- Corticosteroid use.
- HIV infection, particularly advance HIV.
- Tenofovir ART leads to initial bone loss that usually stabilizes within few years.
- Diabetes, hyperthyroidism, HCV and chronic liver disease.
- Other chronic medical conditions, myeloma, endocrine abnormalities, etc.

39.2 Assessment

- The WHO Fracture Risk Assessment Tool (FRAX) is an online calculator developed to predict 10-year probability of fracture based on clinical risk factors (age, BMI etc.) and does not require a DXA (bone mineral density) scan.⁵⁹
- Loss of height can occur from severe bone loss due to loss of vertebral body height.

39.3 Prevention and management of osteoporosis and fracture

- Table 34-1 , details important measures for prevention and management of osteoporosis. The emphasis should be placed on stopping smoking, a balanced diet including adequate calcium intake, adequate vitamin D intake, maintaining healthy weight range, weight bearing exercise (e.g. walking), and minimizing alcohol intake.
- Avoid long courses of corticosteroids unless absolutely necessary, and use the lowest effective dose possible.
- If the patient has an osteoporotic fracture (wrist, hip, vertebral, as a result of minimal trauma), consider switching from TDF to another agent if feasible.

⁵⁹ The online calculator is country specific, the closest in terms of patient characteristics would be the Thai version available at <http://www.shef.ac.uk/FRAX/tool.aspx?country=57>

Chapter40. Kidney disease

Multiple factors contribute to kidney disease in PLHIV, and kidney injury is often diagnosed late because patients are either asymptomatic or have non-specific symptoms.

40.1 Investigation of Kidney disease

Table 40-1 Tests used in the investigation of kidney function

Urine tests
Urine dipstick, includes; <ul style="list-style-type: none"> • Glucose: positive in poorly controlled diabetes, and in TDF renal tubular toxicity • Nitrites and leukocytes: positive in urinary tract infections (UTI) • Blood: if positive with nitrites + leukocytes = UTI, if not consider nephritis (→ check BP) • Protein: positive in many kinds of kidney injury, including: <ul style="list-style-type: none"> • UTI (with nitrites and leukocytes) • Nephritis (with blood) • Nephritic syndrome – often ≥ 2+ • Acute or chronic tubular damage (e.g. from TDF)
Urine albumin / creatinine ratio (ACR): <ul style="list-style-type: none"> • Elevated in diabetic nephropathy (often negative dipstick protein and creatinine +/- N).
Urine microscopy <ul style="list-style-type: none"> • Leukocytes, red blood cells, and organisms (UTI) <ul style="list-style-type: none"> • If available perform culture for identification and antimicrobial sensitivity • Red cell morphology; <ul style="list-style-type: none"> • Dysmorphic red blood cells; originate from kidney (nephritis). • Normal red blood cells; come from the lower urinary tract.
Blood tests
Serum Creatinine <ul style="list-style-type: none"> • Creatinine is a natural chemical excreted in the urine. • Serum creatinine rises when it is not cleared properly and usually indicates kidney injury.
<ul style="list-style-type: none"> • Creatinine clearance / estimated Glomerular Filtration Rate (eGFR) <ul style="list-style-type: none"> • A more accurate assessment of kidney function than serum creatinine. • The eGFR drops in kidney injury (Normal eGFR = > 90ml/min) • The eGFR may be calculated by the Cockcroft – Gault equation: $\text{eGFR ml/min} = (140 - \text{age}) \times \text{weight (kg)} / \text{serum creatinine } (\mu\text{mol/l}) \text{ (male)}$ $\text{eGFR ml/min} = (140 - \text{age}) \times \text{weight (kg)} \times 0.85 / \text{serum creatinine } (\mu\text{mol/l}) \text{ (female)}$
<ul style="list-style-type: none"> • Serum electrolytes: potassium, sodium, phosphate, bicarbonate, urate • CBC: normocytic anaemia (MCV normal) is common in chronic kidney injury.
Renal tract ultrasound
<ul style="list-style-type: none"> • Chronic kidney disease usually → small kidneys (<9cm) • Acute kidney disease may → large kidneys (>12 cm) e.g. HIVAN • Renal tract obstruction <ul style="list-style-type: none"> • Bilateral ureteric obstruction (often caused by TB lymphadenopathy) • Lower renal tract obstruction – e.g. prostatic enlargement

See algorithms for the investigation of abnormal creatinine, and urine dipstick:

- Figure 47-1 Creatinine evaluation algorithm
- Figure 47-2 Urine dipstick algorithm.

40.2 Acute kidney injury

40.2.1 Pre-renal acute kidney injury

Usually results from an episode of hypotension, due to:

- Sepsis
 - Volume loss e.g. dehydration due to diarrhoea
 - Vascular cause e.g. myocardial infarct
- **Diagnosis:** clinical assessment of hydration status, evidence of sepsis.
 - **Management:**
 - Rehydration, usually requiring IV fluids
 - Treat the cause of sepsis if present
 - Avoid nephrotoxic drugs (NSAIDs, aminoglycosides)
 - If renal function doesn't improve quickly
 - Investigate for additional cause of renal impairment
 - Adjust renally excreted drug doses according to creatinine clearance (see Table 47-1 Drug dose adjustments in patients with renal failure)
 - Monitor the renal function for changes in eGFR, as to whether further drug dose adjustments are required.

40.2.2 Post renal acute kidney injury

Obstruction (e.g. TB ureteric obstruction)

- Diagnosis: an ultrasound is needed to confirm ureteric obstruction and hydronephrosis.
- If ultrasound is not available transfer the patient to a facility where it is, however if this is not possible and other clinical findings suggest TB, then it is reasonable to commence TB treatment and monitor the renal function.

40.2.3 Intrinsic kidney injury

Intrinsic causes of renal failure are many, drug reactions are important:

- Tenofovir (TDF) toxicity (see below)
- Cotrimoxazole and rifampicin toxicity
 - Interstitial nephritis – patients present with flu like symptoms, flank pain, fever.
 - Rifampicin toxicity occurs more commonly when stopped and then restarted.

40.3 Chronic kidney disease

40.3.1 Chronic kidney disease caused by hypertension + /or diabetes

- Diagnosis is by consistent history and laboratory evidence
 - Raised creatinine over time, e.g. months
 - Proteinuria on dipstick, raised ACR (if available)
 - Mild anaemia (normocytic MCV)
 - Small kidneys on ultrasound (if available)

Management

- Stop smoking
- Optimize treatment of diabetes and HT
- Include ACE I in regimen e.g. enalapril 2.5mg BD (check BP and potassium)
- Avoid nephrotoxic drugs particularly NSAIDS
- Adjust renally excreted drug doses according to creatinine clearance (see Table 47-1 Drug dose adjustments in patients with renal failure)
- Monitor for changes in eGFR which may require further dose adjustments over time
- Monitor creatinine and if Cr > 250 refer to specialist renal service if available.

40.3.2 HIV associated nephropathy (HIV AN)

- HIV AN is due to direct effect of HIV on the kidney. It is more often associated with advanced HIV and low CD4, however may occur at higher CD4 counts.
- HIV AN is a WHO stage 4 condition
- HIV AN may progress quickly over months to end stage renal disease (ESRD).
- **Diagnosis:**
 - $\geq 2+$ proteinuria, creatinine is usually (but not always) elevated.
 - Hypertension and oedema are rare, and if present look for another cause.
 - Diagnosis is ideally confirmed by biopsy; however this is often not available.
- **Management:**
 - Start ART as soon as possible
 - Treat proteinuria with enalapril 2.5mg BD - check BP and potassium
 - Monitor proteinuria and creatinine 3 monthly x 2, then 6 monthly
 - Avoid nephrotoxic drugs, and adjust renally excreted drugs according to eGFR (see Table 47-1 Drug dose adjustments in patients with renal failure)
 - Monitor the renal function for changes in eGFR which may require further dose adjustments.

Chapter41. Recreational drug use

- In Cambodia people who inject drugs (PWID) and people who use drugs (PWUD) have higher rates of HIV infection than the general population (see Table 43-2 Cambodian HIV prevalence estimates by demographic)
- PLHIV who use drugs, including excessive alcohol, marijuana, amphetamines (yama), and opioid can experience a range of issues that will adversely affect their health.
- Intoxication, withdrawal and overdose can all have adverse outcomes for the patient.
- Importantly drug use can interfere with treatment (including ART) adherence, and adequate nutritional intake.
- Injecting drug use risks blood borne virus acquisition such as hepatitis B and C, injection site infections, septicaemia and bacterial endocarditis.
- Drug use may result in impaired judgment and behaviours that increase risk of HIV transmission.
- Patients should be provided with education regarding the risks associated with drug use, about harm reduction (including safe disposal of injecting equipment), and referred to partners involved in harm reduction and if relevant, methadone replacement therapy. For Methadone Maintenance Therapy for Injection Drug User, please refer patient to Methadone Maintenance Therapy (MMT1) clinic at Khmer Soviet Friendship Hospital and MMT2 clinic at Mean Chey RH in Khan Chbar Ampov (to be functioned in 2016).

Chapter42. Mental Health

- PLHIV are vulnerable to range of mental health issues including depression, anxiety, substance abuse, and other psychiatric conditions.
- PLHIV are also at risk developing HIV related dementia.
- These may interfere with treatment (including ART) adherence, and treatments may involve potential side effects and drug interactions.
- Efavirenz may have side effects, which exacerbate mental health problems so consider changing this drug if it is implicated.
- See: Annex 49 Mental Health: Figure 49-1 Common Presentations of Mental Health conditions
- For further information see the mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health setting. Mental Health Gap Action Programme 2010. World Health Organization available at: <http://www.paho.org/mhgap/en/> .

42.1 Depression

Depression is very common and is under-diagnosed in PLHIV. It can contribute to loss to follow-up and adherence to ART.

42.1.1 Clinical presentation of depression

- Persistent low mood, poor motivation, poor concentration, lack of energy

- Tearful or agitated
- Sleep disturbance
- Low self-esteem, lack of self-care/ personal hygiene
- Changes in appetite and weight.
- Alcohol or other drug abuse.
- Decreased ability to function on a day-to-day basis

42.1.2 Screening for depression

Table 42-1 Screening questions for Depression

1. During the past month, have you felt like you were losing interest or pleasure in doing things?
2. Have you felt down, depressed or helpless?
 - If a patient appears depressed, it is important to assess their risk for suicide:
 - Have you ever thought about giving up?
 - Have you ever thought about ending your life?
 - If yes, ask about what circumstances have they thought of this, and if they have any thoughts or plans to hurt themselves?

42.1.3 Assessment and management of depression

- Rule out an underlying medical cause for the depression (e.g. check TFT if available).
- Look for any potential cause: explore emotional and social issues.
- Refer to a counsellor, support group, or mental health services as appropriate.
- If severe, an assessment for the need for antidepressant medication should be made and commenced within 1 week

Drug treatment

Many antidepressants interact with ART drugs so always check for drug interactions, if commencing or your patient is already taking an antidepressant⁶⁰.

Table 42-2 Psychiatric drug interactions with ART

Psychiatric drug	NRTI	NNRTI	PI
Diazepam (oral)	OK	EFV potentially ↓ exposure to diazepam	PI potentially ↑ exposure to diazepam
Midazolam (IMI)	OK	Contraindicated as EFV ↑↑ exposure to midazolam	Caution as PI ↑ exposure to midazolam
Haloperidol (oral /IMI)	OK	EFV potentially ↓ exposure to haloperidol	Caution as PI ↑ exposure to amitryptaline/SSRI/ haloperidol, All cause QT prolongation. Avoid if possible, otherwise use lower dose of amitryptaline/SSRI/ haloperidol and monitor ECG.
Amitriptyline	OK	OK	
SSRI – fluoxetine, sertraline	OK	OK	
SSRI – sertraline, venlafaxine, citalopram	OK	EFV potentially ↓ levels of SSRI	

⁶⁰ www.hiv-druginteractions.org/

42.2 The confused patient: psychosis vs medical illness?

If a patient is confused it is very important to distinguish if they have a delirium due to a treatable medical cause, or a primary psychiatric illness.

- A delirium is characterized by fluctuating global cognitive impairment associated with behavioural abnormalities.

Table 42-3 Distinguishing medical from psychiatric illness⁶¹

	Delirium secondary to medical causes	Psychosis as asymptom of psychiatric illness
Cause	Medical: Infection/hypoxia/hypoglycaemia/ intracerebral pathology/ hepatic encephalopathy / drug related	Psychiatric: Schizophrenia, Mood disorders with psychotic features
Onset	Onset over hours or days.	More gradual onset
	Fluctuating mental status.	Not fluctuating
	Loss of normal sleep / wake cycle. Disturbance of consciousness. Agitation, tremor	No disturbance of consciousness Delusions
Orientation	Disorientated to time, person, place	Usually orientated
Hallucinations	Visual hallucinations	Hallucinations – usually auditory
Memory	Short term memory loss	No memory loss
Attention	Difficulty paying attention	Attention ok
History	Unusual to have history of same	Often history of previous episodes

Assessment and management of delirium

- History (including drug use) and full physical examination, to look for a medical cause.
- Review medications and stop any that may be exacerbating the problem.
- Perform blood glucose level, and any other relevant investigations.
- Consider LP to rule out CNS infection (e.g. TB, cryptococcus).
- Check oxygen saturation (if machine available).
- If alcohol withdrawal is suspected, give IVI thiamine (prior to IVI glucose).
- Manage the patient in a quiet room, have family with them.
- Explain clearly to the patient what is going on, and repeat as necessary.
- Delirium may persist for some time after resolution of the medical precipitant; advise the family to keep the patient safe if discharged.

Management of psychosis:

- Refer to mental health service

⁶¹ Adapted from MSF HIV/TB Clinical guide 2015.

42.3 Management of a Behavioural Emergency

Occasionally a situation occurs where an individual is highly agitated, and is behaving in a way that puts themselves and others at risk.

- Try to maintain a calm quiet environment, enlist the support of helpful family or friends, and remove others that may be contributing to the individual's agitation.
- Talk to the patient calmly and clearly, and explain clearly what is going on.

For urgent (temporary) management of agitation / aggression while arranging to transfer a patient to hospital, antipsychotic and sedative medication may be considered when non-pharmacological measures fail.

Consider drug interactions prior to drug administration (see Table 42-2 Psychiatric drug interaction with ART)

Many antidepressants interact with ART drugs so always check for drug interactions, if commencing or your patients is already taking an antidepressant.

Use oral medication if possible: (take time to gently persuade the patient, enlist the help of a trusted family member or friend)

- 1st line: Diazepam 5 -10mg orally, repeats every 2 -6 hours according to clinical response up to a maximum of 60mg in 24 hours.
- 2nd line: Haloperidol 0.5 -2mg orally, repeat every 2 hours according to clinical response, up to a maximum of 5-10mg in 24 hours.

If oral route of administration is not possible:

- Haloperidol 5 – 10mg IMI.

Monitoring

- Take care not to over-sedate, be aware of cumulative and delayed effects as a result of multiple dosing, and synergism between agents.
- Monitor closely – every 15 minutes for
 - Reduced conscious state
 - Hypotension, respiratory depression, airway obstruction, aspiration
 - Potential injuries to patient or others

Transfer promptly to hospital for further investigation and management.

Post exposure prophylaxis

Chapter 43. Post exposure prophylaxis

Post exposure prophylaxis (PEP) refers to taking ARV by an HIV negative individual, in order to prevent acquisition of HIV, after a high-risk exposure to an HIV positive (or HIV unknown) source.

- PEP consists of a regimen of 3 ARV agents that must be started as soon as possible after exposure, and continued daily for 28 days post exposure.
- PEP may be considered after occupational injury such as a needle-stick injury in health care workers (HCW), or after sexual exposure particularly to victims of sexual assault.
- Any prescription of post-exposure prophylaxis should follow consent based on an understanding of the risks and benefits, including discussion of possible side effects and the importance of full adherence to post-exposure prophylaxis.

43.1 Risks of HIV transmission

Body fluids that pose a risk of HIV infection:

- Blood, blood-stained saliva, breast-milk, genital secretions and cerebrospinal, amniotic, rectal, peritoneal, synovial, pericardial or pleural fluids

Body fluids that do not pose a significant risk of HIV infection, and therefore do not require PEP

- Tears, non-blood stained saliva, urine and sweat.

Table 43-1. Routes of HIV transmission and average transmission risk per episode

Exposure from an HIV infected source	Estimated risk of HIV transmission per episode ⁶²
Sexual exposure (via blood, semen, vaginal fluids)	
• Insertive vaginal intercourse (female to male transmission)	1/2500 (0.04%)
• Receptive vaginal intercourse (male to female transmission)	1/1250 (0.08%)
• Receptive anal intercourse (male to male (MSM) or male to female transmission) without withdrawal prior to ejaculation	1/70 (1.43%)
• Receptive anal intercourse with withdrawal prior to ejaculation	1/155 (0.64%)
• Insertive anal intercourse, uncircumcised (MSM)	1/160 (0.62%)
• Insertive anal intercourse, circumcised (MSM)	1/900 (0.1%)
• Oral sex: insertive or receptive (male or female)	Extremely low
Blood exposure	
• Intravenous Drug Use: contaminated injecting equipment	1/125
• Occupational needle stick (NSI) or other sharps exposure	1/440
• Blood transfusion	1/1.1 (90%)
Other exposure	
• Mucus membrane or non-intact skin exposure	< 1/1000

⁶² Post-Exposure Prophylaxis after Non-Occupational and Occupational exposure to HIV National Guidelines. ASHM 2013. Available at www.ashm.org.au.

Factors that increase the risk of HIV transmission

- High HIV Viral load in the source individual - when seroconverting or advanced disease
- Parenteral transmission:
 - Penetrating injury with a hollow bore needle, +/- or direct injection into vein or artery.
- **Sexual transmission:**
 - Source or exposed individual has an STI, particularly genital ulcer disease and gonococcus infection.
 - Breach in genital mucosa (trauma, infection).
 - Breach in oral mucosa in the case of oral sex.
 - Uncircumcised HIV negative male in the case of insertive vaginal or anal sex.

To estimate the risk from an exposure from an unknown source:

Risk of transmission = risk per exposure x risk of source being HIV positive (prevalence)

Table 43-2 Cambodian HIV prevalence estimates by demographic

Population / subpopulation	Prevalence
General adult population	0.6%
Injecting drug users (PWID)	24.8%
Non injecting drug users (PWUD)	4.4%
Entertainment worker (>7 sex partners/week)	13.9%
Transgender M→F	9.8%
MSM	2.3%

Examples of calculations of estimates of risk of a particular event in Cambodia

However note that:

- 1) The real risk may increase due to biological factors outlined above that increase the risk
- 2) In the case of rape the demographic of the source(s) may be unknown.

- The risk to a HCW who has a needle stick injury from a known PLHIV = 1/440 or 0.23%
- The risk to a HCW who has a needle stick injury from a person from the general adult population, HIV status unknown = 1/440 (0.23%) x 0.6% = 0.0014%
- The risk to a man who experienced condom breakage during vaginal sex with an entertainment worker = 1/2500 x 13.9% = 0.0056%
- The risk to a man who is anally raped (assume by MSM) = 1/70 x 2.3% = 0.033%
- The risk to a woman who is vaginally raped by man from general population = 1/1250 x 0.6% = 0.00048%
- The risk to a woman who is vaginally raped by a PWID = 1/1250 x 24.8% = 0.02%

Multiple exposures, and from multiple sources should be added to estimate risk:

- The risk to a woman who is vaginally and anally raped by a PWUD (1/1250 x 4.4%)+ (1/70 x 4.4%) = 0.0035% + 0.06% = 0.07%
- The risk to a woman who is vaginally raped by 5 PWUD = 5 x 1/1250 x 4.4% = 0.018%

43.2 Occupational exposure in HCW

- PEP is most effective if given **within 4 hours** of exposure but may be given up to 72 hours.
- Offer PEP in the case of occupational exposure from HIV+ patient if:
 - Deep puncture wound with a hollow bore needle
 - Needle-stick injury after it was used for IM/IV/subcutaneous injection,
 - Injury from a sharp instrument visibly contaminated with blood.
 - Exposure for > 1min to a large quantity of blood to non-intact skin or mucus membrane.
 - Exposures similar to blood involving CSF, synovial fluid, pleural, pericardial, or amniotic fluid.

Regarding the source patient:

- If the source is known to have an undetectable VL the risk of transmission might be much reduced, however given the parenteral route of transmission it is still reasonable to consider PEP.
- If the source patient's HIV status is unknown → ask them to have an HIV test, and perform as quickly as possible.
- The counselling of the source should take place in a confidential setting and their legal right to refuse testing respected.
- If the source is known to have ART failure, start PEP and discuss with an expert.

43.3 Sexual exposure

- PEP should be started as soon as possible, and within 72 hours.
- If the sexual exposure is from a source person known to have an undetectable VL (e.g. condom breakage from HIV+ spouse), the risk is extremely low and PEP is not indicated.

43.4 PEP regimen

- Adherence to the **full 28 day regimen** is critical to the effectiveness of the intervention
- **2 NRTI + PI ARV drug regimens are preferred**, at standard treatment doses.
 - **TDF 300mg + 3TC 300mg + ATV /r 300/100mg once daily x 28 days**
- The NRTI backbone of TDF + 3TC is well tolerated, and a PI is effective in the case of transmitted NNRTI resistance.
- If a third drug is not available or contraindicated, a two NRTI ARV regimen is acceptable provided the exposure is not from a source with known or suspected ART failure.
- Efavirenz is a possible 3rd PEP agent, however it may not be effective in the setting of transmitted NNRTI resistance, and the early CNS side effects may be difficult in someone who has anxiety related to the recent exposure.
- There is no contraindication to PEP for pregnant or lactating women.
- There is a theoretical risk of hepatic flare among people infected with HBV once TDF + 3TC -based PEP is stopped, as has been seen for people receiving ART. Assessment of HBV infection status should not be a precondition for offering TDF+ 3TC -based PEP, but people known HBV infection should be clinically monitored for hepatic flare after discontinuation of TDF+3TC -based PEP.

43.5 Post Exposure Prophylaxis Care Pathway

<ul style="list-style-type: none">• Assessment and immediate management (Table 50-1 NCHADS PEP Clinic visits and reporting form)
<ul style="list-style-type: none">➤ First aid<ul style="list-style-type: none">○ Oral exposure: spit out blood/body fluids and rinse with water.○ Wounds: wash wounds /skin sites that had contact with blood / body fluids.○ Mucous membranes and eyes: irrigate with water /saline (remove contact lenses).○ Do not inject antiseptics or disinfectants into wounds.○ Do not douche the vagina or rectum after sexual exposure➤ HIV testing of the exposed and the source (if possible)<ul style="list-style-type: none">○ Do not delay initiation of PEP around testing, it can be started and ceased if source is found to be HIV negative, or exposed is found to be HIV positive➤ Assess risk and eligibility for PEP based on the nature of the exposure and source HIV status



<ul style="list-style-type: none">• Counselling re risks and options re PEP
<ul style="list-style-type: none">➤ Explain the estimated risk of transmission (see above)➤ Explain the risks and benefits of PEP:<ul style="list-style-type: none">○ PEP significantly reduces but does not eliminate the risk of transmission○ PEP has to be taken continuously for 28 days○ PEP ARV side effects➤ Obtain verbal informed consent to initiate PEP



<ul style="list-style-type: none">• Initiate PEP as soon as possible following exposure, TAKE THE FIRST DOSE NOW!
<ul style="list-style-type: none">➤ Check for drug interactions with any concurrent medications➤ Provide adherence counseling and drug information➤ Do not delay PEP whilst gathering information or filling in paperwork➤ Standard PEP ARV regimen:<ul style="list-style-type: none">○ TDF 300mg + 3TC 300mg + ATV /r 300/100mg once daily x 28 days○ Take the first dose straight away.○ Give initial prescription / supply for 4 days



<ul style="list-style-type: none">• Assess and provide emergency contraception and STI treatment in the context of sexual exposure.
<ul style="list-style-type: none">➤ Presumptive treatment of STI with Azithromycin 1g and Cefixime 400mg stat.➤ Emergency contraception, and baseline + follow up pregnancy testing.



- **Assess for exposure to other infections**
- HBV: high risk through parenteral and sexual exposure.
- HCV: high risk through parenteral, and if traumatic sexual exposure.
- Tetanus - Individuals who sustain wounds (bites, abrasions or cuts) should have their tetanus status assessed and be offered immunization if indicated.



- **Explain need for secondary prevention:**
- Measures must be taken to avoid secondary transmission of possible HIV infection until HIV Ab check in 3 months.
- Use condoms, safe-injecting practices, and avoid blood donation. Risks and benefits of continuing to breast-feed should be discussed.



- **For sexual assault provide/refer for specific psychosocial support**⁶³
- See also NCHADS STI guidelines which detail management of sexual assault⁶⁴



- **Complete documentation:**
- See Table 50-1 NCHADS PEP Clinic visits and reporting form



- **Follow up on PEP**
- Return to the clinic in 3 -4 days for assessment of adherence and tolerability, and check that all results are available and that PEP is still indicated.
- If the source is established to be HIV negative, post-exposure prophylaxis should be discontinued.
- Prescribe further 24 days



- **Follow up testing**
- HIV test 3 months after exposure
- Syphilis test at 3 months after sexual assault.
- HBV, HCV testing at 6 months after exposure if indicated.

⁶³ Responding to intimate partner violence and sexual violence against women: WHO clinical and policy guidelines. Geneva: World Health Organization; 2013

⁶⁴ National guidelines on sexually transmitted infections (STI) and reproductive tract infections (RTI) case management. 2010 Module 6 Ch 5 p 212

Annexes

44. Annex: WHO Tables

Table 44-1 WHO staging system for adults and adolescents (≥ 15 years)

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (under 10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpeszoster Angular cheilitis Recurrent oral ulcerations Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical stage 3
Unexplained severe weight loss (over 10% of presumed or measured body weight) Unexplained chronic diarrhea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease) Acutenecrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained 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
HIV wasting syndrome Pneumocystis jiroveci pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non tuberculous mycobacteria infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (histoplasmosis, coccidiomycosis) Recurrent septicaemia (including nontyphoidal Salmonella) Lymphoma (cerebral or B cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance 2006.

45. Annex: Routine clinical consultation visit guides

The following guidance is consistent with the National initial and subsequent visit form.

Table 45-1 Initial clinical visit guide

Follow the National forms for assessment checklist and documentation.	<ul style="list-style-type: none"> · National Adult Initial visit form · National Adult Patient Visit form · PNTT initial assessment form (counselor)
Points to include in the National Adult Initial visit form	
TB past history TB contact TB Screening and IPT	PHx TB (<i>Drug-sensitive or resistant?</i>) Recent/current contact with a TB case? TB screening (fever, cough, night sweats, weight loss) Any positive (any visit) → Clinical exam, 3x sputum BK, CXR All negative, check ALT/AST → INH prophylaxis
Other past medical history Include: Co-infections Non Communicable disease Mental health	Hepatitis B and C, and STI HT, renal disease etc even if not currently on treatment. Depression or other psychiatric history
ARV treatment history	Include any ARV previously received, including PEP.
OI Prophylaxis history	Check adherence when on (current or past) OI prophylaxis
Medications	Use generic drug names. Note timing, duration, adverse effects and adherence Note traditional medicines CHECK for drug – drug interactions
Drug allergies	Nature of the reaction (rash, fever etc)
Reproductive health and STI	Check for history of STI and current symptoms Ask about reproductive wishes and plans?
Current medical history	Presenting issues
Recreation substance use	Alcohol (frequency, type, amount) Smoking Other drugs - list drug and route of administration, IDU?
HIV disclosure	Current disclosure status? Plans?
Examination Initial visit requires comprehensive physical examination.	Vital signs, weight, height → calculate BMI ⁶⁵ , waist circumference. Examination; including mental status, neurological – central + peripheral, skin/mouth, CVS, Respiratory, Abdomen.
WHO clinical staging	Take history specific to HIV staging; including weight loss, recurrent infections, herpes zoster etc.
Investigations	Order investigations according to <ul style="list-style-type: none"> · Routine Ix - · Further Ix as clinically indicated
Management - Information and counseling	Give information re HIV including OI prophylaxis and ART. Advise re nutrition, substance use, healthy lifestyle. Refer for adherence counseling MMM, psychosocial support or other services as required ⁶⁶
Management - medical	Treat current illnesses as clinically indicated. Refer to other medical services if required.
Medication	Initiate OI prophylaxis according to schedule
Follow up	Schedule for 1 week.

⁶⁵ BMI = weight (kg) / Height (m)²

⁶⁶ See 'Continuum of Care for people living with HIV/AIDS – Operational Framework' for ways to link ART into the comprehensive care approach

Table 45-2 Second and subsequent clinical visit guide

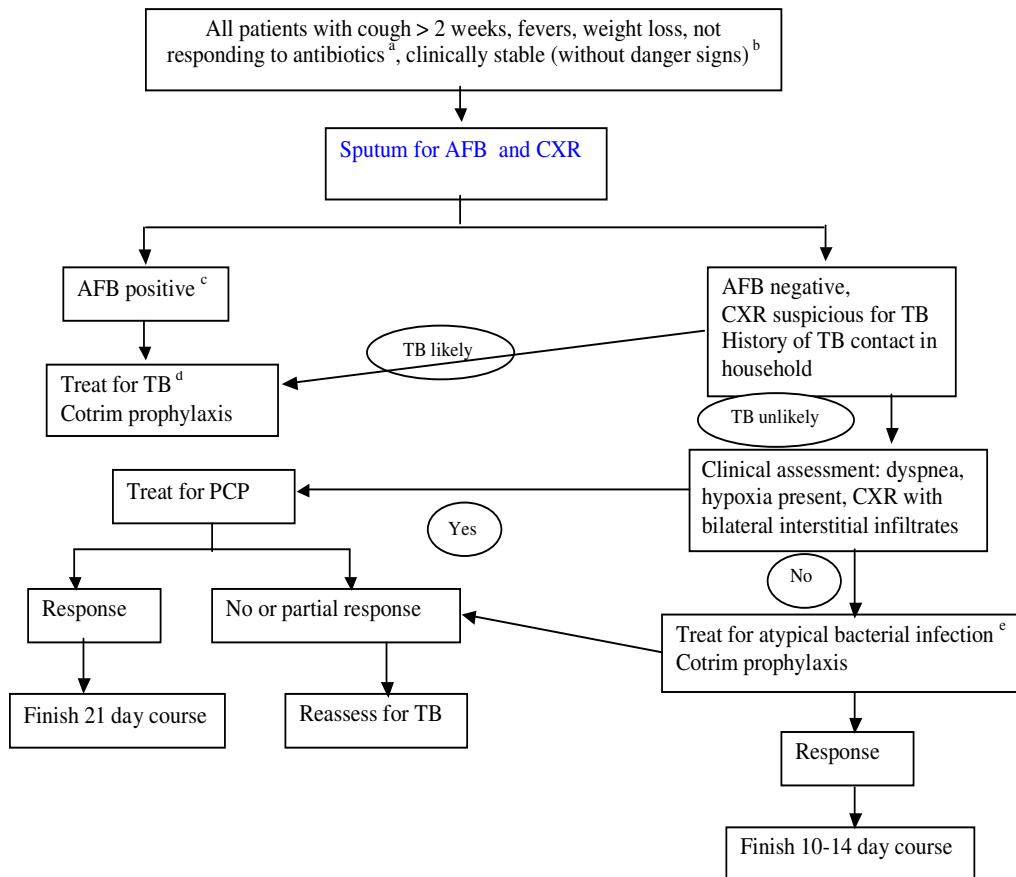
Follow the National forms for assessment checklist.	<ul style="list-style-type: none"> · National Adult Patient Visit form · Adult updated information form
Points to include in the assessment and documented in visit forms:	
History	<p>New symptoms? Review active medical problems</p>
TB screening every visit If eligible start INH prophylaxis at 2 weeks after start ART	<p>Recent/current contact with a TB case? (<i>Drug-sensitive or resistant?</i>) TB – screening (fever, cough, night sweats, weight loss) Any positive → Clinical exam, 3 x sputum AFB, CXR All negative and ALT/AST < 3 x ULN → eligible for INH prophylaxis</p>
OI Prophylaxis	Adherence, side effects.
ARV	Ready to start? If started, review adherence, side effects.
Reproductive health and STI	<p>Review pregnancy status and reproductive plans? Condom + contraception use STI symptoms</p>
Mental health	<p>New symptoms? Review current mental health issues.</p>
Recreation substance use	Support stop smoking, and harm reduction
HIV disclosure	Review, Support disclosure
Examination	<p>Vital signs, weight, (BMI, waist circumference) Observe for change in mental state + physical appearance Target examination according to current medical issues, observations in the consultation, new symptoms and test results.</p>
Investigations	<p>Follow up results of routine and clinically indicated Ix. Further Ix as clinically indicated</p>
Medications	<p>Update medication list Review adverse effects and adherence Check drug – drug doses, and interactions</p>
Drug allergies	Update
WHO clinical staging	Review WHO stage → correct/ advance if necessary
Management - information and counseling	<p>Reinforce information re HIV OI prophylaxis and ART. Advise re nutrition, substance abuse, and healthy lifestyle. Refer for adherence support, MMM, psychosocial support or other services as required</p>
Management - medical	<p>Treat current illnesses as clinically indicated Initiate / cease OI prophylaxis according to schedule Initiate / plan / continue ART Refer for adherence support, other services as required.</p>
Follow up	<p>If 2nd visit – follow up in 1 week for ART, If start ART this visit – follow up in 2 weeks, If stable – follow up 1 – 3 month (depending on if on INH)</p>

46. Annex Tuberculosis: TB/HIV Algorithms

The following algorithms are copied directly from the National TB HIV guidelines⁶⁷

Figure 46-1 Algorithm 1 Diagnosis and Treatment of TB in PLHIV

Algorithm 1: Diagnosis and treatment of tuberculosis in PLHIV

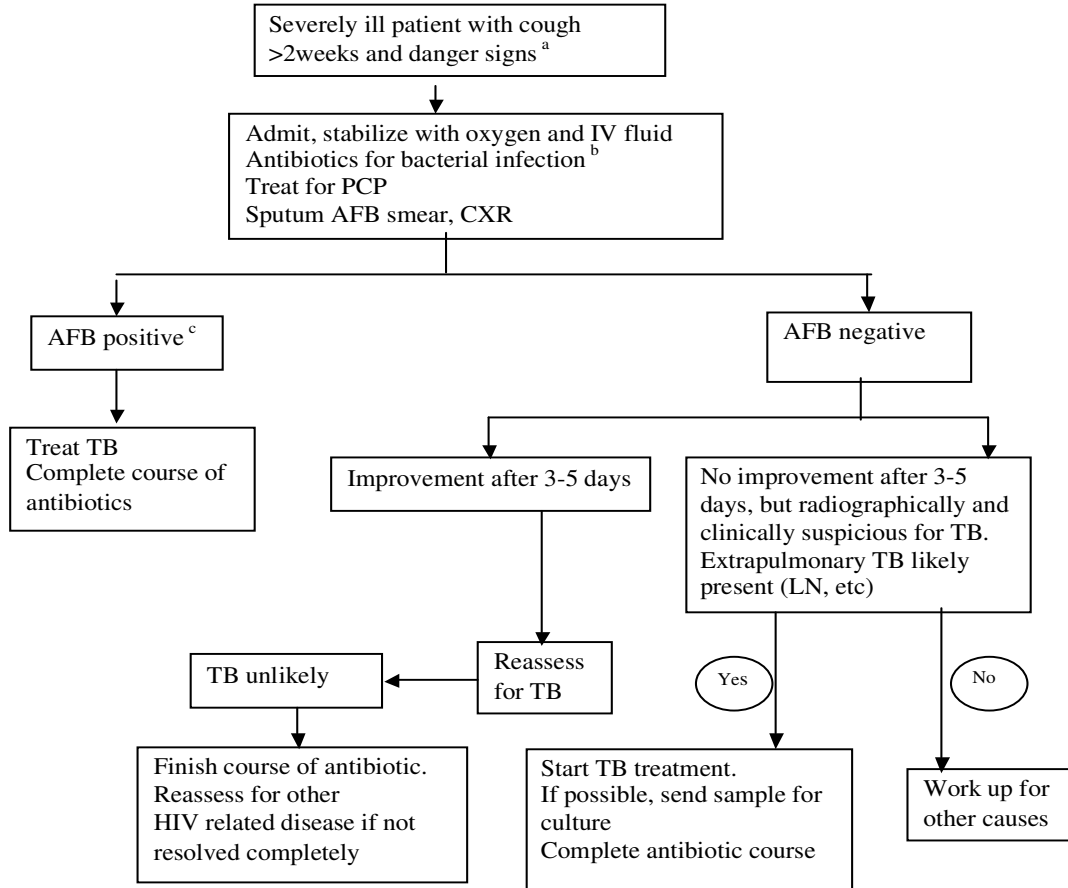


- Amoxicillin, Amoxicillin + Clavulanic acid, or Cefuroxime
- The danger signs include any **one** of: respiratory rate > 30/minute, fever >39 °C, pulse rate > 120/minute and unable to walk unaided
- AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears
- If patient had been previously treated for TB, or is currently at 5th month of TB treatment, resistance should be suspected and MTB culture should be done
- Erythromycin or Doxycycline to cover atypical bacteria should be considered. Use of fluoroquinolones is discouraged to prevent TB resistance

⁶⁷ Kingdom of Cambodia, Ministry of Health. National Clinical Guideline for the Management of TB/HIV Co-infection. English 2008, Khmer 2013 <http://www.cenat.gov.kh/km/documents/guidelines-and-sops>

Figure 46-2 Algorithm 2: Diagnosis of tuberculosis in severely ill PLHIV

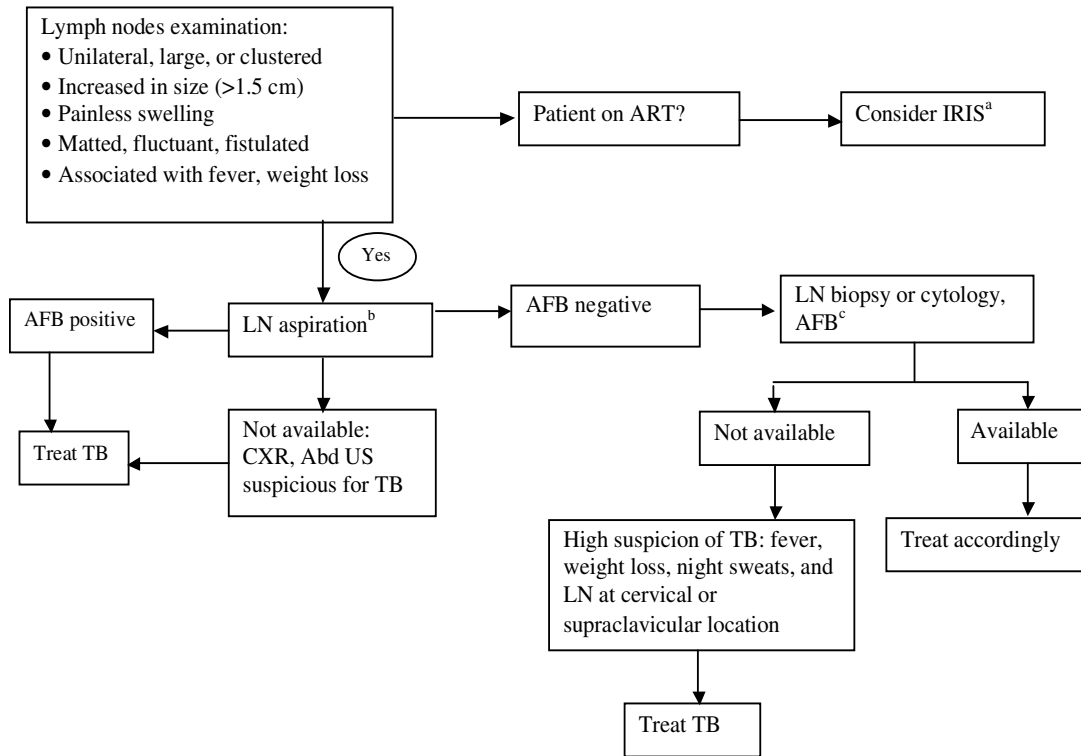
Algorithm 2: Diagnosis of tuberculosis in severely ill PLHIV



- a. The danger signs include any **one** of: respiratory rate > 30/minute, fever >39 °C, pulse rate > 120/minute and unable to walk unaided
- b. Amoxilline, Amoxiline + Clavulanic acide, Cefuroxime plus Erythromycine or Doxycycline to cover both typical and atypical bacteria should be considered. Use of fluoroquinolones is discouraged to prevent TB resistance
- c. AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.

Figure 46-3 Algorithm 3: Clinical management of lymphadenopathy in PLHIV

Algorithm 3: Clinical management of lymphadenopathy in PLHIV



Note:

^a. Patients on HAART can develop lymphadenopathy in the framework of an immune reconstitution inflammatory syndrome (IRIS), especially with TB and MAC, but also with penicilliosis, cryptococcosis and malignancies. Treatment for OI should be started if not already given. HAART should be continued, Steroids (prednisone at 1 mg/kg/day) is helpful in severe IRIS and can be used at full dose for 1-2 weeks, then taper over 1-2 weeks

^b. Do a wide needle aspirate (18G needle) of lymph nodes and send materials for AFB and Gram stains ,and KOH.

^c. If LN aspiration remains negative for AFB, LN biopsy would be justified, if available, and histology, cytology and AFB smear should be performed.

Figure 46-4 Algorithm 4 Management of abdominal lymphadenopathy

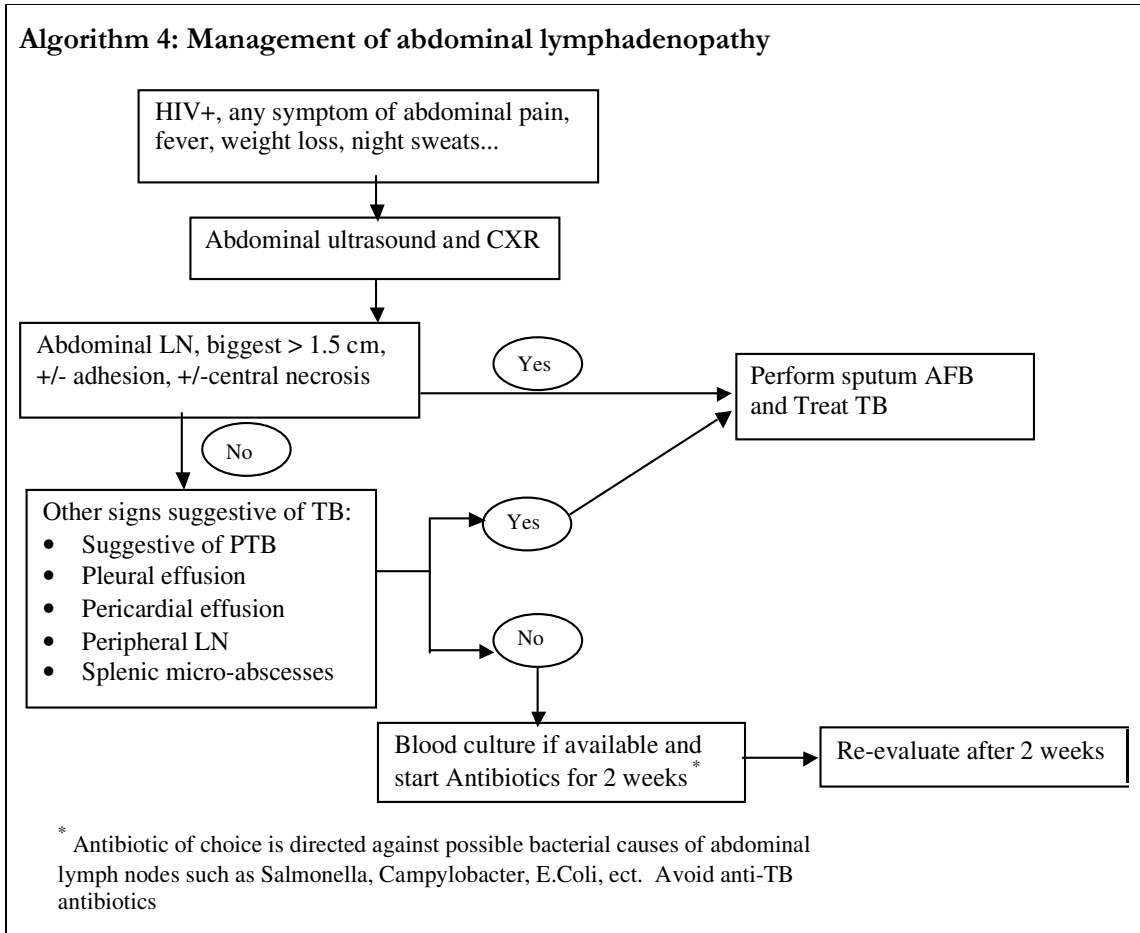


Figure 46-5 Algorithm 5 Management of pleural effusion in PLHIV

Algorithm 5: Management of pleural effusion in PLHIV

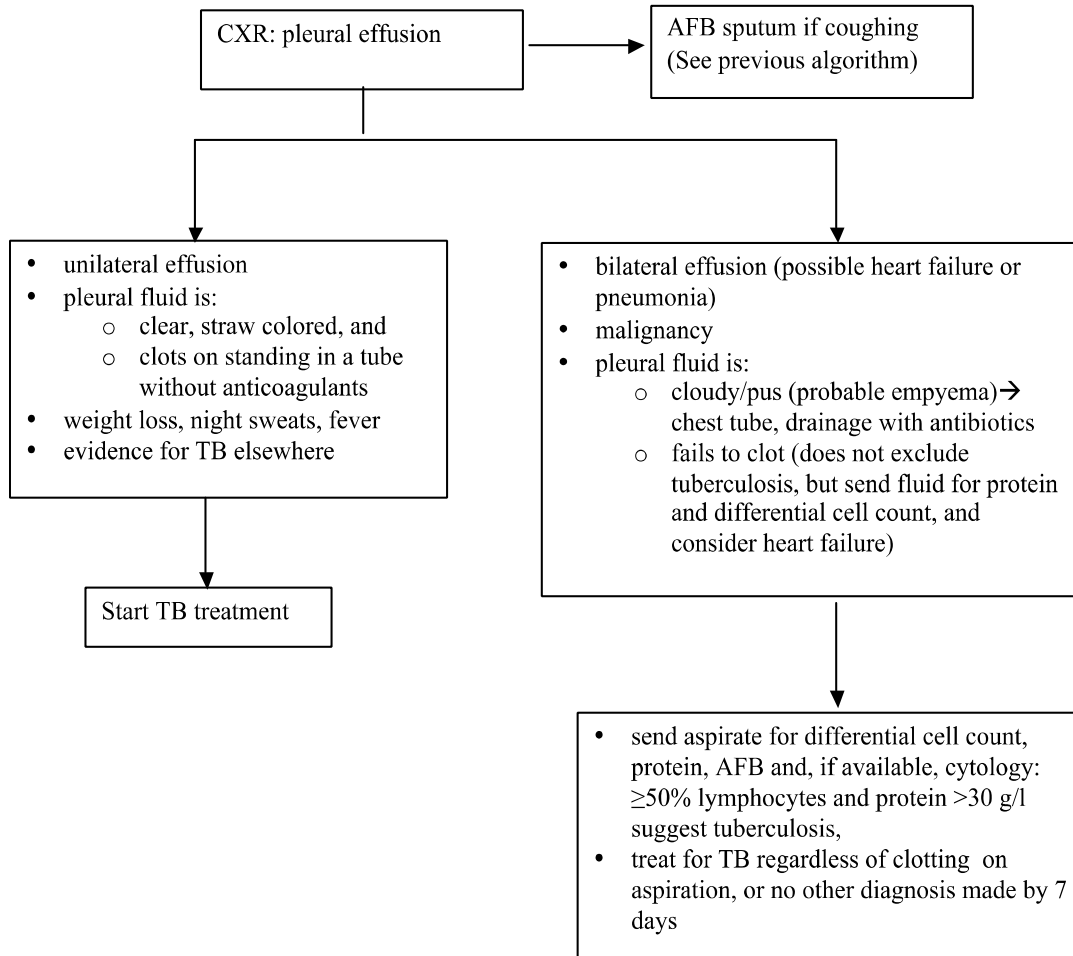


Figure 46-6 Algorithm 6 Management of pericardial effusion in PLHIV

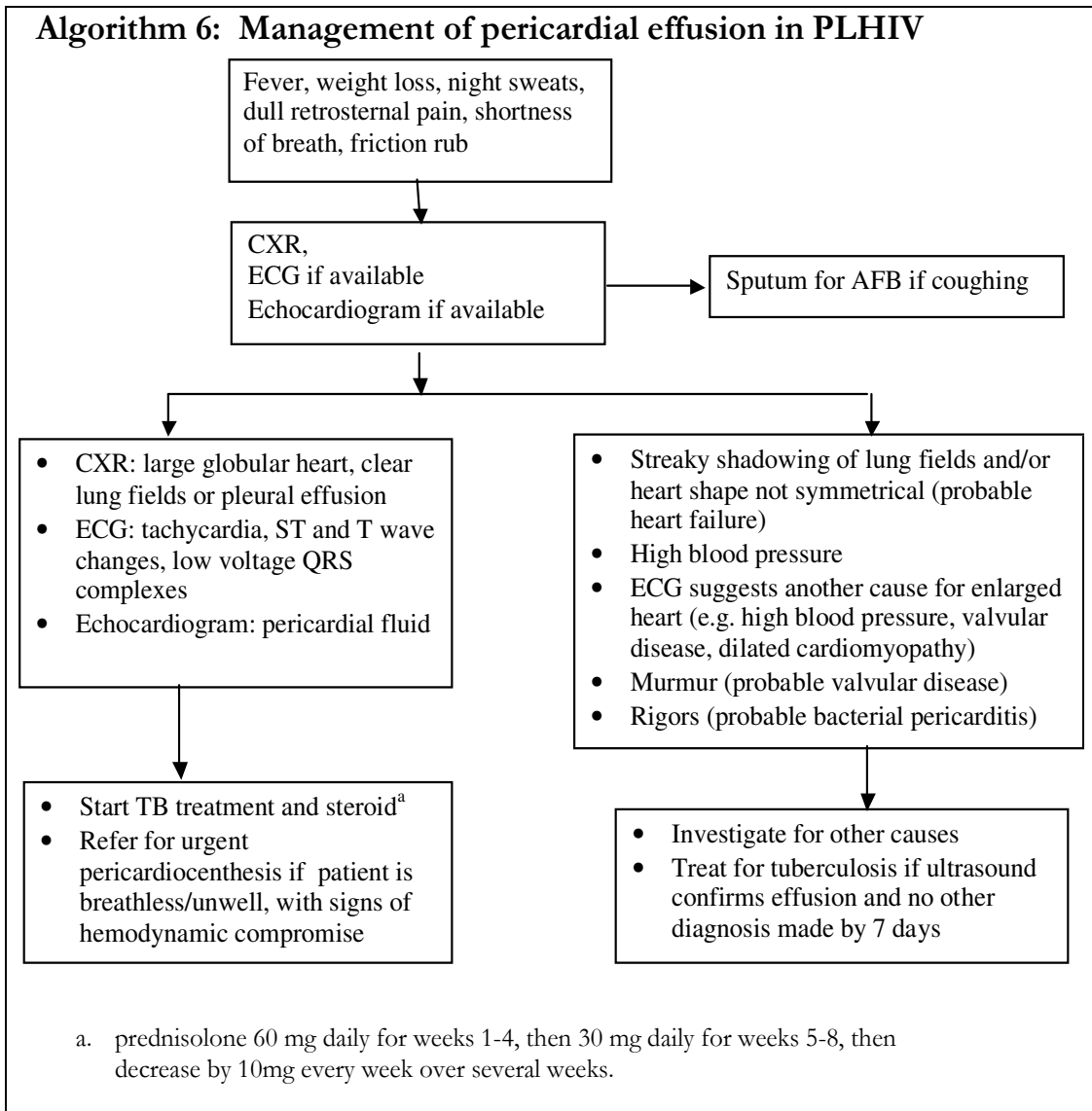
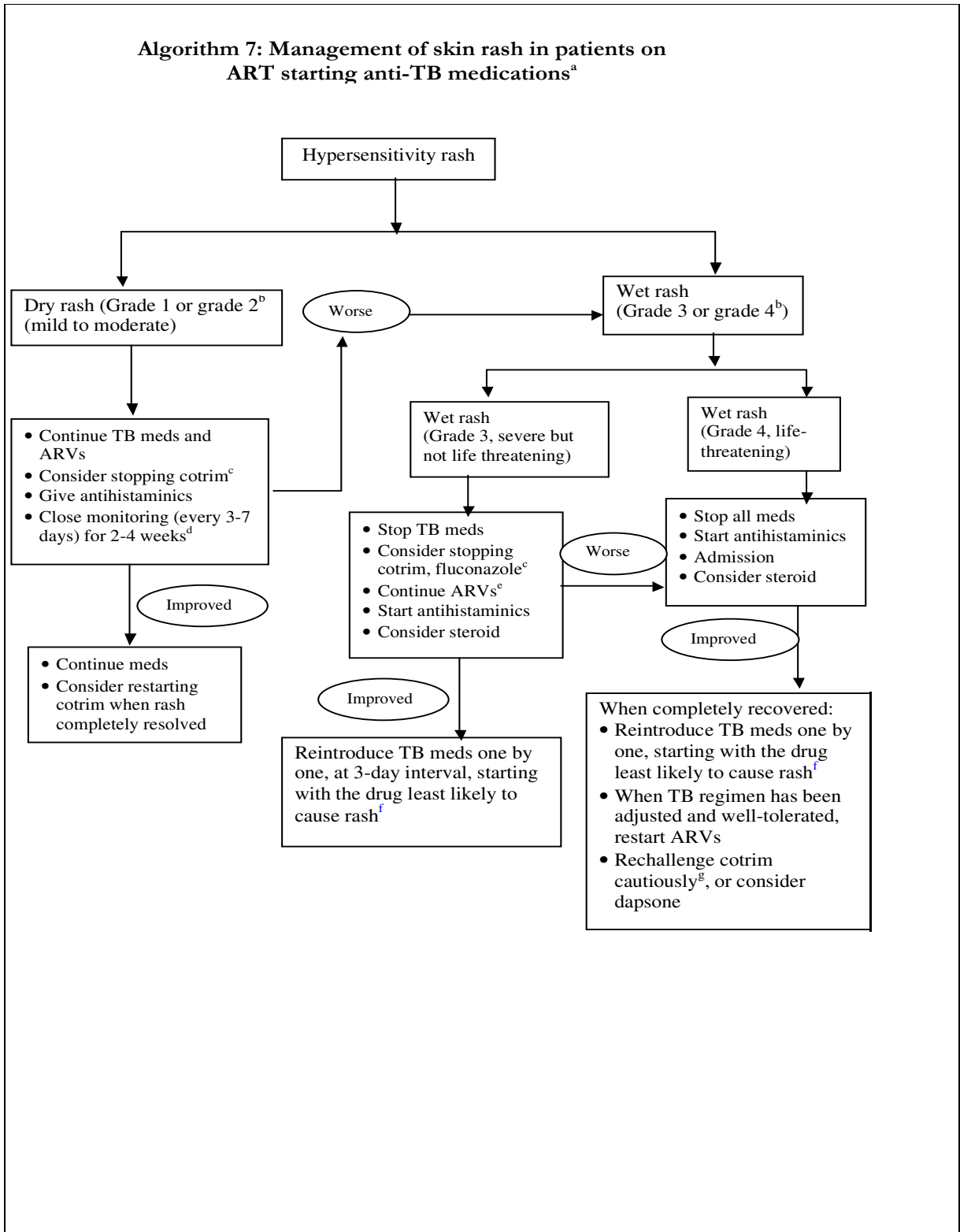



Figure 46-7 Algorithm 7 Management of skin rash in patients on ART starting anti-TB medications



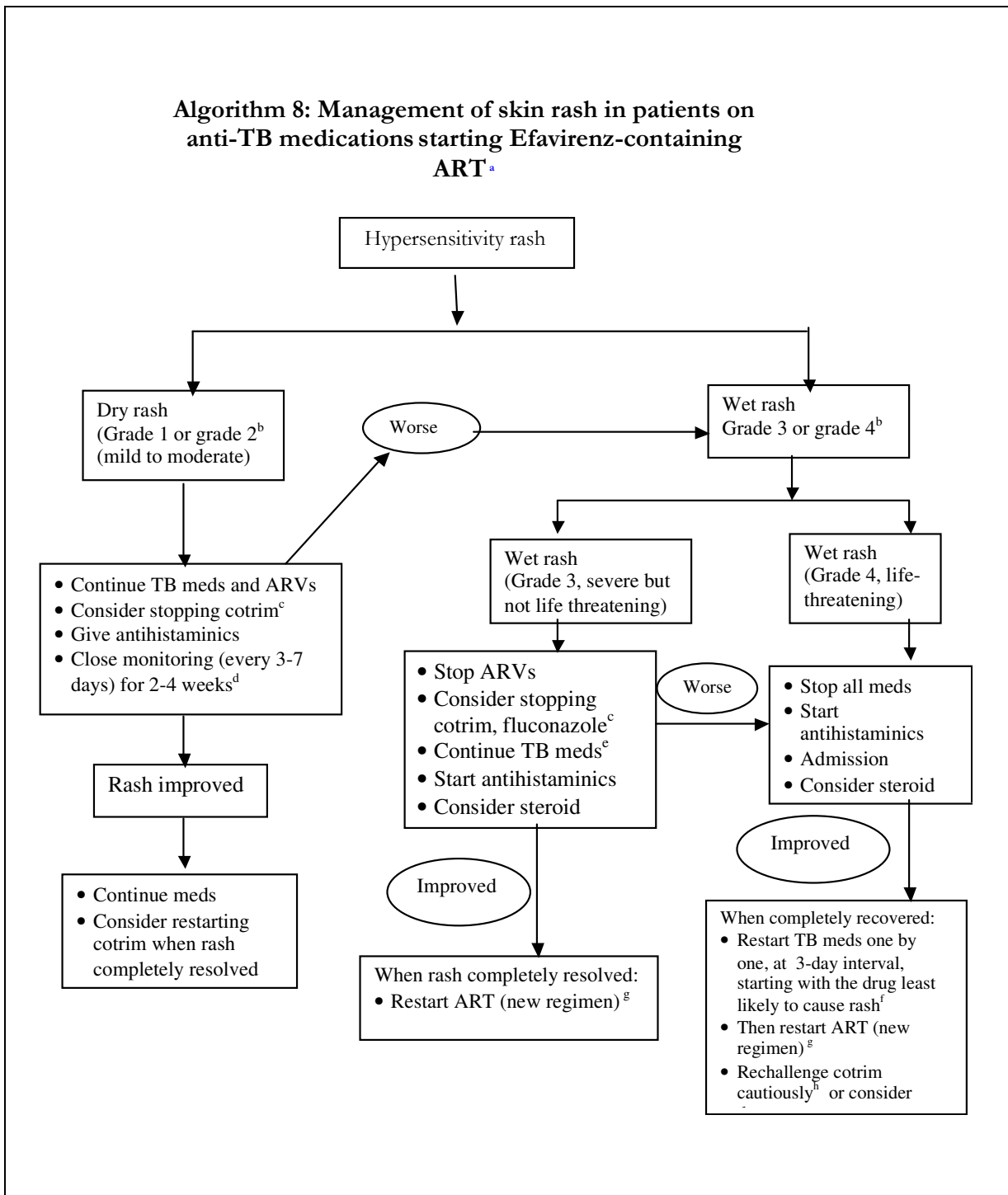
Notice:

- a. Patient already received ART for 6 weeks or more than 6 weeks before starting TB treatment
- b. Defining level of skin rash (ref):
 - 1. Level 1 (mild): erythema, pruritus
 - 2. Level2 (moderate): diffuse maculopapular rash, or dry desquamation
 - 3. Level 3 (severe): vesiculation (moist desquamation) or ulcer > 50 % of body.
 - 4. Level 4 (life threatening) : have any signs of the below: extensive rash with desquamation, angioedema, serum sickness-like reaction, rash with systemic symptoms such as fever, blistering, conjunctivitis, oral lesions, exfoliative dermatitis, Stevens- Johnson syndrome, toxic epidermal necrosis (TEN) (WHO).
- c. Consider stop cotrim or fluconazole if rash has just recently started (within the last 6 weeks)
- d. Closely monitor and follow up the skin rash evolution. Tell patient to come back soonest when the skin rash is worsening.
- e. ARV can be continued if it was already used for more than 6 weeks
- f. Restarting TB drug, after drug reaction, shall be followed the table:

Drug	Drug reaction possibility	Challenge Dose		
		Day 1	Day 2	Day3
Isoniazide	Less likely	50mg	300mg	300mg
Rifampicin		75mg	300mg	Full dose
Pyrazinamide		250mg	1000mg	Full dose
Ethambutol		100mg	500mg	Full dose
Streptomycine	Most likely	125mg	500mg	Full dose

- g. Cotrimoxazole must not be restarted if suspected of causing allergy reaction..

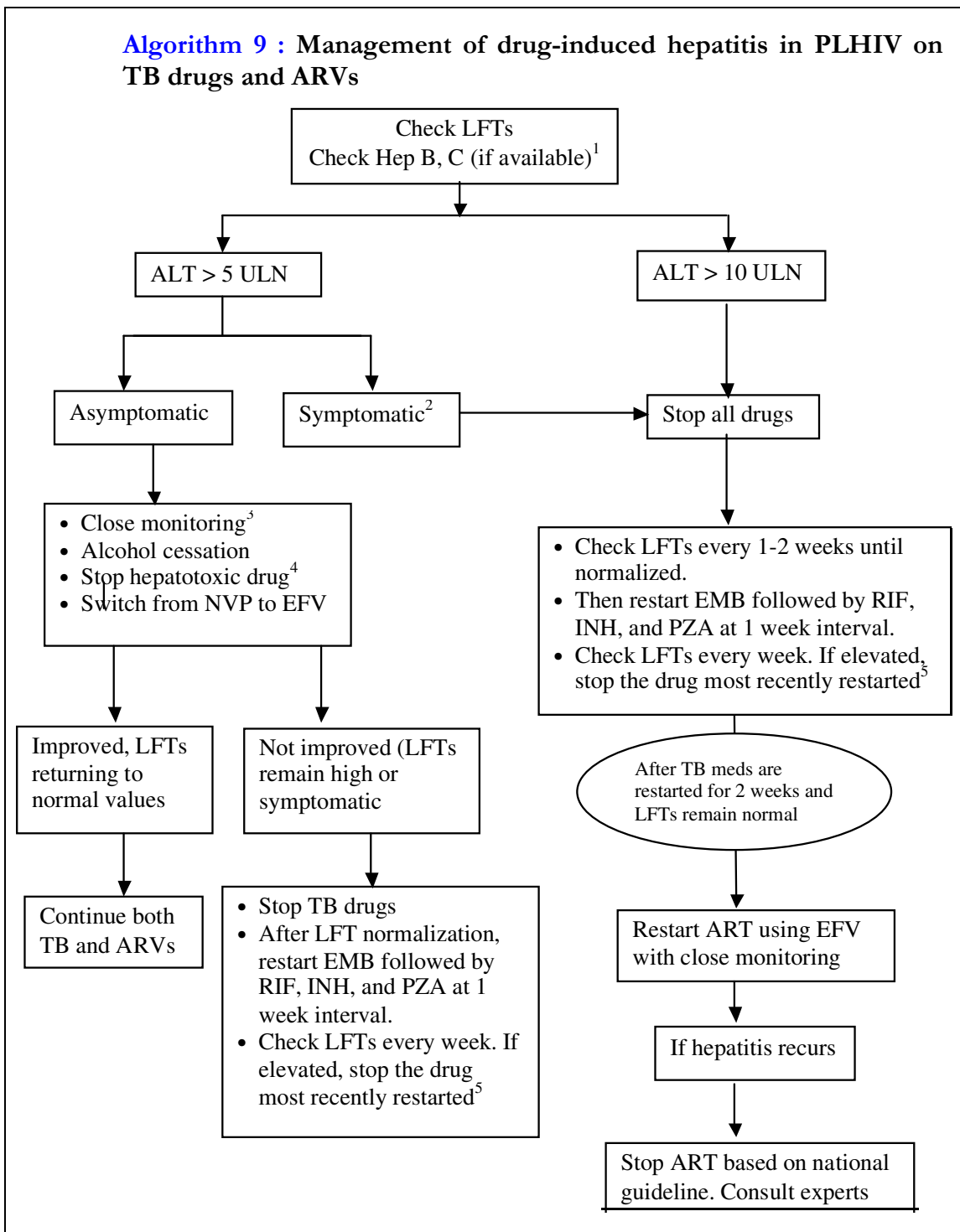
Figure 46-8 Algorithm 8 Management of skin rash in patients on anti- TB medications starting Efavirenz-containing ART



Notice:

- a. Patient already received TB treatment for 6 weeks or more than 6 weeks before initiating ARV. If ART started before this time frame and developed skin rash due to any drug, discuss with expert.
- b. Defining level of skin rash (see previous algorithm)
- c. Consider stop cotrimoxazole or fluconazole if rash has just recently started (within the last 6 weeks)
- d. Closely monitor and follow up the skin rash evolutions. Tell patient to come back soonest possible when skin rash is worsening.
- e. TB drug can be continued if it was already used for more than 6 weeks
- f. Restating TB drug after drug allergy reaction: see previous algorithm. Treatment formula needs to be adjusted to avoid drugs interaction with ARVs. Please see the below.
- g. Suppose patient is on first line ART treatment with 2NRTIs and 1 NNRTI. The ARV which likely caused skin rash is NVP or EFV. 2NRTIs drug should be restarted and the third drug should be selected. Options are:
 - PI containing formula: PI + 2NRTIs, however, Rifampicin will reduce PI blood concentration to sub therapeutic level. Additional of ritonavir is needed to solve the effect. Example: for lopinavir/ritonavir (Kaletra, Aluvia) the adjusted doses are lopinavir 400mg/ritonavir 400mg twice daily when concomitantly use with Rifampicin. This option provides high therapeutic level for TB-HIV but has liver toxicity, more adverse effect and higher price. Ritonavir might be not available by itself. Using TB treatment formula without Rifampicin after attack phase is Isoniazide and Ethambutol. PI dose is not need to be adjusted. This TB treatment formula is not for severe TB such as miliary TB or disseminated TB or meningitis TB.
 - Triple NRTI formula: the feasible option is 3NRTIs which contain AZT + 3TC +ABC or TDF. This formula rarely causes liver toxicity and has no drug interaction with Rifampicin but has less potential against HIV virus; thus it is risky to failure and drug resistance. There are 3-5% that Abacavir can lead to hypersensitivity syndrome such as skin rash and systemic signs and other symptoms which can be confused with this case.
 - Nevirapine can be alternative to efavirenz in case of mild to moderate (level 1and level2) skin reaction, and EFV can also be an alternative for NVP. Be noticed that switching from EFV to NVP can make possibility of 50% skin rash (it, however, consists of only 20% in reality). Switching drug vice versa in the same group because of severe and life threatening skin reaction is generally not recommended because of class-specific toxicity risk (WHO).
- h. Cotrimoxazole must not be restarted if suspected of causing allergy reaction. For mild skin rash, cotrimoxazole can be considered to restart with desensitization as following:
 - Cotrimoxazole suspension of 40mg TMP + 200mg SMX per 5 ml: 1ml daily for 3 days, 2ml for 3 days and consecutively do the same scaling up until the dose is up to 1SS for 3 days and 1 DS in next day.
 - If contrimoxazole suspension is not available, use 80/400mg (480mg, SS) one tablet. Starting every 3 days with 1/8 tablet, 1/4 tablet, 1/2 tablet, 3/4 tablet then 1 tablet per day. If well tolerance or no problem, dose can be increased up to 1 DS on next day.

Figure 46-9 Algorithm 9 Management of drug induced hepatitis in PLHIV on TB drugs and ARVs



Notice:

1. Patient with hepatitis B and/ or chronic hepatitis C. Hepatitis C is easily has hepatitis caused by TB drug and ARVs.
2. Symptom of Hepatitis: sclera icterus, nausea/vomiting, right upper quadrant pain, anorexia, fever.
3. Close monitor means patient exam and checking LFTs every 1-2 weeks.
4. Check patient's drug list to stop any non-essential hepatotoxic drug. Stop fluconazole if the use is for primary prophylaxis.
5. LFTs will sometimes return to normal by restarting TB drug method. PZA and INH are the drug likely caused elevated ALT/AST. Elevated Bilirubin is always caused by Rifampicin. Physician must start with PZA in this case. But in case of INH or RFM are the causes, the duration of treatment will be increased and substitute with less liver toxicity drug. Consult with expert.
LFTs can also be elevated after IRIS caused by hepatitis B and or chronic hepatitis C and can become normal in many months later.

47. Annex Kidney disease

Monitor for changes in eGFR which may require further dose adjustments over time.

Table 47-1 Drug dose adjustments in patients with renal failure⁶⁸

Drug	creatinine clearance (CrCl, in ml/min) or eGFR				
ARVs					
3TC	Clearance >50	Clearance 30–49	Clearance 15–29	Clearance 5–14	Clearance <5
	150 mg bd or 300 daily	150 mg daily	150 mg stat then 100 mg daily	150 mg stat then 50 mg daily	50 mg stat then 25 mg daily
d4T	Clearance >50		Clearance 25–50		Clearance 10–25
	30 mg bd		15 mg bd		15 mg daily
Drug	Cr clearance/eGFR >50 Give usual dose		Cr clearance/eGFR 10–50 Dose or % of usual dose		Cr clearance/eGFR <10 Dose or % of usual dose
AZT	300 mg bd		No adjustment needed		300 mg daily
TDF	300 mg nocte		AVOID		AVOID
abacavir	No adjustment needed		No adjustment needed		No adjustment needed
nevirapine	No adjustment needed		No adjustment needed		No adjustment needed
efavirenz	No adjustment needed		No adjustment needed		No adjustment needed
PIs	No adjustment needed		No adjustment needed		No adjustment needed
Anti-hypertensives					
enalapril	2.5–10 mg bd		75–100%		50%
atenolol	25–50 mg daily		50%		25%
HCTZ	12.5–25mg daily		100%		avoid
amlodipine	5–10 mg daily		No adjustment needed		No adjustment needed
doxazosin	2–4 mg daily		No adjustment needed		No adjustment needed
Diabetic meds					
gliclazide.	40–80 mg bd		AVOID		AVOID
glibenclamide	2.5–5 mg bd		AVOID		AVOID
metformin	500–1000 mg bd		25%		AVOID

⁶⁸ All renal table and algorithms are copied from MSF HIV/TB clinical guide 2015 appendix 25 + 26

Anti-fungals			
fluconazole	200–400 daily	50%	50%
itraconazole	100–200 bd	100%	50% IV form contraindicated
Anti-virals			
acyclovir	200–800mg 4–12 hourly	100%	200 mg bd
Drug	Creatinine clearance or eGFR		
	>50 Give usual dose	10-50 Dose or % of usual dose	<10 Dose or % of usual dose
Antibiotics			
amoxicillin	250–1000 mg tds	Every 8–12 hours	Every 24 hours
azithromycin	500 mg daily	No adjustment needed	No adjustment needed
ceftriaxone	1–2 g daily	No adjustment needed	No adjustment needed
clarithromycin	250–500 mg bd	50%–100%	50%
ciprofloxacin	250–750 mg bd	50%–75%	50%
clindamycin		No adjustment needed	No adjustment needed
co-trimoxazole prophylaxis	2 tabs daily (480 mg tabs)	No adjustment needed	No adjustment needed
co-trimoxazole treatment	2 bd–4 qid (480 mg tabs)	50%	Seek advice
erythromycin		No adjustment needed	No adjustment needed
linezolid		No adjustment needed	No adjustment needed
moxifloxacin	400 mg daily	No adjustment needed	No adjustment needed
ofloxacin	200–400 mg bd	Daily dose	Daily dose
penicillin g	0.5–4 MU 4–6 hourly	75%	25%
TB drugs see separate document below			
Miscellaneous			
NSAIDs	AVOID	AVOID	AVOID
metoclopramide	10 mg tds	75%	50%
omeprazole	20–40 mg daily	No adjustment needed	No adjustment needed
ranitidine	150–300 mg nocte	50%	25%

Table 47-2 TB drug adjustment for Cr Clearance < 30mmol/min

Drug frequency	Change in frequency when CrCl < 30 ml/min	Recommended dose and frequency for patients with creatinine
isoniazid	No change	300 mg once daily, or 900 mg 3 x week
rifampicin	No change	600 mg once daily, or 600 mg 3 x week
pyrazinamide	Yes	25–35 mg/kg/dose 3 x week
ethambutol	Yes	15–25 mg/kg/dose 3 x week
ofloxacin	Yes	600–800 mg/kg/dose 3 x week
moxifloxacin	No change	400 mg once daily
terizidone	Yes	250 mg once daily, or 500 mg 3 x week
ethionamide	No change	250–500 mg/dose daily
PAS	No change	4 g/dose, twice daily
streptomycin	Yes	12–15 mg/kg/dose 2 or 3 x week
capreomycin	Yes	12–15 mg/kg/dose 2 or 3 x week
kanamycin	Yes	12–15 mg/kg/dose 2 or 3 x week

Figure 47-1 Creatinine evaluation algorithm

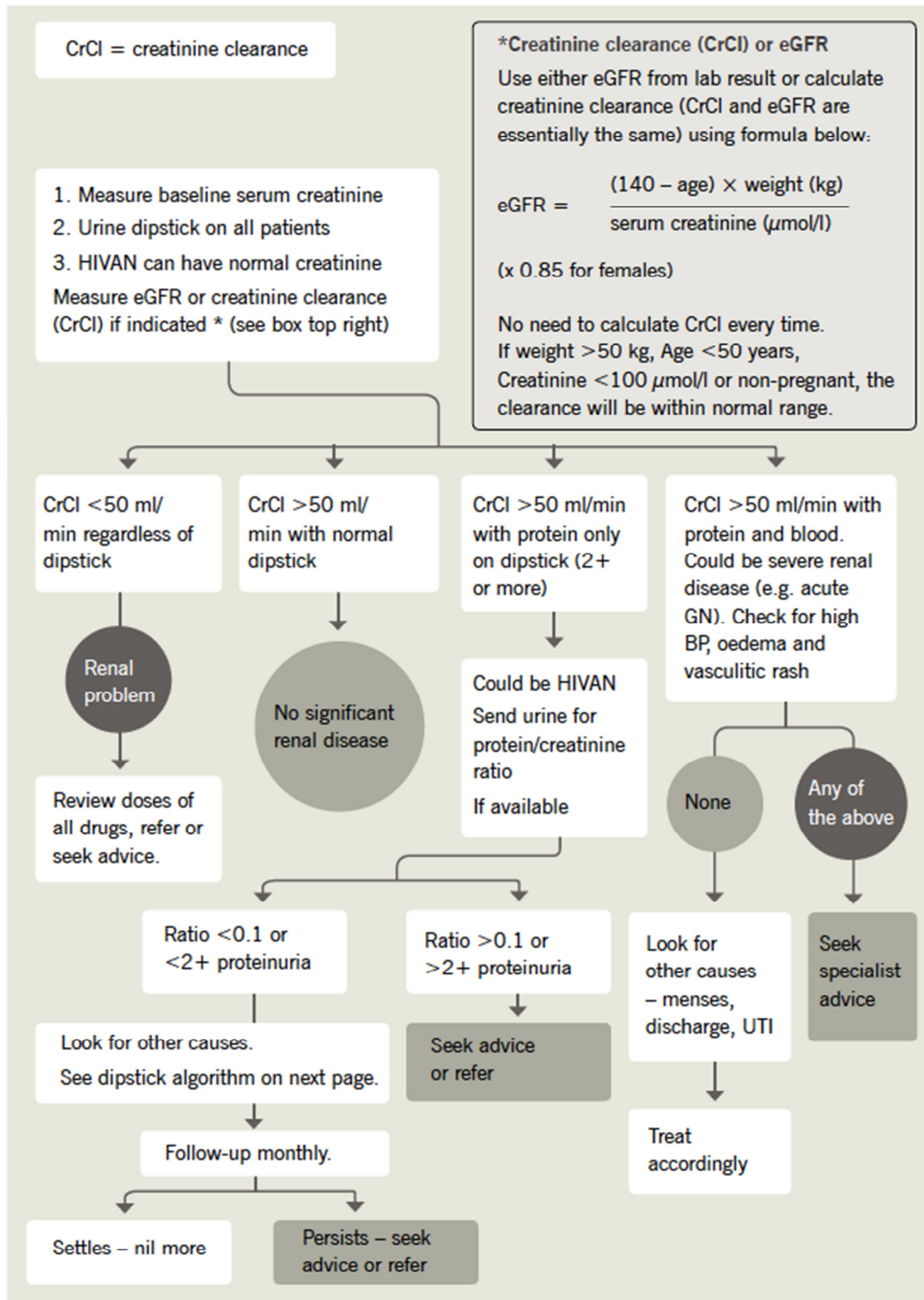
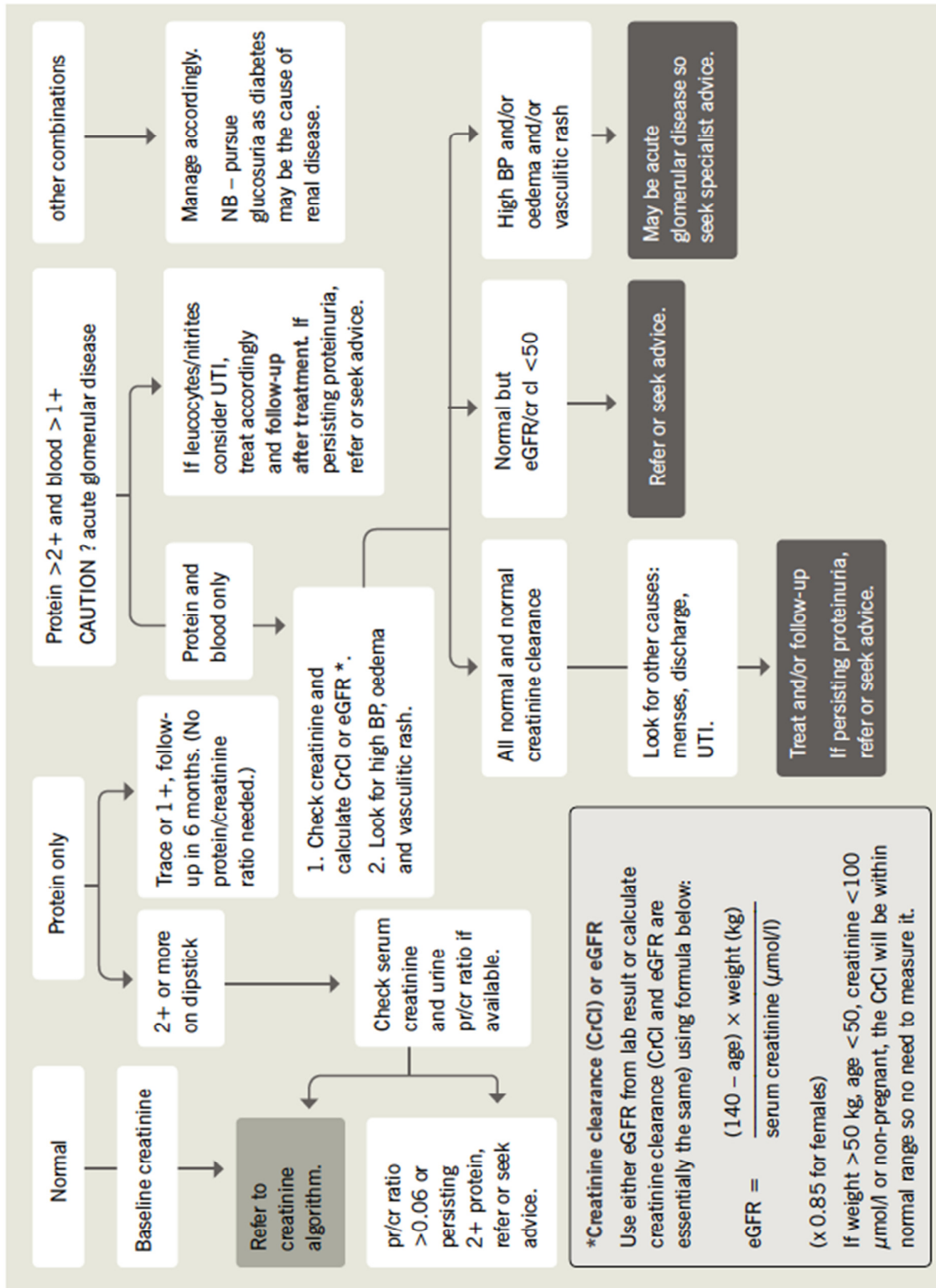


Figure 47-2 Urine dipstick algorithm



48. Annex Diabetes

Figure 48-1 Food pyramid for Diabetes Type 2 (from Mopotsyo organisation)

ជំងឺ ជាង

ទំនាក់ ទំនាម ទំនៀម

ប្រើថ្នាំតាមវេជ្ជបញ្ជារបស់គ្រូពេទ្យ ហាត់ប្រាណរាល់ថ្ងៃ គឺក្នុងមួយថ្ងៃ
ហាត់កន្លះម៉ោង ឬមួយម៉ោង

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នេះគឺជាតារាងម្ហូបអាហារសម្រាប់អ្នកជំងឺទឹកនោមផ្អែមកម្ពុជាដែលមានក្រុមស្ថិតិខ្ពស់ពេក ប៉ុន្តែពុំមានកើតជំងឺអ្វីផ្សេងទៀតទេ ដូចជាកូលេស្តេរ៉ូលខ្ពស់ជាដើម ។ អ្នកត្រូវដឹងកិច្ចការក្នុងការស្របសម្រួលអ្នកដោយខ្លួនឯង និងគ្រប់គ្រងវាអោយបានល្អ ។ ការហូបអាហារណាដែលមានសុខភាពល្អ ព្រមទាំងធ្វើលំហាត់ប្រាណ និងប្រើថ្នាំអោយបានត្រឹមត្រូវតាមវេជ្ជបញ្ជារបស់គ្រូពេទ្យនោះនឹងអាចធ្វើអោយកិច្ចការក្នុងការស្របសម្រួលអ្នកមានលំនឹងបានល្អឡើងវិញ ។

49. Annex Mental Health

Figure 49-1 Common Presentations of Mental Health conditions⁶⁹

mhGAP-IG Master Chart: Which priority condition(s) should be assessed?

1. These common presentations indicate the need for assessment.
2. If people present with features from more than one condition, then all relevant conditions need to be assessed.
3. All conditions apply to all ages, unless otherwise specified.

COMMON PRESENTATION	CONDITION TO BE ASSESSED	GO TO
<ul style="list-style-type: none"> ▶ Low energy; fatigue; sleep or appetite problems ▶ Persistent sad or anxious mood; irritability ▶ Low interest or pleasure in activities that used to be interesting or enjoyable ▶ Multiple symptoms with no clear physical cause (e.g. aches and pains, palpitations, numbness) ▶ Difficulties in carrying out usual work, school, domestic or social activities 	Depression * * *	DEP
<ul style="list-style-type: none"> ▶ Abnormal or disorganized behaviour (e.g. incoherent or irrelevant speech, unusual appearance, self-neglect, unkempt appearance) ▶ Delusions (a false firmly held belief or suspicion) ▶ Hallucinations (hearing voices or seeing things that are not there) ▶ Neglecting usual responsibilities related to work, school, domestic or social activities ▶ Manic symptoms (several days of being abnormally happy, too energetic, too talkative, very irritable, not sleeping, reckless behaviour) 	Psychosis *	PSY
<ul style="list-style-type: none"> ▶ Convulsive movement or fits/seizures ▶ During the convulsion: <ul style="list-style-type: none"> – loss of consciousness or impaired consciousness – stiffness, rigidity – tongue bite, injury, incontinence of urine or faeces ▶ After the convulsion: fatigue, drowsiness, sleepiness, confusion, abnormal behaviour, headache, muscle aches, or weakness on one side of the body 	Epilepsy/ Seizures	EPI
<ul style="list-style-type: none"> ▶ Delayed development: much slower learning than other children of same age in activities such as: smiling, sitting, standing, walking, talking/communicating and other areas of development, such as reading and writing ▶ Abnormalities in communication; restricted, repetitive behaviour ▶ Difficulties in carrying out everyday activities normal for that age 	Developmental Disorders	DEV  Children and adolescents
<ul style="list-style-type: none"> ▶ Excessive inattention and absent-mindedness, repeatedly stopping tasks before completion and switching to other activities ▶ Excessive over-activity: excessive running around, extreme difficulties remaining seated, excessive talking or fidgeting ▶ Excessive impulsivity: frequently doing things without forethought ▶ Repeated and continued behaviour that disturbs others (e.g. unusually frequent and severe temper tantrums, cruel behaviour, persistent and severe disobedience, stealing) ▶ Sudden changes in behaviour or peer relations, including withdrawal and anger 	Behavioural Disorders	BEH  Children and adolescents
<ul style="list-style-type: none"> ▶ Decline or problems with memory (severe forgetfulness) and orientation (awareness of time, place and person) ▶ Mood or behavioural problems such as apathy (appearing uninterested) or irritability ▶ Loss of emotional control – easily upset, irritable or tearful ▶ Difficulties in carrying out usual work, domestic or social activities 	Dementia	DEM  Older people
<ul style="list-style-type: none"> ▶ Appearing to be under the influence of alcohol (e.g. smell of alcohol, looks intoxicated, hangover) ▶ Presenting with an injury ▶ Somatic symptoms associated with alcohol use (e.g. insomnia, fatigue, anorexia, nausea, vomiting, indigestion, diarrhoea, headaches) ▶ Difficulties in carrying out usual work, school, domestic or social activities 	Alcohol Use Disorders	ALC
<ul style="list-style-type: none"> ▶ Appearing drug-affected (e.g. low energy, agitated, fidgeting, slurred speech) ▶ Signs of drug use (injection marks, skin infection, unkempt appearance) ▶ Requesting prescriptions for sedative medication (sleeping tablets, opioids) ▶ Financial difficulties or crime-related legal problems ▶ Difficulties in carrying out usual work, domestic or social activities 	Drug Use Disorders	DRU
<ul style="list-style-type: none"> ▶ Current thoughts, plan or act of self-harm or suicide ▶ History of thoughts, plan or act of self-harm or suicide 	Self-harm / Suicide	SUI

⁶⁹ mhGAP Intervention Guide. World Health Organization 2010

50. ANNEX PEP

Table 50-1 NCHADS PEP Clinic visits and reporting form

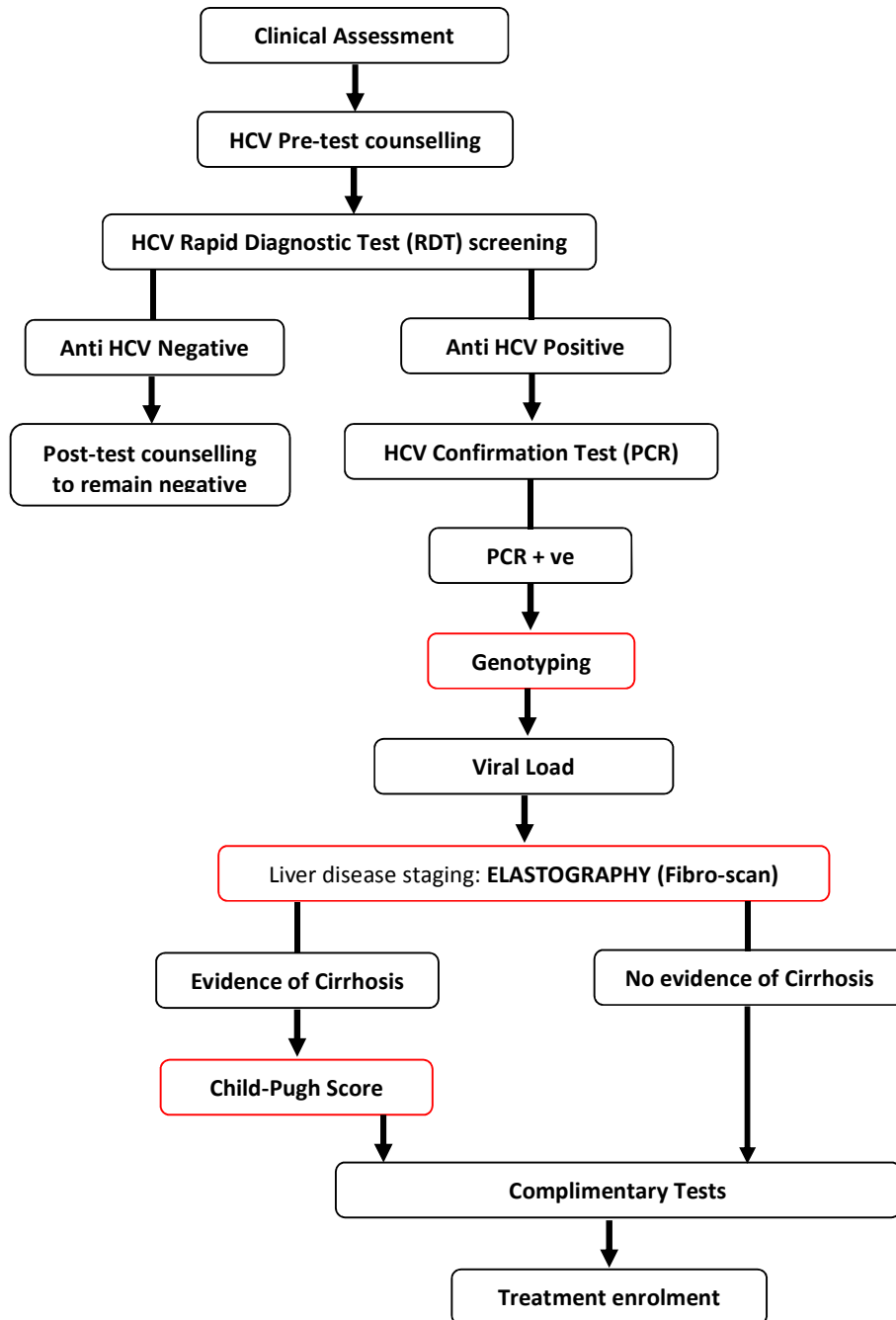
See PEP guideline, and follow PEP care pathway for steps in PEP management.	
Demographic details	
Name _____	Phone no: _____
DOB ___/___/_____	Sex _____
Age _____	Clinic number _____
	Date of first visit ___/___/_____
Category of exposure	
Occupational <input type="checkbox"/>	Timing of exposure
Discordant couple <input type="checkbox"/>	Date of exposure ___/___/_____
Victim of sexual assault <input type="checkbox"/>	Time of exposure _____
	Hours from exposure to PEP _____
Source person HIV status (If HIV negative do not start/or discontinue PEP when known)	
At time of presentation: Pos___ Neg___ Unknown___	
If PLHIV are they on ART? Yes___ No___ Unknown___	
Date commenced ART ___/___/_____	
Most recent VL result _____	Date ___/___/_____:
Is source person available for HIV test? Yes___ No___	
Is the source person high risk for HIV (could be in the window period?) Yes___ No___	
Source HIV status follow up result: Pos___ Neg___ Unknown___	Date ___/___/_____
Exposed person's HIV status (If HIV positive do not start/or discontinue PEP when known)	
At time of presentation: Pos___ Neg___ Unknown___	
Ever had HIV test? Yes___ No___	Date ___/___/_____
HIV test at baseline: Pos___ Neg___ Unknown___	Date ___/___/_____
HIV test 3M post exposure: Pos___ Neg___ Unknown___	Date ___/___/_____
1. Nature of exposure: Occupational	
Health care facility _____	
Deep injection of contaminated hollow bore needle: <input type="checkbox"/>	
Other parenteral exposure to blood or body fluids <input type="checkbox"/>	
Mucus membrane exposure: <input type="checkbox"/>	
Describe exposure _____	
2. Nature of exposure: Discordant couple	
Receptive vaginal <input type="checkbox"/>	Receptive anal. <input type="checkbox"/>
Receptive oral with ejaculation <input type="checkbox"/>	
Insertive vaginal <input type="checkbox"/>	Insertive anal <input type="checkbox"/>
Condom used? Yes___ No___ UK___	Condom broke? Yes___ No___ Unknown___
Exposed male circumcised? Yes___ No___	
Evidence of trauma; bleeding or mucosal tear? Yes___ No___ Unknown___	
Describe exposure _____	
3. Nature of exposure: Victim of sexual assault	
Receptive vaginal <input type="checkbox"/>	Receptive anal. <input type="checkbox"/>
Receptive oral with ejaculation <input type="checkbox"/>	

Condom used? Yes__ Unknown __ Condom broke? Yes__ No__ Unknown __ Evidence of trauma; bleeding or mucosal tear? Yes__ No__ Unknown __ Number of perpetrators? _____ Describe exposure
Is PEP clinically indicated? Yes__ No__ Describe:
Patient counselled and verbally consented to PEP? Yes__ No__
Regimen prescribed: TDF + 3TC+ ATV/r <input type="checkbox"/> Other/describe
Time 1st dose taken? (give as soon as possible, whilst in the consultation) _____
If sexual exposure (discordant couple or victim of sexual assault) Emergency contraception: Prescribed__ Refused__ Not indicated__ STI presumptive treatment: Prescribed__ Refused__ Not indicated__ Referral for psychosocial support?
Exposure to other infections: Source HBV+ Yes__ No__ Unknown __ Recipient? Yes__ No__ Unknown __ Source HCV+ Yes__ No__ UK__ Recipient? Yes__ No__ Unknown __ Tetanus vaccination indicated? Yes__ No__ given? <input type="checkbox"/>
Explained need for secondary prevention <input type="checkbox"/>
Follow up appointment (stress the importance of this): Date __/__/____
Doctor to sign
Follow up consultation (3 – 4 days) Date __/__/____ Attend? <input type="checkbox"/> If not → Notify for Active Case Management
Follow up consultation (3 – 4 days) Date __/__/____ Side effects? Yes__ No__ Describe: Adherent? Yes__ No__ Describe: Blood test from source checked? <input type="checkbox"/> Result _____ (if HIV negative, discontinue PEP) Blood test from exposed checked? <input type="checkbox"/> Result _____ (if HIV positive, discontinue PEP) Continue PEP? Yes__ No__ Explain: Same regimen? Yes__ No__ Explain
Follow up appointment: (stress the importance of this): Date __/__/____
Doctor to sign
Follow up (3 months) Date __/__/____ Attend? <input type="checkbox"/> If not → Notify for Active Case Management
Follow up (3 months) Date __/__/____ Adherent to all PEP ? Yes__ No__ Describe: Symptoms or signs of possible acute HIV infection? Yes__ No__ Describe: HIV test performed <input type="checkbox"/> (complete results section on front page) STI screen <input type="checkbox"/> HBV Ab <input type="checkbox"/> HCV Ab <input type="checkbox"/> Pregnancy test <input type="checkbox"/> Follow up required? Yes__ No__ Describe:
Doctor to sign

51. ANNEX HCV diagnostic algorithm

Figure 51-1 HCV diagnosis and assessment algorithm

Diagnostic Algorithm



The flow diagram above shows the current international standard diagnostic algorithm. This is expected to be updated and adopted for Cambodia as more information is available with the use of DAAs which are expected to simplify the diagnostic and treatment process.

52. ANNEX WHO drug interactions table

Table 52-1: Key ARV drug interactions and suggested management

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and peg-interferon alfa-2a	Substitute AZT with TDF
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the dose of LPV/r or substitute with three NRTIs (for children)
	Halofantrine and lumefantrine	Use an alternative antimalarial agent
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
	Simeprevir	Use alternative DAA
	Ombitasvir/paritaprevir/ritonavir + dasabuvir	Use alternative DAA
DTG	Carbamazepine, phenobarbital and phenytoin	Use alternative anticonvulsant agent
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: Fe, Ca-, Mg- or Zn-multivitamin supplements; cation-containing laxatives and Al-, Ca- or Mg- containing antacids. Monitor for virologic efficacy.
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
	Simeprevir	Use alternative DAA
	Ombitasvir/paritaprevir/ritonavir + dasabuvir	Use alternative DAA
NVP	Astemizole and terfenadine	Use an alternative anti-histamine agent
	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent
	Simeprevir	Use alternative DAA
	Ombitasvir/paritaprevir/ritonavir + dasabuvir	Use alternative DAA

This table was developed using the University of Liverpool's drug interaction charts, a resource which can be found online at www.hiv-druginteractions.org and www.hep-druginteractions.org. A more comprehensive table of ARV drug interactions is available on the Annex 13 of WHO Clinical Guidelines: Antiretroviral Therapy 2015 to be launched at New York in June 2016.

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