KINGDOM OF CAMBODIA
NATION RELIGION KING

MINISTRY OF HEALTH

NATIONAL HIV CLINICAL MANAGEMENT GUIDELINES FOR ADULTS AND ADOLESCENTS

Fifth edition 2020

NATIONAL CENTER FOR HIV/AIDS, DERMATOLOGY AND STD (NCHADS)

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PREFACE

Cambodia is one of the successful countries in the Western Pacific Region in the responses to HIV epidemic in reducing the HIV prevalence among people aged 15 – 49 years old from 1.7% in 1998 to 0.5% in 2018. The estimation of People Living with HIV (PLHIV) is 73,000.[1] After achieved the 90-90-90 targets in 2017, Cambodia announced its intent to further control the HIV epidemic by achieving the UNAIDS 95-95-95 targets (95% of those infected know their status; 95% of those HIV+ enrolled in ART; 95% of those on treatment are virally suppressed at 12 months) and moving towards the elimination of new HIV infection by 2025.

One of key successful elements of HIV response, Cambodia has developed and published the first HIV clinical guidelines during the launch of COC in 2003 to ensure high quality HIV/AIDS care and treatment. The guidelines were revised in November 2007, 2012, 2015 and 2019 as the Anti-retroviral therapy sites expanded and ensure the clinical knowledge and quality treatment are up to date to the intentional scientific standard align with 2019 WHO recommendations and other resources on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection.

During a series of technical working group meetings and at a consultative workshop, staff from NCHADS, the National Pediatric Hospital, the University of Health Sciences, Angkor Hospital for Children, HIV/AIDS clinical mentors, UN agencies, and other non-governmental organization (NGO) partners reviewed and revised the guidelines. Their comments were incorporated, and field experiences were reflected in this revised edition.

The Ministry of Health has officially approved the National HIV Clinical Management Guidelines for adults and Adolescents and encourages clinicians to reference the guidelines when providing antiretroviral therapy to HIV-infected adults and adolescents in Cambodia.

Phnom Penh, 20, October 2020
For Minister for Health

Prof. ENG HUOT
SECRETARY OF STATE

[1] UNAIDS. Country fact sheet, Cambodia 2018 https://www.unaids.org/en/regionscountries/countries/cambodia

ACKNOWLEDGEMENTS

The National Center for HIV/AIDS, Dermatology, and STD (NCHADS) would like to acknowledge the dedication of the members of the AIDS Care Technical Working Group in the revision of the National HIV Clinical Management Guidelines for adults and adolescents in Cambodia. Throughout the process, they contributed high quality suggestions, enthusiasm, and hard work.

The process of revising these guidelines represents continued achievement in providing high-quality HIV/AIDS treatment and care to HIV-infected adults and adolescents in Cambodia, and ensures the treatment provided incorporates the latest knowledge in the field.

I would like to take this special occasion to thank the technical working group members includes:
NCHADS staff (Dr. Samreth Sovannarith, Dr. Ngauv Bora and Dr. Ky Sovathanna) for coordinating the revision of the guidelines. I would like to express my gratitude and thank to the WHO (Dr. Deng Serongkea), National Pediatric Hospital (Dr. Huot Chantheany), the University of Health Sciences (Prof. Olivier Segeral), Angkor Hospital for Children (Dr. Seng Tray), FHI 360 (Dr. Chel Sarim, Dr. Steve Wignall), US-CDC (Dr. Chan Sodara and Dr. Elfriede Ampong Agyemang), Clinton Health Access Initiative (Ms. Mr. Stanston Hor, Ms. Sivantha Hul and Ms. Caroline Barnett, Dr. Herb Harwell and Dr. Jason Brophy), AIDS Health Foundation (Dr. Men Pagnaraot), Center of HOPE (Dr. Phe Thong), MAGNA (Ms. Denisa Augustin) who have actively participated in revising the guidelines.

Lastly, I would like to thank Dr. Song Ngak, technical assistant to develop this guidelines and all partners, civil societies, partners, and clinicians at OI/ART clinics who have provided their inputs during the development process and provide treatment, care and support to PLHIV in Cambodia.

Phnom Penh, 28, September 2020
Director of the National Center for
HIV/AIDS, Dermatology and STD

Dr.LY PENH SUN

ABBREVIATION

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

TPHA	Treponemal pallidum particle agglutination
TST	Tuberculin skin test
US	Ultrasound
UTI	Urinary tract infection
WBC	White blood cell
WHO	World Health Organization
XDR	Extensively drug-resistant
Z	Pyrazinamide

INTRODUCTION

This HIV clinical management guideline is updated from the 2015 guidelines and mainly based on the new WHO consolidated guidelines 2016 and its supplement in 2019.

This is a consolidated guideline, including sections on antiretroviral therapy and opportunistic infections for adults and adolescences, which were previously contained in two separate documents. In addition to avoiding repetition, it is intentionally 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 antiretroviral therapy, increases the risks and complications associated with metabolic and non–communicable diseases (NCD) 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 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 services, and to provide “adolescent appropriate” care in the adult services.

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 MTB/RIF test, and includes the expanded recommendation for all PLHIV to have a course of tuberculose preventive 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 is now available to PLHIV with HCV coinfection in Cambodia. Tenofovir and 3TC are included now in standard ART for HIV, these treatments are also active against HBV. It is important the clinician has a good understanding of these common co-infections when managing ART, 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 and same day treatment to all confirmed HIV diagnosed patients. This guideline also includes the updated ART regimens including standard 1st line regimen of TDF + 3TC + DTG for all PLHIV ≥ 30 kg including pregnant women, and ATV/r as the preferred PI in 2nd line ART. The EFV 400mg tablets is available, and therefore gives guidance as to who to switch to this lower dose, which has been demonstrated to be equally effective to the 600mg dose for most patients.

Prevention of opportunistic infections has been updated to cryptococcal antigen screening to take the place of routine fluconazole prophylaxis.

The sections on Pre-Exposure Prophylaxis (PrEP) has been included and Post Exposure Prophylaxis (PEP) is updated to include new ARV regimens and is expanded from provision to health care workers to also include victims of sexual assault.

CHAPTER 1: 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, sharing food or by insects.

Table 1: Routes of HIV transmission, average transmission risk per episode

Exposure from an HIV infected source	Estimated risk of HIV transmission per episode[2]
Sexual exposure (via blood, semen, vaginal fluids)	
• 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) *without* withdrawal prior to ejaculation	1/70
• Receptive anal intercourse *with* 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
Blood exposure	
• Intravenous Drug Use: contaminated injecting equipment	1/125
• Occupational needle stick (NSI) or other sharps exposure	1/440
Other exposure	
• Mucus membrane or non- intact skin exposure	< 1/1000

1.3 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.

[2] 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 behavior:
  - Multiple sexual partners
  - Sex with sex workers
  - Sex partners with high-risk behavior (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.

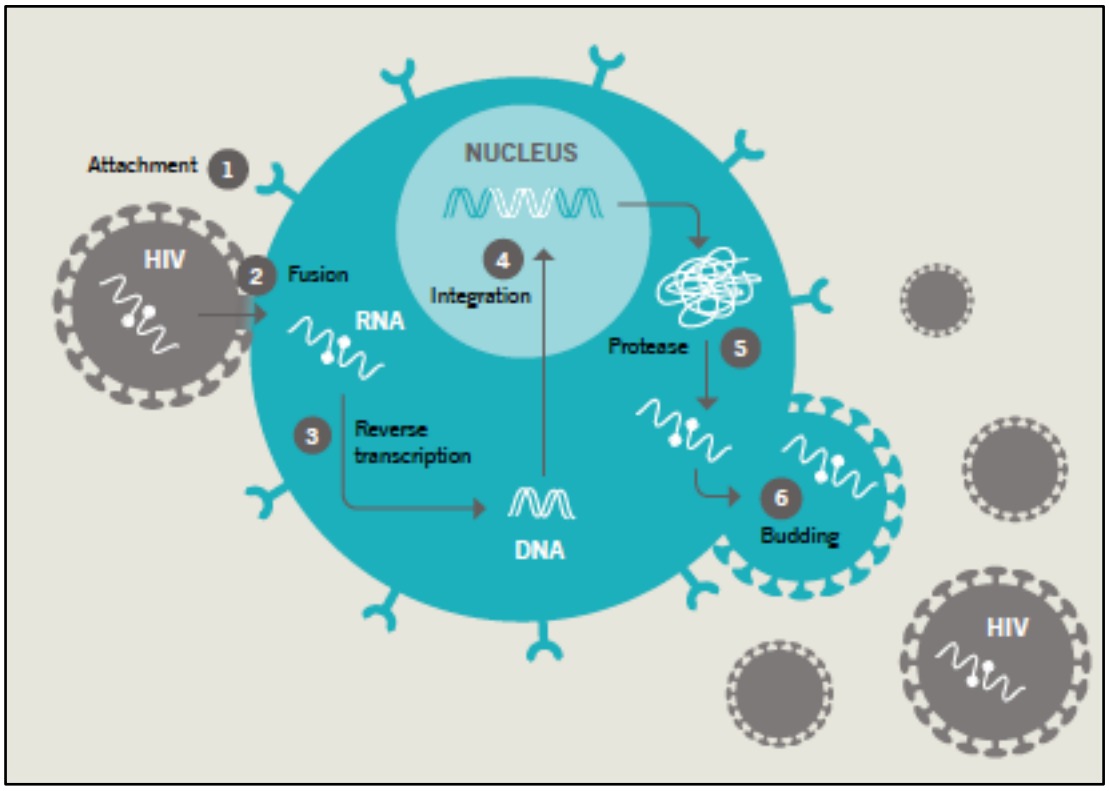
Protective factors against HIV acquisition

- Pre-exposure prophylaxis (PrEP): ART taken by the HIV negative partner prior to sexual exposure is very effective at reducing the risk of HIV acquisition in an exposed individual, see Chapter PrEP, *page 179*.
- Post – exposure prophylaxis (PEP): ART taken for 1 month post exposure reduces the risk of acquisition of HIV in an individual exposed via occupational (e.g. needle stick injury), or sexual exposure ("non – occupational") see Chapter PEP, *page 174*.

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 → 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: Life cycle of HIV[3]



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 suffer a self-limiting mononucleosis-like seroconversion illness.
- The immune system response causes the viral load to decrease markedly ("virological set point") and CD4 cell count increases back to near baseline levels.

1.3.2 Clinical latency

- A period when 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 → decline in CD4 cell count; median loss of 80 cells/year.

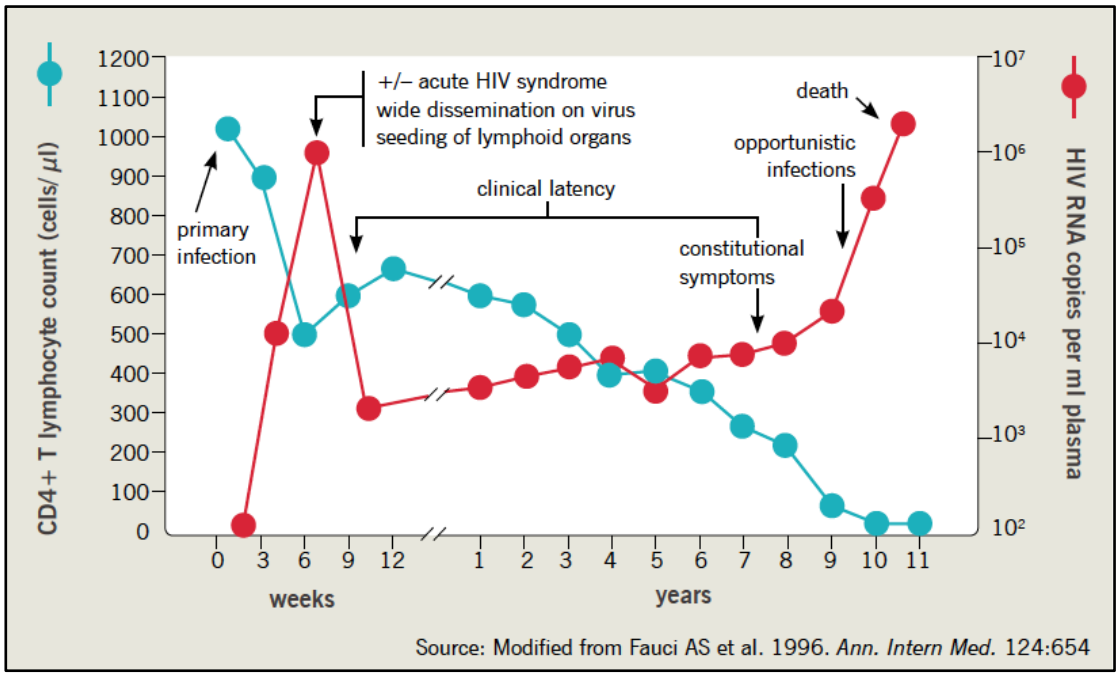
1.3.3 Advanced HIV infection

- Without treatment individuals ultimately progress to develop WHO stage 2 – 4 HIV related illness and AIDS.
- Progression to AIDS (WHO stage 3 or 4, CD4 < 200 cells/mm3) occurs a median of 10 years after initial infection with HIV. Factors which may cause faster progression to AIDS are PLHIV > 40 years, and co-infections, especially tuberculosis.

[3] HIV TB Clinical Guide 8th edition. Medicines Sans Frontieres. 2015

- All children < 5 years old with HIV are considered as having advanced HIV disease.[4]

Figure 2: Natural History of HIV infection[5]



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

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

1.4.2 Causes of clinical presentations

1. Immunodeficiency
    - Infections

[4] WHO HIV clinical guideline 2017.
[5] 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 and TB
5. Medication: side effects/drug interactions
6. Immune reconstitution syndrome
   - 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 and 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 Guilian Barre Syndrome.
- Transient immunosuppression opportunistic infections, e.g. oral candidiasis, or PJP.

Laboratory features:

- Thrombocytopenia, leucopenia, raised liver enzymes.
- HIV serology: HIV antibody test may be positive or negative for up to 3 weeks after onset of symptoms.
- If HIV Ag/Ab is negative at the time of illness and → 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, which informs the WHO classification system of clinical and laboratory conditions stage 1 – 4. (Table 58: WHO staging system adults and adolescents (≥ 15 years), *page 183*.

Table 2: HIV related conditions, risk by CD4 count[6]

CD4 count	Condition
Any CD4 count	• Persistent generalized 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/µL (when severe OIs begin to appear)	• Oral candidiasis (i.e. thrush) • Oesophageal candidiasis • Oral hairy leukoplakia (OHL) • Pneumocystis jiroveci (carrini) pneumonia (PCP) • Cryptosporidiosis • Lymphoma (non-CNS) • Kaposi's sarcoma (KS) • HIV-associated dementia
< 100 cells/µL	• Toxoplasmosis • Cryptococcal meningitis (CCM) • Cytomegalovirus infection (eye) • Wasting syndrome
< 50 cells/µL	• 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 Population) using HIV Rapid tests, Alere Determine Ag/Ab 4th generation according to a standard algorithm.[7]

HIV testing should target high-risk sexually active people include Men have Sex with Men, Drug Users, Entertainment Workers, Street Based Sex Workers, index cases and sexual partners of risk groups.

[6] Adapted from MSF HIV/TB Guide 2015
[7] Leter on revision of HIV Testing and Counseling (HTC), NCHADS 2017
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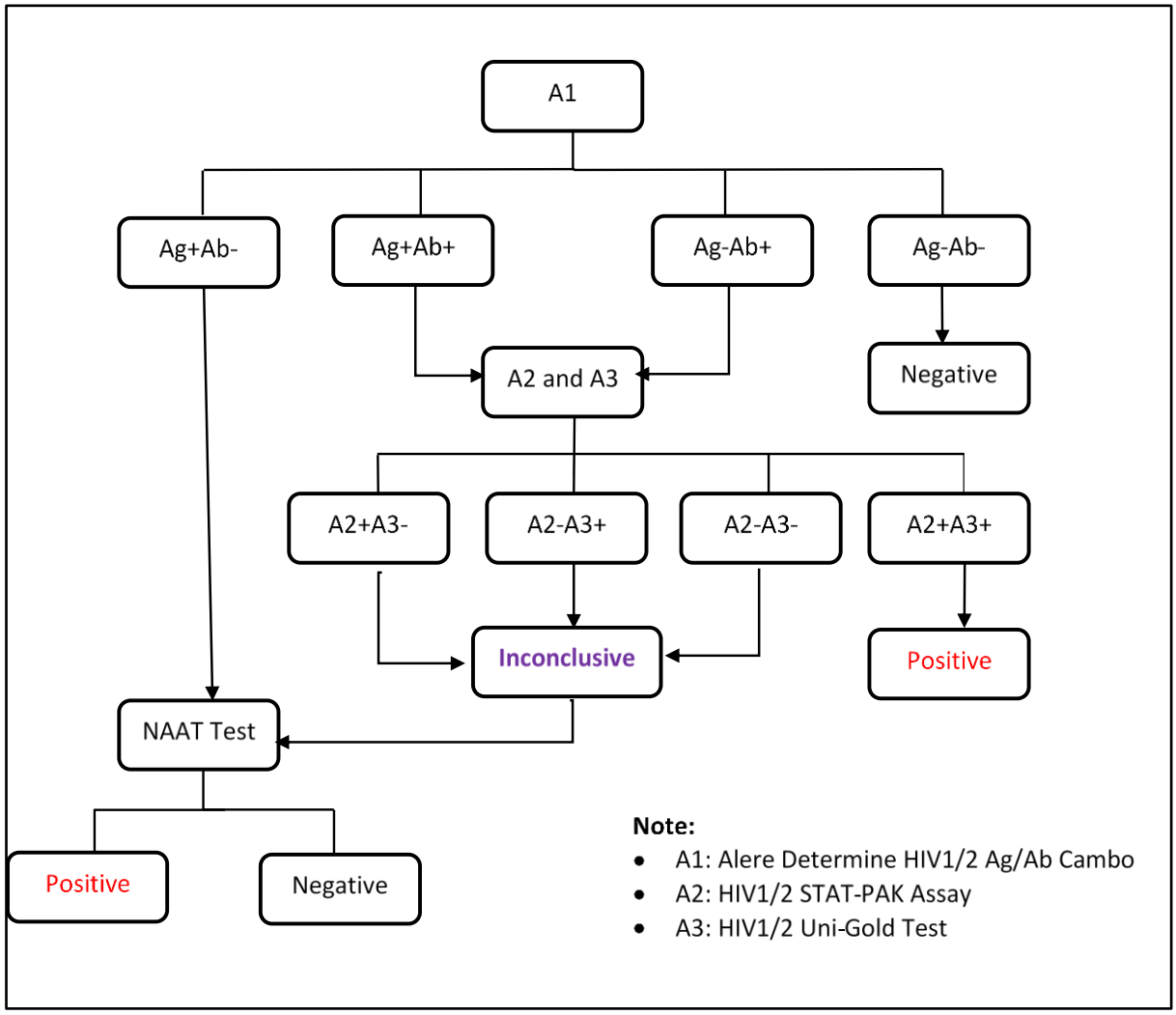
Figure 3: HIV testing algorithm



** For high risk group, if the result of screening test is positive at community and confirmation test is negative, s/he should be followed up next month for HIV re-testing.

If HIV is suspected:

- Provide information to the patient on the importance of HIV testing.
- Refer the patient to a HIV testing at community or 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.

1.6 Antiretroviral therapy

- Antiretroviral therapy (ART) is the mainstay of HIV treatment and is now recommended for all PLHIV regardless of CD4 count and starting ART at same day of the day HIV diagnosis if it is eligible for the criteria of same day ART initiation (SDI) (SDI concept note reference).

- ARV drugs from at least 2 classes target the HIV lifecycle at different stages in the HIV attachment and replicative process. Combination ART rapidly suppresses the replication of HIV leading to a rapid fall in the amount of HIV in the blood (HIV viral load) 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 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 if taken by uninfected individuals as Post Exposure Prophylaxis after occupational (PEP) or non-occupational (NPEP) parenteral or sexual exposure, and as Pre Exposure Prophylaxis (PrEP) to prevent sexual transmission in heterosexual, MSM and TG encounters.

1.6.1 Aims of antiretroviral therapy

- 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.

- Reduction in HIV transmission (TasP) and acquisition (PEP and PrEP) for individual and population health benefits:
  - Sexual transmission (see sub-title: 1.6.3 Treatment as prevention)
  - Mother to child transmission (PMTCT)
  - Injection drug use.
  - Occupational exposure.

1.6.2 Principles of combination ART

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)
- Good adherence to the regimen must be maintained.

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, making 2nd line ART less effective and if patient on 2nd line then it will be limited for the 3rd line ARV regimen, and resistant virus can be transmitted to others. If virological failure is detected early, a 2nd line regimen including at least 2 new drugs usually supresses the VL once again.

1.6.3 Treatment as Prevention (TasP) and U=U

- **What is Undetectable = Untransmittable?**

  Undetectable = Untransmittable, often shortened to U=U, is the health promotion campaign to promote understanding of the updated clinical findings that demonstrate if someone is on ART and has a sustained undetectable viral load, there is effectively no risk of sexually transmitting the virus to an HIV-negative partner. According to the Prevention Access Campaign (2017), the U=U message is an unprecedented opportunity to transform the lives of millions of people living with, and affected by, HIV and to radically transform the field. It argues that message of U=U has the potential to:

  - Improve the lives of people with HIV by dramatically reducing the shame and fear of sexual transmission, and opening possibilities for conceiving children without alternative means of insemination.
  - Dismantle HIV stigma at community, clinical, and personal levels.
  - Encourage people living with HIV to start and stay on treatment, which keeps them and their partners healthy.
  - Strengthen advocacy efforts for universal access to treatment, care, and diagnostics to save lives and bring us closer to ending the epidemic.

- **Implication of U=U**

  The implications of U=U are highly significant. For so long, being HIV positive has carried stigma, stemming largely from the person with HIV being perceived as a risk to others. This negative characterisation, which has been around since the beginning of the epidemic, has also been internalised by some people with HIV.

  An understanding of U=U can go a long way to alleviating HIV transmission-related anxiety. It can empower people with HIV to be comfortable in the totality of who they are and have a greater confidence to pursue a full sex life.

  Clinicians are likely the first professionals with whom a newly diagnosed person will be able to safely speak. Amidst the understandable fear and concern they may experience, the message of U=U is crucial. This will be particularly so if it gives people with HIV the confidence to disclose their status. It can help substantially address any already existing HIV-related stigma. It can also serve as a significant additional incentive to consider starting ART.[8]

[8] (ASHM. (2017). Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines. Available at http://viruseradication.com/journal-details/Australasian_Society_for_HIV,_Viral_Hepatitis_and_Sexual_ Health_Medicine HIV_pre-exposure_prophylaxis: clinical_guidelines.

- 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 (within 4 hours but no longer than 72 hours) 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 months.
- 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 (PEP), *page 174*.

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).[9]
- 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, STIs and pregnancy etc.
- For more detail on PrEP management see chapter 44, *page 179.*

1.6.7 ARV drugs available in Cambodia[10]

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
    - Tenofovir (TDF)
    - Zidovudine (AZT or ZDV)
    - Lamivudine (3TC)
    - Abacavir (ABC)

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
    - Efavirenz (EFV)
    - Nevirapine (NVP) is going to be phased out soon

3. Protease Inhibitors (PI)

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

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

- Atazanavir combined with low dose Ritonavir (RTV/r)
- Lopinavir combined with low dose Ritonavir (LPV/r)
- Darunavir (DRV)
- Ritonavir (RTV)

4. Integrase Strand Transfer Inhibitors (INSTIs)
    - Dolutegravir (DTG)
    - Raltegravir (RTG)

The integrase inhibitor class agent is utilised in 1st, 2nd and 3rd line ART regimens and for virological failure in highly treatment experienced individuals.

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

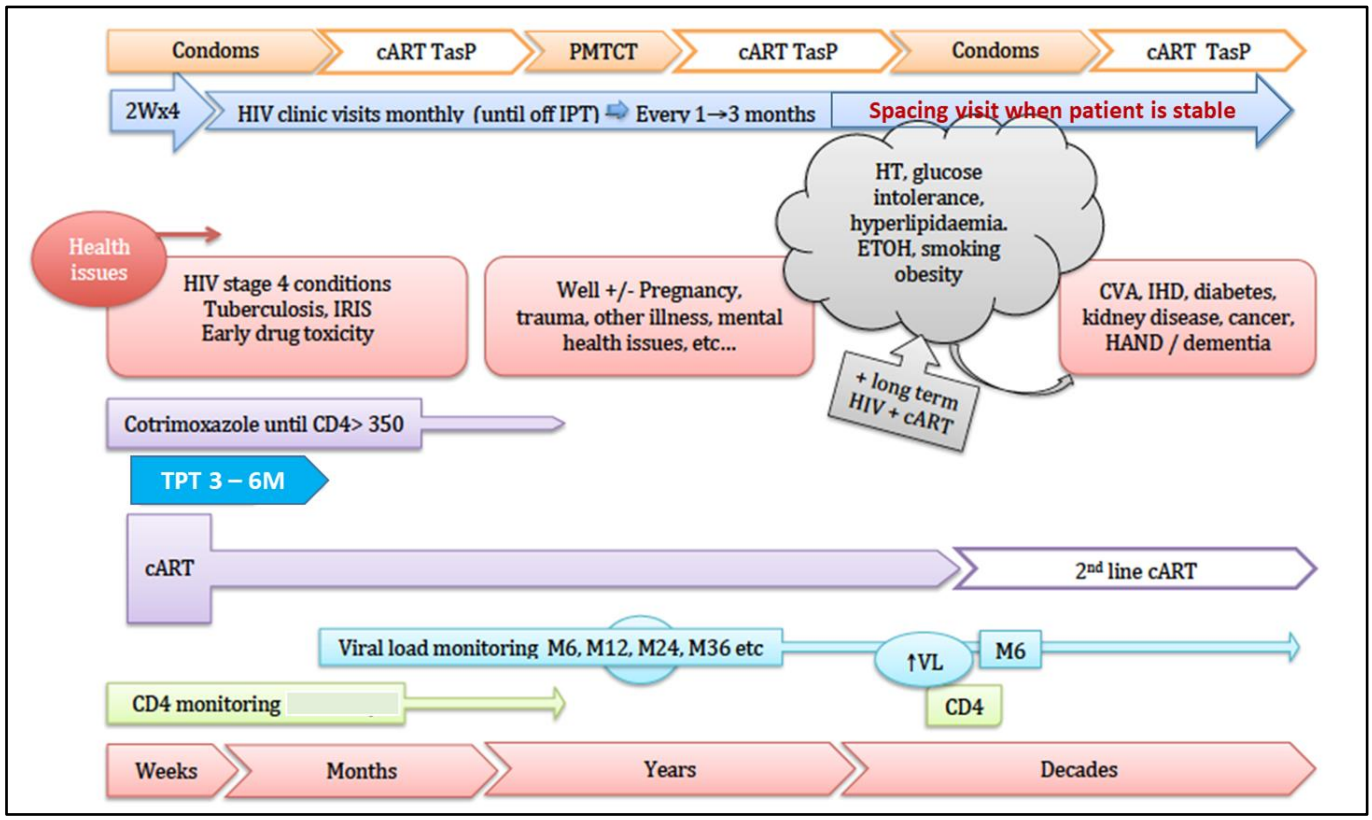
It is anticipated that newer agents in these classes (e.g. NNRTI Etravirine) will be available in Cambodia.

CHAPTER 2: ROUTINE SCHEDULE OF CLINICAL CONSULTATIONS

2.1 Objectives of the early clinical consultations

- Register the patients in the registration book and develop patient record file (new enrolled patients).
- Provide counseling on HIV infection and the benefits of ART to improve quality of life and life expectancy and to reduce the risk of HIV transmission.
- Provide counseling to women of childbearing age on possible future pregnancies.
- Provide counselling on lifelong treatment, side effect of drugs and adherence.
- Provide counseling on how to keep themselves healthier.
- Diagnose and treat any current OI or other medical illness.
- Screen for TB, and either refer for further investigation and treatment or commence TPT.
- 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.

Figure 4: HIV clinical pathway



2.2 Objectives of consultations once the PLHIV is established on ART

- Evaluate quality of life
- 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.

2.3 Laboratory testing timed with clinical consultations

- Laboratory tests should be performed on the same day as clinical visits. It includes VL, CD4 count, CBC, renal and liver function tests, and others.
- Clinicians should anticipate when the next VL is due and CD4 need to be repeated when on OI prophylaxis and schedule the next visit on a day when laboratory testing is possible.
- On the following schedule this is indicated, as xYz (e.g. $_{5}$-6-$_{7}$ 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 Forms, which also serve as checklists of steps for the assessment and follow up of patients. Each point should be followed and documented carefully.
Document clearly, as data is entered into the National database and used for HIV program activity.

More detail regarding clinical assessment see Chapter 45: Annex 2 Routine clinical consultation visit guide, *page 184*.

Table 3: Clinic visit routine schedule

Week	Clinical	Adherence counseling	Laboratory testing	Drugs start /Stop
Week 0	✓	✓	✓	Start ART (If eligible for same day ART initiation)
Week 1		✓		
Week 2	✓	✓		Start Cotrimoxazole if CD4 ≤ 350 or on TB treatment Start Fluconazole preventive therapy if eligible[11] see chapter 7, *page 53.*
Month 1	✓	✓	✓	Start TPT based on regimen used, if eligible see chapter 6, *page 45*.
Every 1 M whilst on TPT	✓	✓	✓ VL at month $_{5}$6$_{7}$	Stop TPT based on regimen used (M6 for IPT and M3 for 3HP)

[11] See flowchart: Cryptococcal antigen screening for asymptomatic patients, page 57

After stop TPT, still on Cotrimoxazole				
Every 1 – 3 months (According to clinical status, + adherence)	✓	✓	✓VL at M $_{5}6_{7}$ then M $_{11}12_{13}$, M $_{23}24_{25}$ etc. ✓CD4 every $_{5}6_{7}$ M	Stop Cotrimoxazole or Fluconazole according to criteria (see Chapter 5: Primary prophylaxis, sub-chapter 5.1 Cotrimoxazole primary prophylaxis, *page 41*)
After stop Cotrimoxazole				
Every 3-6 months	✓	✓	✓VL at every $_{11}12_{13}$ Months	Stable patients on ART ≥ 1 year with viral load < 40 copies/ml are allow for providing ARV drugs up to 6 months ref. Multi Month Scripting (MMS document, *page 2*).

Table 4: 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?
• Cough - any time, any duration
• Fever – anytime, any duration
• Drenching night sweats ≥ 2 weeks duration
• Loss of weight? AND weight the patient at each visit and compare with previous visit.

Table 5: Routine Laboratory investigation

Test	Start ART if eligible for same day ART	Monitoring on 1st line	Treatment failure	Monitoring on 2nd line
HIV Ag/Ab	✓			
CD4 count	but no need to wait for the result before start ART	CD4 every 6 M if on OI prophylaxis No CD4 monitoring once off OI prophylaxis	If new OI including TB At time of switch to 2nd line ART regimen.	CD4 every 6 M if on OI prophylaxis No CD4 monitoring once off OI prophylaxis
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)		if on TDF M1, M3 then every 12M		If on TDF M1, M3 then every 12M. If not on TDF

				every 12 M
HBsAg	if ↑ ALT if considering not starting TDF in ART		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 6: Primary Prophylaxis for opportunistic infection

	Criteria to initiate	Dose	Criteria to stop
Cotrimoxazole	See chapter 5: 5.1 Cotrimoxazole primary prophylaxis, *page 41.*		
	CD4 ≤350 TB at any CD4 WHO stage 3 or 4 All adolescents If not contraindicated	1 DS; (TMP-160mg, SMX-800mg) tablet daily or 2 SS; (TMP-80mg, SMX-400mg) tablets daily.	Age ≥ 20 years and No active TB, and VL undetectable and CD4 > 350 on two occasions > 6 months apart.
Tuberculosis preventive therapy (TPT)	See Chapter 6: Screening for TB and assessment for TB Preventive Therapy (TPT), *page 45.*		
	All PLHIV (including pregnant women) without active TB should have TPT one course If not contraindicated.	Isoniazid 300mg/day + pyridoxine 25 mg/day (if weight < 40kg Isoniazid 200mg/day) See doses of 3 HP regimen, *page 47*.	After 6 months for IPT and 3 months for 3HP
Primary Cryptococcus prophylaxie	See Chapter 7: Cryptococcus screening and prevention, *page 53.*		
	PLHIV with CD4 < 100 If not contraindicated	Fluconazole 100mg/ day	VL undetectable and CD4 > 100 on two occasions > 6 months apart.

Table 7: 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, Hypertension, diabetes, etc.
• Diet: most people need to pay attention to eat • 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 flavors (e.g. lemon juice, pepper) and herbs. • Minimize processed foods (usually high in salt, fat, sugar)
Weight: Maintain BMI between 18.5 – 22.9 (Chapter 33: Nutrition screening and weight management, *page 148.*
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)

Specific populations

CHAPTER 3: WOMEN OF CHILDBEARING 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 is recommended to optimize her own health and for PMTCT is after 6 – 12 months on ART, with undetectable VL, evidence of the increase of CD4 count and completion of treatment for OI.

3.2 Contraception

- Women who wants to delay or avoids pregnancy, contraception should be discussed:
  - Promote 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 (Ritonavir). Injectables (Depo- Provera) or (long acting reversible contraception (LARC) such as implants and Intra Uterine Device (IUD) are preferred.

3.3 Emergency contraception for women on ART

- Emergency contraception (as early as possible ≤4 days).
- If on rifampicin, EFV or PI (Ritonavir), double dose (usual dose is 1.5mg) = 3mg levonorgestral taken as single dose[12]

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 + DTG) and cotrimoxazole if indicated.
- A special focus should be made on supporting adherence to ART in 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)
- Coordination of the management for PMTCT and HIV prophylaxis and testing in the infant should be guided by the NCHADS and MCH SOP for the boosted linked response,[13] and the NCHADS Paediatric HIV treatment guidelines.

[12] MSF HIV/TB Clinical guide 2015, page 85

[13] 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

CHAPTER 4: ADOLESCENTS

- WHO defines adolescents as 10 – 19 years old.[14]
- 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, who may 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 sexual and reproductive health service.

HIV 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 perinatally 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 does 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 adhere to their treatment. They also have a need for family planning and STI services.

Transition into 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.

[14] 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

Most HIV-infected adolescents' transition to adult care between **15 and 20 years of age.** Adolescents who demonstrate independence in making their own decisions and show responsibility for their own care may be ready 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

At the clinic level organisational arrangements required include:

1. Identifying a focal point for communication between the adult and paediatric services.
2. Developing a specific orientation procedure to acquaint the newly transitioned patient to the adult clinic environment, that includes as following:
   - 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.

3. Organisational arrangements for improving the "adolescent friendliness" of the clinic to be considered include:
   - Create a specific clinic time each week for adolescent attendance.
   - Structure this clinic time for shorter waiting periods, and longer consultation times.
   - Invite a counsellor/PSW from the paediatric clinic to join this session.
   - Enable MMM (peer support) adolescent specific activities.
   - Ensure where possible that fees are not charged to the Adolescent.
   - Partner with NGO to provide specific adolescent support to compliment clinic services (where possible).
   - Foster a clinic culture where staff remain non-judgemental and respectful at all times.

4. The paediatric clinic staff will prepare the adolescent for transfer to the adult clinic as follows:
   a) Develop a transition plan with the adolescent, families, and care providers.
   b) 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.

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

Post transition to Adult clinic
The adult care provider must work with the paediatric team if 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 trustful relatives or friends.

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.

Group counselling should be used 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 forum 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 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.

- ***Disclosure to others, risks, and benefits:*** Adolescents should be counselled about:
  - *Potential benefits of disclosure,* such as disclosure (a) to others to obtain the support they need for HIV care and treatment and (b) to sexual partners 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 care givers 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 has individual and public health ramifications.
- Providing a clinical service that is “adolescent friendly” and meets their 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 Key clinical and management issues regarding adolescent care

- WHO clinical staging for adolescents ≥ 15 years is the same as adults, < 15 years is the same as paediatrics.
- Initiation of ART in adolescents is same as adults.
- ART regimen for adolescents ≥ 30kg is the same as for adults. DTG in combination with other NRTIs (except TDF) is recommended for adolescents/adults weighting ≥ 20 kg. For those, whose weight <20 kg, the regimens are same as for children.
- 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.
- TB screening and criteria for TPT are the same for adolescents as adults.
- Cryptococcal screening is also the same for adolescents as adults.

Antiretroviral therapy and prevention of Opportunistic infections

CHAPTER 5: PRIMARY PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS

5.1 Cotrimoxazole primary prophylaxis

- The primary aim of cotrimoxazole prophylaxis is to prevent Pneumocystis Jirovecii Pneumonia (PJP) (previously called Pneumocystis Carrinii Pneumonia (PCP), toxoplasmosis, and major bacterial illness.
- Cotrimoxazole can be commenced 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 illnesses to prevent recurrence).

- Cotrimoxazole is a combination tablet of trimethoprim (TMP), and sulfamethoxazole (SMX).
  Formulations of cotrimoxazole:
  - Cotrimoxazole double strength (DS) = TMP 160mg/SMX 800mg (or 960mg)
  - Cotrimoxazole single strength (SS) = TMP 80mg/SMX 400mg (or 480mg)
  - Cotrimoxazole oral suspension = TMP 40mg/SMX 200mg per 5 ml.

Dosing and administration

- If ≥ 35kg, Cotrimoxazole 960mg x 1 daily or cotrimoxazole 480mg tablets 2 times daily.
  If < 35kg, Cotrimoxazole 480mg 1 time daily.
- If the standard dose of cotrimoxazole is not tolerated (depending on the reason) either reduce the dose of cotrimoxazole to 1 SS tablet daily or use Dapsone 100mg orally once a day if available (for prevention of PJP only – see below).
- Take cotrimoxazole with food to prevent GIT side effects.

5.2 Criteria for Cotrimoxazole prophylaxis

Table 8: Criteria for starting, continuing and stopping cotrimoxazole

	Adolescent (11-19 years)	Adults (≥20 years)
When to start cotrimoxazole	All regardless of CD4 count	• CD4 ≤ 350 cells/mm^3 * • All patients with TB • WHO stage 3 or 4 regardless of CD4 count.
When to continue cotrimoxazole	ALL	• 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)	• CD4 count > 350 cells/mm^3 on 2 measurements at least 6 months apart *and* undetectable VL *and* completed TB treatment.

* Start cotrimoxazole at the third visit. When 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/mm^3 or active TB, cotrimoxazole prophylaxis should be recommenced, and the same stopping criteria is used.

5.4 Contraindications to cotrimoxazole

- Severe allergy to cotrimoxazole or other sulfa drugs
- Severe liver disease
- Severe anaemia or neutropenia
- Severe renal disease: (eGFR< 15mL/min), for moderate impairment (15 – 50mL/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 of malaria (do not use any additional malaria preventive treatment).

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 necrolysis.
- Systemic: fever, dyspnoea and 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 pancytopaenia. (see below Table 9: Management of Cotrimoxazole hypersensitivity rash) 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 9: 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 multiform, moist desquamation	Discontinue cotrimoxazole immediately Hospitalize for supportive care **Never restart cotrimoxazole.**

- Dapsone is less effective than cotrimoxazole in preventing PCP and 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 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 10: 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 SS TMP 80mg/SMX 400mg tablet
Day 6 and continue:	One 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/day 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 PJP 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.

CHAPTER 6: SCREENING FOR TB AND ASSESSMENT FOR TB PREVENTIVE THERAPY (TPT)

- 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.[15]
- Cambodia has a high burden of TB and consequently a high prevalence of latent TB infection in the population.
- PLHIV with TB infection have a 30-50% lifetime risk of developing active TB when having latent TB infection.
- Latent TB infection could be treated with a course of TB drugs as preventive therapy that considerably reduces the risk of development of active TB.

See Chapter 13: Tuberculosis, sub-title 13.7: Diagnosis and Management TB, *page 85*.

6.1 Screening for symptoms of active tuberculosis

Adults and adolescents living with HIV should be screened for TB with a clinical algorithm at *every* clinic visit at ART services. People with immunocompromised systems are at elevated risk of developing active TB which is one of the key risks of mortality among PLHIV. Systematic screening can increase uptake of TPT in order to reduce morbidity and mortality of TB among PLHIV. The regular contact tracing and TB screening should occur particularly among PLHIV at ART service. PLHIV are at higher risk of TB diseases even they are on ART with high CD4 count.

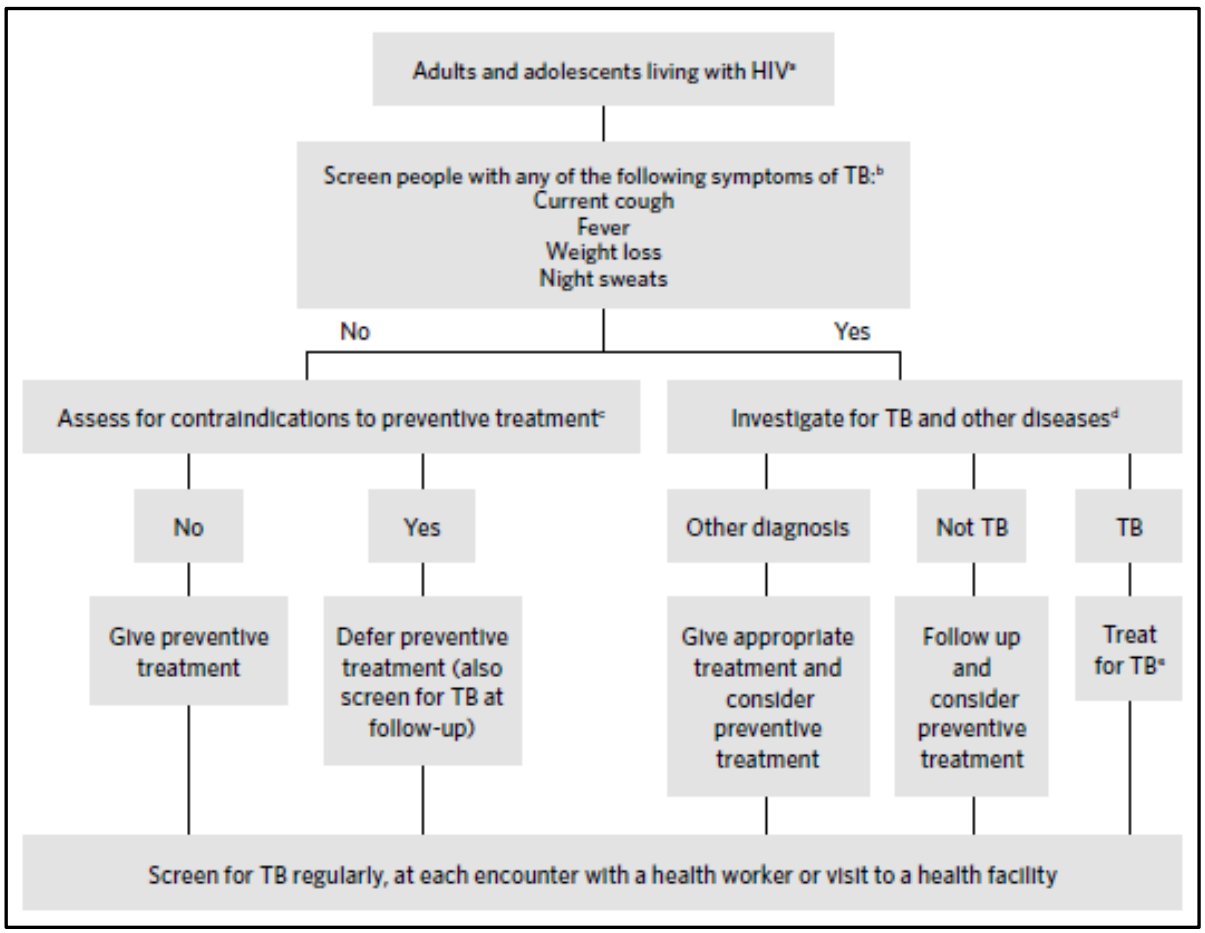
Table 11: TB clinical screening

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 weight the patient at each visit and compare with previous visit.

- PLHIV who have cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB by Chest X Ray and GeneXpert testing 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 TPT unless contra-indicated.
- LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years. (Strong recommendation, moderate-quality evidence. Updated recommendation WHO Latent TB Infection Guideline 2018).

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

Figure 5: Algorithm for TB screening for Adult and Adolescent PLHIV[16]



[a] Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce TB transmission in all settings in which care is provided.
[b] Chest X-ray along with sputum test can be done if available, particularly for PLHIV, but is not required to diagnose TB.
[c] Contraindications include active hepatitis, regular and heavy alcohol consumption and having a signs and symptoms of peripheral neuropathy pre-TPT. History of TB and current pregnancy should not be contraindications for starting preventive treatment. Although LTBI testing is not a requirement for initiating preventive treatment, it may be done as a part of eligibility screening where feasible.
[d] Xpert MTB/RIF should be used as the initial diagnostic test for TB.
[e] Resume regular screening for TB after completion of treatment for active disease.
A person with HIV (infant, child, adolescent and adult) is close contact to a case of pulmonary TB should be offered a course of TPT after exclusion of active TB disease.

[16] CENAT TPT drafted guideline 2019

6.2 Option of TPT, dosage and duration

A) LTBI Treatment regimen for PLHIV

Table 12: Treatmen regimen for isoniazid and rifapentine

Drug regimen	Dose	Considerations
INH daily therapy for 6 months	**Isoniazid:** 5 mg/kg (Max dose per day: 300mg) Plus Vit B6 25mg daily	Daily taken for 6 months
Weekly isoniazid and rifapentine for 3 months (3HP) for all PLHIV ≥ 2 years	**INH** 15 mg/kg (Max dose per day: 900mg) **Rifapentine:** • 10–14 kg = 300 mg • > 14–25kg = 450 mg • > 25–32kg = 600 mg • > 32–50 kg = 750 mg • > 50 kg = 900 mg Plus Vit B6 25mg daily	It is a total of **12 doses.** The drugs should be issued once in 30 days or align with ART schedule if health care providers thrust on patients' adherence. Missed doses can be taken subsequently.

- **3 months of Isoniazid and Rifapentine (3HP):** This is a weekly 2-drug combination regimen consisting of 12 doses. In addition, a supplement of 25 mg of Vit B6 may be given. The drugs should be issued once in 30 days or aligned with ART schedule. Treatment completion is considered when patients completed at least 11 doses over 16 weeks. Missed doses can be taken subsequently. This regimen is ideally best given under a programme of strict supervision.
- There is a new regimen of TB preventive therapy that is not included in this guideline but will be recommended and endorsed by WHO soon.

B) LTBI treatment for household contacts of MDR TB patients

- Confirmation of infection by LTBI testing is required before individualized treatment is initiated.
- The choice of regimen needs to be made in consultation with the TB specialist at the provincial level.
- PLHIV close contacts of Rif-resistant cases without resistance to INH shall be offered IPT.
- PLHIV close contacts of MDR-TB cases shall undergo a LTBI testing unless their CD4 number is below 200mm^3 or they have advanced HIV disease. The regimen shall be chosen in consultation with the national MDR-TB advisory committee.
- The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events.
- The preventive treatment should be given only to household or close contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV).
- Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.

Special Precautions while selecting LTBI treatment Regimen

The medications used in LTBI treatment are very safe but special attention should be given while selecting regimen in some individuals as mentioned below.

Table 13: Precaution while enrolling for LTBI treament

Condition	Precautions
Individuals with abnormal Liver Function Tests If ALT/AST > 3 x ULN, please do not provide.	All the LTBI drugs are potentially hepatotoxic, hence LTBI treatment should not be initiated until the liver function tests become normal
Known case of chronic hepatitis, acute liver failure, chronic renal failure, Uncontrolled diabetes, Gout, porphyria & anemia with G6PD deficiency	LTBI Treatment may be considered based on liver function tests and sound clinical judgment.
Chronic alcoholic individuals	LTBI Treatment may be considered based on liver function tests and sound clinical judgment.
Breast feeding and Pregnant mothers	Do liver function tests before initiating on LTBI treatment. 3HP regimen is contraindicated.
Peripheral neuropathy with signs and symptoms of numbness, blurring, tingling of hands or feet	LTBI Treatment causes neuropathic toxicity and requires asking for even vitamin B6 is provided. If it happens, increase dose of pyridoxine to 50 mg daily, and if still persistent, stop TPT.

Guidance to health care providers during treatment of latent tuberculosis infection (LTBI) with a combination regimen of isoniazid and rifapentine in 12 once-weekly doses (3HP)

- Evaluate all for active tuberculosis disease both before and during treatment of LTBI.
- Inform the patient or parents about possible adverse effects and instruct them to seek medical attention when symptoms of possible adverse reaction first appear, particularly drug hypersensitivity reactions, rash, hypotension, or thrombocytopenia.
- As rifapentine may also antagonize hormonal contraceptives, women who use hormonal birth control should be counseled to add or switch to a barrier method.
- Conduct monthly evaluations to assess treatment adherence and adverse effects, with repeated patient education regarding adverse effects at each visit.
- Order baseline hepatic chemistry blood tests (at least aspartate aminotransferase [AST]) for patients with the following specific conditions: human immunodeficiency virus infection, liver disorders, postpartum period (≤3 months after delivery), regular alcohol use, injection drug use, or use of medications with known possible interactions.
- Conduct blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease. Discontinue 3HP if a serum AST concentration is ≥3 times the upper limit of normal.
- In case of a possible severe adverse reaction, discontinue 3HP and provide supportive medical care. Conservative management and continuation of 3HP under observation can be considered in the presence of mild to moderate adverse events as determined by health care provider.

Contraindications

- INH-based TB preventive therapy treatment is not recommended for contacts of INH resistant TB.
- INH should not be given to persons with known pre-existing liver damage to avoid an additive effect on liver function.
- INH can cause peripheral neuropathy. It must be very cautious when INH is provided to persons who have severe disease. Vitamin B6 helps prevent peripheral neurophathy.
- 3HP should not be given to children less than 2 years old.
- 3HP should not be given to pregnant or breastfeeding women as there is currently insufficient data to support the use of rifapentine in pregnancy.
- Rifamycine based preventive regimens are not recommended for contacts of a rifampin resistant TB case. Delay the start of any Rifamycine based TPT if a person with HIV is on malaria treatment. If malaria occurs during TPT using a combination of drugs including rifamycines, continue treatment except in case of severe malaria.

6.4 Side effects:

- TPT 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. It may present with anorexia, nausea, vomiting, jaundice
  - Peripheral neuropathy: It can be tingling/burning/numbness in the hands and feet – largely prevented with pyridoxine, the dose can be increased to 100mg daily if symptoms appear. If persistent, cease INH.
  - Hypersensitivity reaction
  - **Flu-like syndrome: Rate is approximately 3 to 4%.**
    - Fevers or chills PLUS
    - Weakness, fatigue, muscle or bone aches, tachycardia or palpitations, flushing, syncope, dizziness, headaches, conjunctivitis, sweats, other similar symptoms.
  - Skin problem is rare. It presents in rash, itching, swelling of face or lips (angioedema), anaphylaxis
  - Respiratory problem is rare. It presents shortness of breath, bronchospasm.
  - Severe hypersensitivity–rare < 0.3%. Hypotension, tachycardia, syncope, bronchospasm, anaphylaxis.

6.5 Counseling on TPT to the patient:

- The patient has been informed and understands to take
  - IPT for 6 months duration
  - Weekly isoniazid and rifapentine for 3 months (3HP).
- 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 TPT

The patient should return to clinic every month – at each time, health care providers should perform as follows:

- Assess for any clinical indication of drug toxicity
- Assess adherence
- Screen for active TB (every visit, continue whilst on, and after TPT)
- Dispense 1 month of drugs to patients based on the regimen used or align with the ART schedule if patients adhere to treatment plus pyridoxine.

As individuals who receive treatment for LTBI do not have active disease, their risk for adverse events during treatment must be minimized. Adverse reactions have been associated with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy, and hepatotoxicity), rifampicin and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance, and hepatotoxicity). While most of these reactions are minor and occur rarely, specific attention should be paid to preventing drug-induced hepatotoxicity.

Individuals receiving treatment for LTBI should be monitored routinely at monthly visits to health care providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. Patients receiving treatment should be advised to contact their health care provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. If a health care provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately.

Isoniazid is generally safe. The primary toxicities of isoniazid are peripheral neuropathy and hepatotoxicity (incidence of significant hepatotoxicity is 0.1%). With the high prevalence of viral hepatitis co-infection among PLHIV and risk of hepatotoxicity and neuropathy from ARTs, it is reasonable to monitor closely for these side effects. Rifamycines associated more frequent adverse events are hypersensitivity reactions, myelosuppression, and liver toxicity. Rifamycines are powerful inducers of cytochrome P450 therefore they present several drug-drug interactions with other drugs, including antibiotics, birth control/hormones, malaria drugs, antifungal drugs and antiretrovirals.

Clinicians should inquire about:

- Adherence to daily doses of isoniazid and pyridoxine (vitamin B6) and/or rifampicin or rifapentine
- Possible side effects: Numbness or tingling in the hands or feet, Nausea, vomiting, Abdominal pain, Anorexia, Dark urine, or Jaundice.
- Patients with pre-existing peripheral neuropathy should be monitored regularly for worsening of these symptoms. If the patient has worsening of severe peripheral neuropathy, vitamin B6 shall be prescribed, if no improvement isoniazid should be discontinued. Pyridoxine is also indicated for patients under TPT at higher risk of neuropathy such as persons with diabetes, renal failure, and alcoholism.

- Enquire about TB symptoms at each visit. If there are symptoms suggestive of active TB (fever, cough, or drenching night sweats). If so, start the diagnostic workup to rule out active TB.
- There is insufficient evidence to support testing of baseline liver function. It is, however, strongly encouraged, where feasible, for individuals with the following risk factors: history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested and DON'T start TPT if liver enzymes are > 3 time of upper normal limit at baseline.
- Liver enzymes (AST and ALT) should be checked at baseline and at month 1 and month 2. If normal, LFT's should be repeated only if symptoms of hepatitis are noted on follow-up. If the patient has abnormal LFT's at baseline, or test positive for hepatitis B or C, then check LFT's monthly for the first 4 months.
    - If AST or ALT are more than 3 times ULN, interrupt treatment.
- Enquire about sign and symptoms of each visit. If signs of hypersensitivity occur under Rifamycines (anaphylaxis, flu-like syndrome, skin rash) treatment shall be interrupted and after clinical re-evaluation an INH based TPT shall be initiated.
- Preventive treatment regimens containing high dose INH and shall be given with pyridoxine (vitamin B6) supplementation (25mg on the day of the weekly dose).
- For patients aged more than 20 years old and or for patients with chronic hepatitis, patients who are pregnant or have recently given birth and/or patients with alcoholism, close monitoring of liver toxicity is indicated possibly including laboratory testing. The only regimen recommended among pregnant women is INH.

6.7 Potential adverse reactions of each drugs and symptom-based approach for evaluation of adverse reactions

Table 14: Potencial adverse reaction and action to be taken

Symptoms	Drugs responsible	Action to be taken
Nausea, vomiting or epigastric discomfort	INH, Rifapentine	Advise individuals not to take medications on empty stomach, reassure & advise them to take medication water. Anti-emetics may be given in rare cases
Flu like syndrome and hypersensitivity	INH and Rifapentine	Withhold 3HP and offer ancillary treatments for symptomatic management as appropriate Bronchodilators Steroids
Mild itching/Rashes	INH and Rifapentine	Withhold 3HP Offer supportive treatment Antihistamines Steroids

Tingling/burning/numbness in the hands and feet	INH	Increase the dose of Vitamin B6 to 50mg and if persistent, stop it.
Hepatitis: Anorexia, Nausea, vomiting, Jaundice	INH, Rifapentine	Stop the medications and evaluate liver function tests.

6.8 Drug interaction

INH increases	Rifapentine decreases
• Anticonvulsants • Anticoagulants • Anti-retrovirals (Efavirenz) • Some SSRIs • Antifungals • Antipsychotics • Anti-malarials (halofantrine)	• Hormonal contraceptives • Anti-retrovirals (PI, NVP) • Antifungals • Anti-coagulants • Diabetic sulfonyureas • Cardiac glycosides • Steroids • Anti-malarials • Anti-psychotics

For further detail, please see the CENAT's Programmatic Management of Latent Tuberculosis Infection, 2019.

CHAPTER 7: 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, with those with CD4 < 50 at particularly high risk.

- Fluconazole has been routinely prescribed in Cambodia as 1st prophylaxis however whilst it reduces the incidence of CM there is not clear evidence that it impacts on survival.
- 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.
- Screening for CRAG followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm3.
- When CRAG screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm3.
- Asymptomatic cryptococcal infection detected by CRAG test may precede clinical disease by weeks – months.
- The most effective prevention strategy is the early commencement of ART, and after commencement of ART a substantial proportion of patients will seroconvert from CRAG positive to CRAG negative.
- Clinical scenarios at the time of diagnosis of CRAG positive include:
  - Symptomatic cryptococcal meningitis (CM)/other cryptococcal disease
  - Asymptomatic cryptococcal meningitis (CM)
  - Isolated positive cryptococcal antigenaemia (IPCA).
- PLHIV diagnosed with symptomatic or asymptomatic CM require hospitalization and standard treatment (see Chapter 17: Cryptococcal meningitis (CM), *page 101.*
- IPCA must be treated with fluconazole 800mg for 2 weeks followed by 400mg for 8 weeks and followed by 200mg/day ≥ 1 year *and* VL undetectable *and* CD4 > 100 cells / mm^3 on two occasions > 6 months apart [17].
- Previous studies in Cambodia have found ~ 20% of symptomatic and asymptomatic PLHIV with CD4 < 100 were CRAG positive, and at another site ~ 8% of asymptomatic patients at the time of entry into HIV treatment were CRAG +.

The advantages of a screen and treat approach: compared with 1st fluconazole prophylaxis

1. Avoid treating those who are at very low risk:
   - Drug complexity, toxicity
   - Women of childbearing age and pregnancy (Pregnancy Cat C)
   - Antifungal drug resistance.
2. Clinical benefits:
   - CRAG + triggers close evaluation and LP to look for active infection (asymptomatic CM) requiring amphotericin.

[17] WHO, Guideline for Managing advanced HIV disease and rapid initiation of anti-retroviral therapy, July 2017

- More intensive treatment of CRAG+ isolated antigenaemia
- And close monitoring after start ART for IRIS.

3. Pre-emptive treatment:
   - Treatment for asymptomatic (IPCA) is safer, more accessible, and less resource intensive than treatment required once symptomatic; hospitalization (amphotericin and Flucitocine/repeated LP).

7.2 Fluconazole first line prophylaxis

Until CRAG is available 1st fluconazole prophylaxis 100mg daily is still recommended according to the following criteria:

- Adult PLHIV with CD4 < 100 cells / mm^3
- Exclusion criteria
  - 1st trimester of pregnancy
  - AST/ALT > 3x ULN.

Monitor AST/ALT at day 0, and month 1 and 2 and if normal, only do again if clinically indicated.

- If HBV or HCV co-infection, or abnormal at AST/ALT at baseline, continue to monitor AST/ALT monthly for 4 months.
- Cease fluconazole if AST/ALT > 3 times of ULN and symptomatic, or AST/ALT > 5 times of ULN and asymptomatic.

Stop fluconazole 1st prophylaxis when VL undetectable and CD4 > 100 on two occasions > 6 months apart.

7.3 Cryptococcal antigen (CRAG) screening

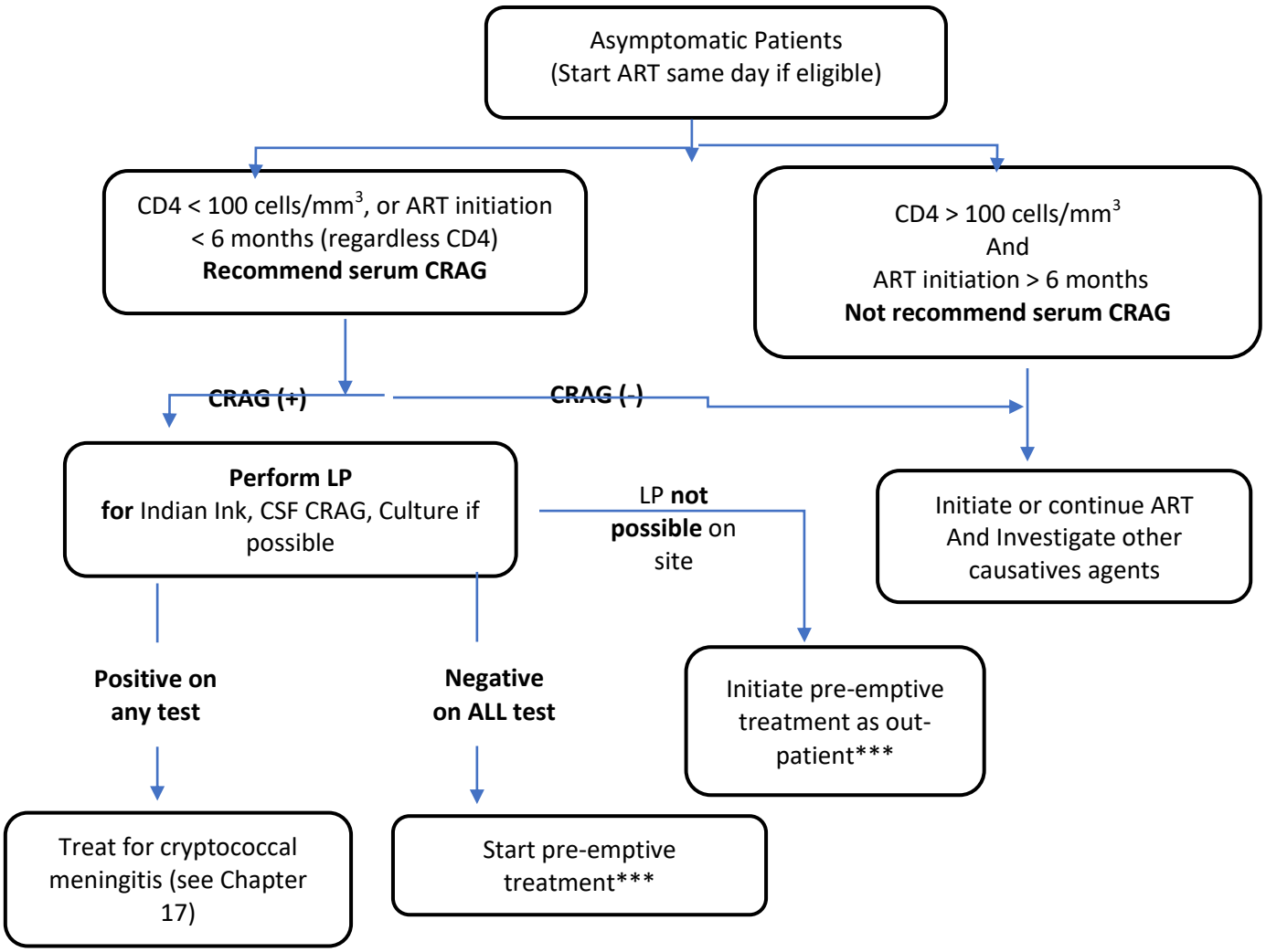
The CRAG testing is for screening purposes only. If a patient has symptoms of meningitis, they should proceed directly to LP rather than wait for CRAG test result. (see chapter 16.2 Investigation and diagnosis of meningitis**,** *page 99*)

- For all newly enrolled adult and adolescent PLHIV, if the CD4 < 100 cells/mm^3 the laboratory will automatically go on to perform a CRAG test on the same day.
- Serum CRAG + $\rightarrow$ call patient to return to be evaluated for symptoms/signs of meningitis.
- Serum CRAG +, and symptoms / signs of meningitis $\rightarrow$ immediately start fluconazole 1200mg one dose and refer for urgent lumbar puncture. (see Chapter 17: Cryptococcal meningitis, *page 101*).
- If serum CRAG positive, and NO SYMPTOMS or SIGNS of meningitis, it is recommended for lumbar puncture where possible for CSF testing (CRAG, India Ink and culture).
  - If the result of any test is positive, treat Cryptococcus meningitis or
  - If all results of tests are negative, start pre-emptive treatment as out-patients.
  - In case of LP is unable to perform, start pre-emptive treatment

- Pre-emptive treatment regimen: fluconazole 800mg/day for 2 weeks followed by 400mg for 8weeks and followed by Fluconazole 200mg/day until ≥ 1 year *and* VL undetectable *and* CD4 > 100 cells/mm^3 on two occasions > 6 months apart.

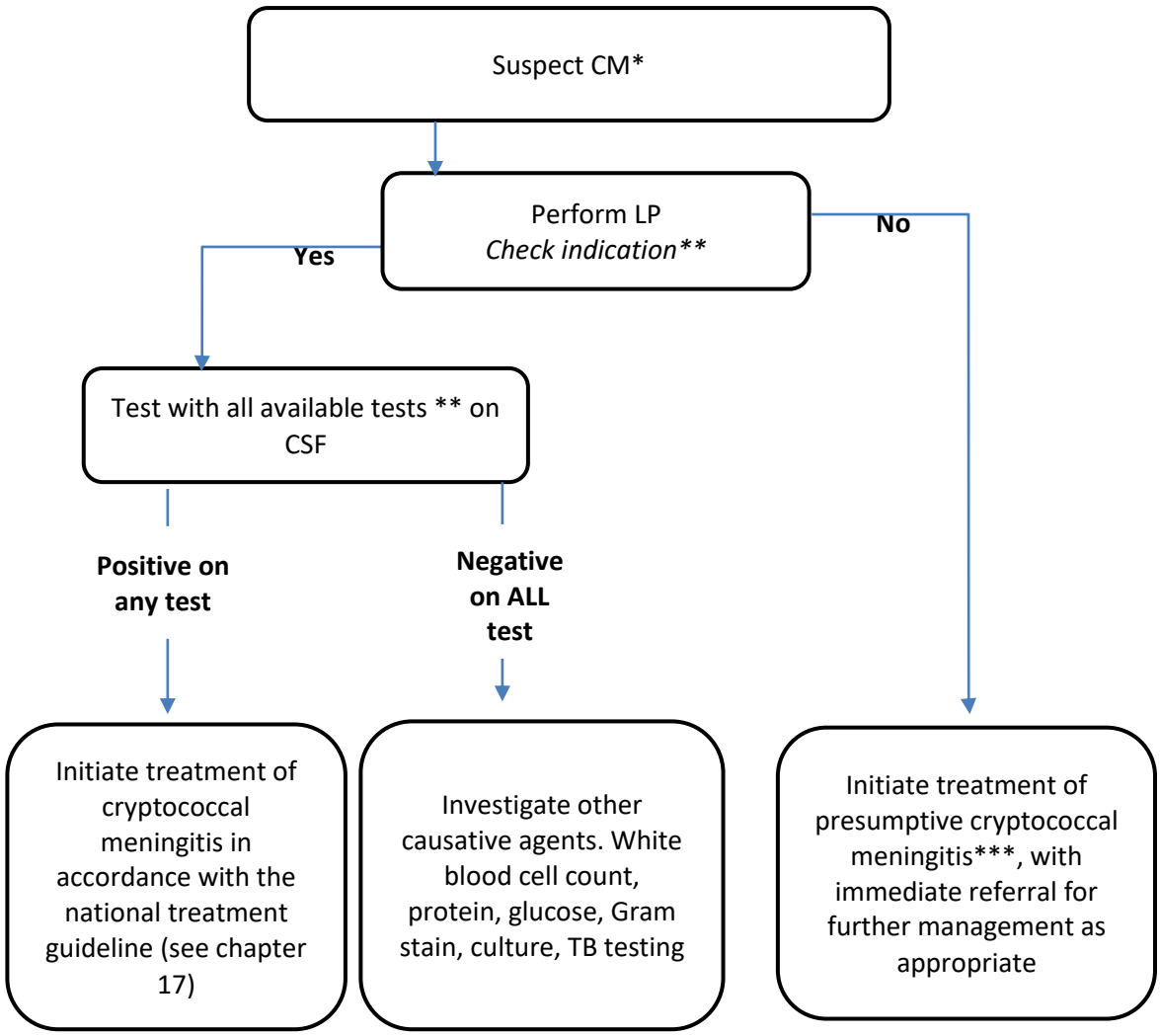
- If CRAG negative → No fluconazole.
- Women of childbearing age who screen CRAG positive should have a pregnancy test prior to starting fluconazole (teratogenic); those who are not pregnant and are started on fluconazole should be advised to avoid pregnancy during treatment.
- CRAG-positive patients who are pregnant should be offered an LP and discussed with an expert before a decision is made regarding management.

Figure 6: Cryptococcal antigen screening for asymptomatic patients



***Start pre-emptive treatment:
Fluconazole 800mg oral daily for 2 weeks; then 400mg for 8 weeks and followed by maintenance of fluconazole 200mg daily until CD4 > 100 cells/mm^3 in 2 consecutive measurements of 6 month apart.

Figure 7: Cryptococcal antigen screening for symptomatic patients



*Headache, neck stiffness, sensitivity to light, seizures, fever, convulsion, blurred vision
** Contraindications consist of focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography. Raised intracranial pressure does not contraindicate lumbar puncture in (suspected) cryptococcal meningitis. Other contraindications include major spinal deformity and patient refusal after fully informed consent was sought.
**all available tests include CRAG, Indian Ink and culture and result provided within 24h
*** provide Fluconazole 1200mg one dose and promptly refer the patient to RH where LP and and management are able to provide.

CHAPTER 8: STARTING COMBINATION ART

ART initiation should be provided **same day** as people have been identified and confirmed as HIV infected.

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

Combination ART (ART) should be offered to all PLHIV regardless of CD4 count. Same Day ART Initiation should be done for all new enrolment patients at ART clinic if they have no contraindication (see below sub-title 8.4: non-eligibility for same day, *page 58*).

Table 15: Criteria to start ART and when to start ART in adults and adolescents

Who should start ART	All regardless of CD4 count

When to start ART	• Start ART at ART clinic on the same day of HIV confirmation at VCCT in case of patient asymptomatic and no contraindication with same day ART.
	• HIV re-test is needed before starting ART but should not wait for the result of re-test. HIV retesting can be performed with the blood that is collected for baseline monitoring purposes include CD4 count, CBC, Liver, and kidney function tests, etc.
	• With some opportunistic infections, delay in ART initiation are required after initiating OI treatment*
	  • Cryptococcal 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 Definition of same day ART initiation

Initiation ART at ART clinic on the same day of HIV confirmation at VCCT for adolescents and adults who have no contraindication to the criteria of the same day ART initiation.

8.3 Eligibility for same day ART initiation

- Anyone with a new confirmed HIV diagnosis
- New HIV infected adolescents and adults enrolled in ART clinic
- No experience using ART, except ARV prophylaxis such as PEP, PrEP and PMTCT.
- Asymptomatic infection
- No use of nephrotoxic drugs
- No history of renal failure.

8.4 Reasons for possible non-eligibility for same day ART initiation

Patients for whom the same day ART might be medically complicated and need prior well managed active opportunistic infection before initiating ART.

- TB symptoms or TB screen positive
- Suspected PCP, cryptococcal meningitis or other severe OIs
- Patient had experience on ART for HIV/AIDS
- Use of nephrotoxic drugs
- Patient with drug use, high toxicity and could not provide counseling.

In case of patient suspected any OI such as TB, PCP, Cryptococcal Meningitis, Toxoplasmosis, etc., diagnosis work-up need to be done and ART initiation is deferred. If patient started OIs treatment or on OIs treatment, ART initiation should be initiated based on the eligibility condition of diseases see table 17: Timing of ART initiation in setting of active OIs, *page 61*.

8.5 First line ART regimens

- **Dolutegravir (DTG)**

An updated systematic review conducted in 2019 to support the guidelines reaffirmed that a first-line regimen of DTG combined with two nucleoside reverse-transcriptase inhibitors (NRTIs) leads to higher viral suppression and lower risk of discontinuing treatment and developing HIV drug resistance compared with EFV 600mg-based regimens among treatment-naïve adults. DTG has other advantages over EFV, including lower potential for drug–drug interactions, more rapid viral suppression, and a higher genetic barrier to developing HIV drug resistance. DTG is also active against HIV-2 infection, which is naturally resistant to EFV, ref https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/.

- **Efavirenz 400 mg**

The updated systematic review found that EFV 400 mg is better tolerated than EFV in standard dose (EFV 600 mg), with lower risk of treatment discontinuation and severe treatment related adverse events. Regimens containing EFV 400 mg and EFV 600 mg were comparable for viral suppression, mortality, and mental and nervous system adverse events. EFV 400 mg can be co-administered with rifampicin containing anti-TB treatment, with co-administration well tolerated and plasma concentrations maintained above the levels considered to be effective. (see Update of recommendations on first – and second line Antiretroviral Regimens, WHO 2019; https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/).

Table 16: Standard 1st line ART regimens

Weight	Preferred first line	Alternative first line	Special circumstances*
20 kg – 30 kg	ABC + 3TC + DTG*	ABC + 3TC + EFV 400	AZT + 3TC + DTG AZT + 3TC + EFV 400 AZT + 3TC + LPV/r ABC + 3TC + LPV/r

> 30 kg	TDF + 3TC + DTG*	TDF + 3TC + EFV 400**	ABC + 3TC + DTG ABC + 3TC + EFV 400 AZT + 3TC + DTG AZT + 3TC + EFV 400 TDF + 3TC + ATV/r (or LPV/r)*** TAF****+ 3TC + DTG

*Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy. Dolutegravir (DTG) is part of a new class of ARVs: the integrase strand transfer inhibitors (INSTIs). DTG offers clinical and programmatic advantages over efavirenz (EFV) for use in first-line therapy.

** EFV 400 mg is expected to be safe for pregnant women to use, like EFV 600 mg. EFV 400 mg can be co-administered with rifampicin containing anti-TB treatment, with co-administration well tolerated and plasma concentrations maintained above the levels considered to be effective.

*** ATV/r is given when age is ≥ 35 kg.

****TAF may be considered for people with established osteoporosis and/or impaired kidney function, if it is available.

8.5.1 Preferred 1st line regimen

TDF 300mg + 3TC 300mg+ DTG 50mg

TDF/3TC/DTG is available as a once-daily, triple fixed-dose combination (FDC)**, once daily regimen.**

- TDF 300mg + 3TC + DTG, FDC tablet is the preferred first line ART regimen provided if there are no contraindications.
- The regimen is highly effective and well tolerated, less drug-drug interactions, to be taken once daily regardless with or without food.
- DTG for TB co-infected patients: Patients taking rifampicin must take an extra dose of DTG 50 mg single tablet until two weeks after stopping rifampicin.
- 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 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.
- The benefits and risks of using DTG at conception were assessed by reviewing the latest data from Botswana, other countries and modelling the population-level risks and benefits of DTG use among women of childbearing potential. The risk of neural tube defects associated with using DTG at conception has declined since the initial report released in May 2018 yet remains statistically significantly higher than in other ARV drug exposure

groups. Continued surveillance is needed to more definitively confirm or refute the neural tube defect signal, and several studies are ongoing to address this.

- A woman-centered and a rights-based approach should be applied to give autonomy in decision-making by providing information about risks and benefits and guidance appropriate to her situation.
- Women should be provided with information about benefits and risks to make an informed choice regarding the use of DTG or other ART. [18]

8.6.2 Contraindications to preferred first line ART

TDF + 3TC + DTG

- TDF is contraindicated in renal failure and should not be started if the eGFR < 50 ml/min.
  - ➢ Substitute ABC – 600mg qD over TDF.

8.7 Alternative first line agents

ABC + 3TC (FDC) + DTG 50mg or EFV 400mg
or
TDF + 3TC + EFV 400

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, then check the VL, 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).

Effavirenz (EFV) 400mg

- Patients who are experiencing significant side effects due to EFV who are currently taking FDC of TDF + 3TC + EFV, can be given the option to switch to DTG + FDC dual NRTI if the last VL undetectable (VL result less than 6 months).
- Patients currently doing well on FDC TDF + 3TC + EFV 600 mg should change to the triple FDC EFV 400 mg as recommended schedule from logistic unit.

[18] https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/.

8.8 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 same day ART initiation of ART improves VL suppression, retention, 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 17: Timing of ART initiation in setting of active OIs

Opportunistic Infection	Time from start treatment for OI and start ART
Tuberculosis[19] CD4 < 50, not TB meningitis: TB meningitis, any CD4: CD4 > 50: *DR-TB any CD4, not meningitis*	 Within 2 weeks 2 – 8 weeks 2 – 8 weeks *Within 2 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

8.9 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.

[19] 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

CHAPTER 9: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

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

9.1 Main contexts in which IRIS occurs

IRIS may occur when the patients in the following condition.

- Previously asymptomatic infections becoming symptomatic (unmasking IRIS)
- Apparent worsening of symptomatic infections even if they are being successfully treated (paradoxical IRIS)
- Reaction to remnants or antigens of previous OIs after ART treatment.

The risk of IRIS is higher for those patients who:

- Started on ART at lower CD4 counts and higher viral loads,
- Where there is a high pathogen burden such as in disseminated infection.
- When 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' seen 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 DR-TB.

- IRIS may occur with many infectious and non-infectious manifestations of HIV:
  - HBV and HCV $\rightarrow$ hepatitis
  - CMV $\rightarrow$ vitritis
  - Dermatological conditions – VZV, folliculitis.
  - CNS conditions – Cryptococcus, toxoplasmosis, TB, JCV, PML
  - Multi organ symptoms – MAC, TB, fungi
  - PCP, peniciliium, histoplasmosis, etc.
  - Kaposi sarcoma
  - Leishmanniasis.

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.
- Consider Investigation of sputum via 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 diagnosis of MAC.
- Start/continue standard treatment for the OI.
- Recommence OI treatment 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 is occasionally required if symptoms become severe (e.g. dyspnea, 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.
3. If high dose prednisolone (>20mg) for more than 2 weeks is planned, treat empirically with albendazole 400mg orally with fatty food 12 hourly for 7 days[20].

[20] 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 SE 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[21].

10. 1 Common side effects

10.1.1 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 but it is already phased out by WHO, lactic acidosis can occur with any NRTI particularly AZT, although is very rare with TDF, ABC, 3TC, FTC.
- 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:** include nausea and vomiting, abdominal pain, dyspnea, 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 is also present in sepsis or circulatory failure, so a thorough clinical assessment is required.

Diagnosis

- A raised lactate of > 5mmol/ litre together with acidosis as measured by low serum bicarbonate (<20mmol/l).

[21] MSF HIV/TB Clinical Guide 2015, and WHO Consolidated guidelines 2013.

- However, when lactate test is not available a low serum bicarbonate (<20mmol/l) which directly tests for acidosis, is adequate for the diagnosis provided the clinical context is compatible.
- Associated abnormalities include ↑ALT/AST and ↑ creatinine kinase.

Management

- If minor symptoms and bicarbonate < 20mmol/ml → switch NRTI from AZT to TDF or ABC.
- If severe symptoms +/or bicarbonate < 15 mmol/ml→ admit the patient to hospital and 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 switch the ATV/r to TDF or ABC.
  - If the patient is already on LPV/r or ATV/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% (but often mild), GIT and respiratory symptoms including cough, dyspnea, 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 rash, 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 can be commenced.

10.2.3 Pancreatitis

- Pancreatitis can also rarely be caused by 3TC.
- Pancreatitis is also caused by gall stones, alcoholism, and hypertriglyceridemia. (associated with PI).
- **Monitoring for pancreatitis:** symptomatic.
- **Clinical presentation**: abdominal pain
- **Diagnosis**: Raised amylase or lipase, abdominal ultrasound.
- **Management:** If the amylase is < 1.5 times than ULN and the symptoms are not severe, and the diagnosis is not clear, review in 1 week with repeat amylase. If unwell, or amylase > 1.5 times than ULN +/or US findings are suggestive, then cease the ART, give supportive care, and when recovered restart ART not containing 3TC.

10.3 Serious side effect 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, *page 165*.
- **Risk factors** include older age, male sex, low body weight, advanced HIV infection, pre-existing decrease in kidney function, comorbidities (diabetes, HTN, HCV co infection) concomitant use of nephrotoxic and renal excreted drugs, and following a ritonavir boosted protease regimen.

Baseline testing and monitoring for TDF toxicity[22]

- Routine baseline creatinine and estimation of eGFR, with ongoing monitoring is strongly advised if resources permit.
- However, WHO advises that baseline creatinine and estimation of eGFR is not mandatory before starting TDF, but should be performed for all high-risk people including older age, pre-existing decrease in kidney function, long term diabetes or HTN, concomitant use of PI, nephrotoxic or renal excreted drugs. [22]
- Do not initiate TDF if eGFR < 50ml/min, or in long term diabetes, uncontrolled hypertension, or renal failure.
- Serum creatinine and urine dipstick should ideally be routinely checked at 0, 1, 3, and 12 months after starting TDF.[23]
- 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 check serum creatinine.

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.

- If HBsAg positive: there is a risk of hepatitis flare once 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.

Adjusting drug doses of ART and other drugs in kidney disease

Regardless of the cause of kidney injury

- Avoid nephrotoxic drugs if at all possible (esp. NSAIDS)
- Alter any drug doses of renally excreted drugs: Table 61: Drug dose adjustments in patients with renal failure, *page 198.*

[22] WHO Consolidated guidelines 2013
[23] MSF HIV/TB clinical guide 2015

- Monitor the renal function for changes in eGFR which may require further dose adjustments.

10.3.2 Haematological 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 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 reinstituted at a later stage.

10.3.3 Hepatotoxicity

- Hepatitis reactions may occur with a wide range of medications including TB drugs, ARV, and other agents used in the context of treating PLHIV, including other antimicrobials, such as cotrimoxazole, fluconazole, lipid lowering agents, 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 times ULN, +/or icterus (jaundice) +/or 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 were on an NNRTI to protect against ineffective monotherapy, however if the patient is critically unwell then the NRTI should be stopped also.
- 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 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 EFV is implicated → start DTG (never use NNRTI again)
  - If DTG is implicated → start PI
  - 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 NV than EFV) and cotrimoxazole.
- For management of a rash clearly caused by cotrimoxazole see Table 9: Management of Cotrimoxazole hypersensitivity ras, *page 45*.
- Rash is also a component of abacavir hypersensitivity however this reaction tends to be dominated by the associated 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 +/- pruritic, 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 EFV, restart using ATV/r once settled.
  - Once established back on ART, reintroduce cotrimoxazole using desensitization regimen.

- Table 10: Cotrimoxazole Desensitization Protocol (adults + adolescents), *page 44*.

- **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

10.4.1 Metabolic effects

- Protease inhibitors contribute to the risk for metabolic disease including hyperglycaemia/ insulin resistance and diabetes, hyperlipidaemia, 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 lopinavir/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 18: 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 Hb D0, M1, M3, every 6M	Switch to TDF or ABC
	Myopathy,		Symptomatic; if muscle pain or weakness check CK	
	Lipoatrophy,	Long term ART	Symptomatic decrease in fat in face, limbs, buttocks	
AZT, TDF	Lactic acidosis, or severe hepatomegaly and steatosis	Prolonged > 6 months NRTI High BMI, female	Symptomatic: if N + V, abdominal pain, dyspnea, fatigue check: bicarbonate, AST/ALT, CK, lactate	If on AZT Switch to TDF or ABC If on TDF or ABC consult an expert.

ARV drug	Toxicity	Risk factors	Monitoring and Management	Switch options
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, uncontrolled HT. Assess and treat other causes of kidney injury (dehydration, BP etc.) *Stop nephrotoxic drugs – esp. NSAIDS* 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	Very rare NRTI class effects			
EFV	CNS – light headedness, abnormal dreams, mental confusion, depression, convulsion	History of depression or seizures	Typically resolve over weeks but may persist.	Change to DTG
	Male gynaecomastia			
EFV and NVP	Hepatotoxicity	Underlying hepatitis disease, hepatotoxic drug NVP only: women CD4 > 250 Men CD4 > 400	AST/ALT D0, M1, M3 Symptomatic monitoring	Switch to DTG or PI
	Rash and hypersensitivity syndrome (Steven's Johnson) (see Chapter 30: Skin disease)			
ATV/r	Indirect hyperbilirubinaemia (clinical jaundice)		If asymptomatic and ALT/AST normal, no change	
	Electrocardiographic abnormalities (PR interval	Pre- existing conduction disease.	Avoid concomitant use of other drugs which may prolong	

ARV drug	Toxicity	Risk factors	Monitoring and Management	Switch options
	prolongation)	Hypokalemia	PR	
	Nephrolithiasis and risk of prematurity			LPV/r (or DRV/r when available)
Protease inhibitors	Hepatotoxicity	Underlying hepatitis disease, hepatotoxic drugs	AST/ALT D0, M1, M3 Symptomatic monitoring	Switch LPV/r or DRV/r to ATV/r
	Diarrhea and GIT (worst with LPV/r)			Switch LPV to ATV/r
	Metabolic syndrome (LPV/r worst), diabetes, dyslipidaemia, pancreatitis	Heritable, and modifiable risk factors	Annual diabetes, and lipids test. BP every visit. Lifestyle advice.	Switch LPV/r to ATV/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, torsarde de points)	Pre- existing conduction disease. Hypokalemia	Avoid concomitant use of other drugs which may prolong QT or PR interval	
	Skin and hypersensitivity reactions			
Dolutegravir (DTG)	Insomnia and headache			
	Hepatotoxicity	Underlying hepatitis disease, hepatotoxic drugs	AST/ALT D0, M1, M3	
	Hypersensitivity reactions			

CHAPTER 11: MONITORING RESPONSE TO ART

There are essentially three levels of monitoring ART.

Table 20: WHO definition of clinical, immunological and vilogical failure, *page 75* and Figure 9: Viral load monitoring, *page 74.*

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 enhanced adherence support, +/- a change in ART to a 2nd line regimen.
- **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 are not available.
- See the 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 +/or IRIS once commenced on ART.
- If CD4 < 350; 6 monthly CD4 monitoring is required until OI prophylaxis can be ceased. After, if routine VL monitoring is available, CD4 monitoring can be ceased.
- In the event of virological failure, the CD4 count should be checked.
- See CD4 testing algorithm below.

11.3 Clinical monitoring

- PLHIV should be monitored for a new or recurrent WHO stage 4 event that may indicate (late) failure of the ART regimen. Table 58: WHO staging system adults and adolescents (≥ 15 years), *page 183*.

Figure 8: CD4 testing algorithm

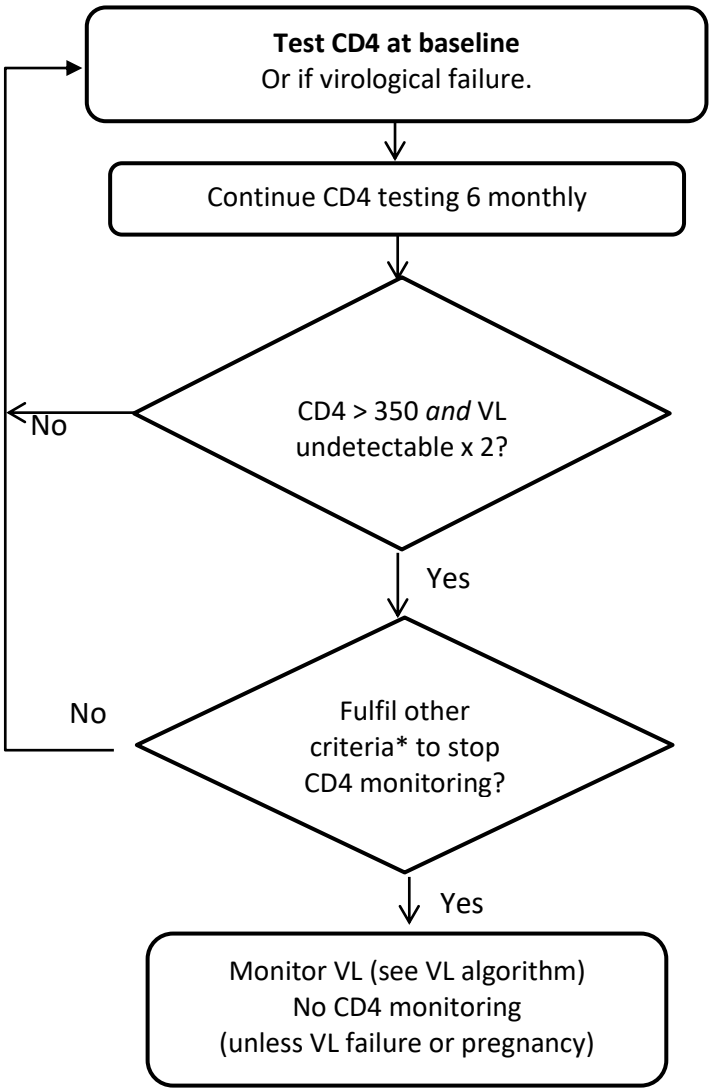


Table 19: When to start/continue and stop CD4 monitoring

Start / continue	Baseline CD4 then 6 monthly until stopping criteria are fulfilled
***Criteria to Stop CD4 monitoring**	On ART for at least 1 year *and all of the following:* • 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/ mm^3 • 2 x undetectable VL • Routine VL monitoring is available
Check CD4 again	Virological failure → recommence CD4 algorithm Pregnancy → recommence algorithm if< 350 +/or VL detectable.

Figure 9: Viral load monitoring

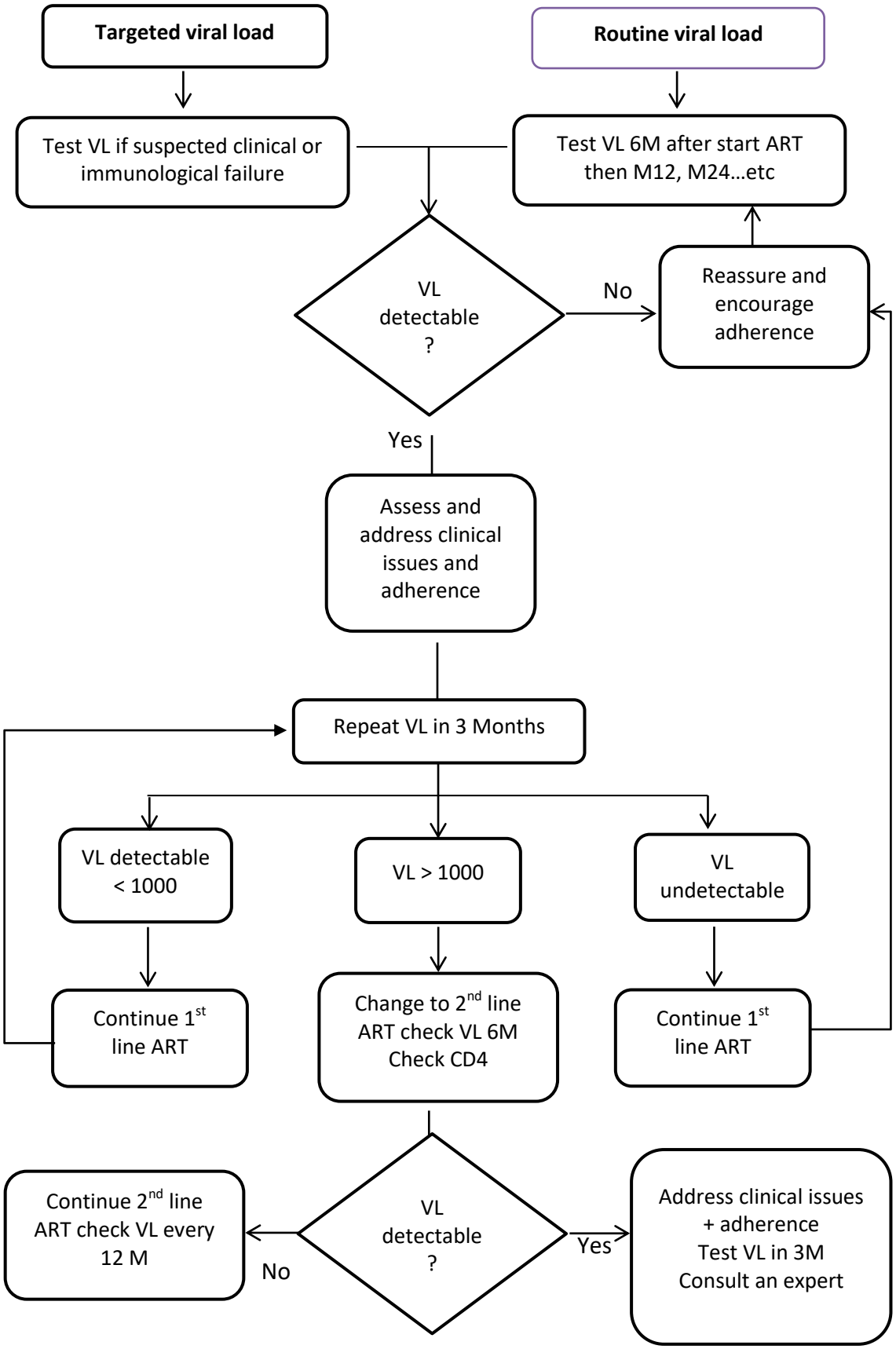


Table 20: WHO definitions of clinical, immunological, and virological failure[24]

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodefiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome[b] occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm³ **Children** Younger than 5 years Persistent CD4 levels below 200 cells/mm³ or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm³	Without concomitant or recent infection to cause a transient decline in the CD4 cell count 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
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support	The optimal threshold for defining virological failure and the need for switching ARV regimen has not been determined An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

[24] WHO Consolidated Guidelines 2013

CHAPTER 12: MANAGEMENT ART 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 public health.

Viral load may be detectable due to:

- ART drug resistance and viral escape.
- Viral replication due to poor adherence.
- 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 increased risk of resistance-associated mutations acquisition and transmission of these 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 diarrhea that may result in short term malabsorption and perform clinical assessment for TB and other opportunistic infections.

Addressing adherence

- Most failure of ART is due to problems with adherence to the regimen. In the event of any level of detectable VL or virological failure 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 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, *page 169*).

- Cognitive barriers including cognitive decline or dementia (see Chapter 20: HIV encephalopathy/dementia, *page 109*).
- 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 is suspected, manage, or refer appropriately.
  - If dementia is suspected (see Chapter 20: HIV encephalopathy/dementia, *page 109)*, manage 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 or counsellors.

Re check the VL in 3 months

- If VL undetectable: reassure the patient and return to routine monitoring (Enhanced Adherence Counselling).
- 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 Viralogical failure on first line treatment

- 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 need for OI prophylaxis.
- If the patient is currently on treatment for active TB and on DTG contained regimen, continue with same regimen but double dose of DTG. If not on DTG contained regimen, switch to DTG contained regimen.

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 21: Standard 2nd line ART regimens, which outlines the sequencing to 2nd line depending on the NRTI backbone used in 1st line ART.

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 21: Standard 2nd line ART regimens

1st Line Regimens Failure	Preferred 2nd Line Regimens
TDF (or ABC) + 3TC +DTG	AZT + 3TC + ATV/r (or LPV/r)
TDF (or ABC) + 3TC + (EFV or NVP)	AZT + 3TC +DTG (or ATV/r or LPV/r)
AZT + 3TC + EFV (or NVP)	TDF* (or ABC) + 3TC +DTG (or ATV/r or LPV/r)
2 NRTI + any PIs**	Refer to NCHADS Technical Working Group on Care and Treatment for discussion

Note: if patient has HBsAg positive and the failure regimen contained TDF in 1st line it is recommended to keep it in the 2nd line regimen.
**TAF is considered to use instead of TDF when it is available in the future*
***If patients on PI contained regimen, the 2nd line ART regimen will be based on genotype testing*

Table 22: Standard 2nd line ART regimens with Hep B Co-infection

1st Line Regimens Failure	Preferred 2nd Line Regimens
TDF + 3TC (or FTC) + DTG	TDF + 3TC (FTC) + AZT + ATV/r (or LPV/r) Or TAF** + 3TC + AZT + ATV/r (or LPV/r)

If patients on PI contained regimen, Treatment regimen will be based on genotype testing
** If TAF is available, it is recommended to use instead of TDF due to less renal toxicity and less reduction of bone mineral density.

Monitoring on 2nd Line ART

- Recheck VL after 6 months, and then 12 monthly.
- If the viral load is detectable, go through the same procedure as for detectable VL on 1st line ART checking clinical and adherence issues, and rechecking VL in 3 months.
- Advise the patient they are at increased risk of sexual transmission, and to use condoms.

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

- Atazanavir / ritonavir 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, and is taken just once daily.
- 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. (In this case double dose lopinavir/r is used).
- 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, which is usually self-limiting within 2 weeks, however ATV/r should be stopped if severe.
- Icterus (jaundice) which if asymptomatic, and ALT/AST are N then is of no concern.
- Headache, nausea, raised liver enzymes.
- Long term metabolic complications: lypodystrophy, diabetes, hyperlipidemia.

- See Chapter 10: Monitoring and substitutions for ART toxicity, *page 64*.
- 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 side effects including GIT upset and hepatotoxicity.
- Regular dose LPV/r = 400mg/100mg BD to be taken with food.

Intergrase inhibitor in 2nd line ART regimen: Dolutegravir

- DTG is preferred for the 3rd drug for 2nd line in case of patient has VL failure to NNRTI in first line ARV regimen. EX, if patient has VL failure with AZT + 3TC + EFV (or NVP) then the preferred 2nd line regimen is TDF + 3TC + DTG (FDC).

12.4 Second line ART failure

In the event of confirmed 2nd line virological failure, failure after EAC, report to AIDS Care Unit of NCHADS by filling in the 2nd line suspicion failure for 2nd line failure form for technical committee to discuss genotype analysis and 3rd lines options.

Points to consider for management of patients failing second line ART: [25]

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 fully active drugs.

12.5 Third line (salvage) regimens

- Using a "new" drug that the patient has not taken before does not ensure that the drug will be fully active, due to drug-class cross-resistance.

[25] 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

- However, there are some 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 regimen, 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 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 (Entercavir is another HBV active agent (not active against HIV), which could be substituted, however it is not 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, even many ARV options are available, maximal virological 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.
- The new available ARV drugs in Cambodia for the 3rd line is Darunavir/ritonavir and Dolutegravir. In the future if there is available of NNRTI, Etravirine and Integrase Inhibitor, Raltegravir, could be used for 3rd line.

The 3rd line ART regimens will be based on the genotyping test result. If the patients are on the second line regimens and suspected of failure, please request the genotype test to review the resistance and consult with AIDS unit of NCHADS.

A proposed third line ART: DRV/r + DTG + 1-2 NRTI

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 10 to 20% annual risk of developing active TB.
- All PLHIV should be clinically screened for TB at every clinic visit or at any time when they exposed to pulmonary TB cases.
- 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. Therefore, it is recommended for GeneXpert testing.
- All PLHIV without active TB should be considered for Tuberculosis Preventive Therapy (TPT)
- See Cambodian National guidelines for detailed background and management of TB/HIV[26] and DR-TB [27].

13.2 Background

- Tuberculosis (TB) is caused by *Mycobacterium tuberculosis complex (MTB).*
- TB is **transmitted** via infectious respiratory droplets in the air originating from a person with active pulmonary TB (PTB) while coughing, talking, laughing, sneezing in a close space.
- 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**.
- TPT can prevent TB infection from developing into active disease very effective.
- **Active TB** manifests as
  - **Pulmonary (PTB)** involving parenchyma of the lungs
  - **Extra pulmonary TB (EPTB)** involving almost any organ in the body.

13.3 TB in Cambodia

- According to the WHO Cambodia TB profile in 2019[28]
  - Cambodia is a country with a high burden of tuberculosis (TB) with 64% of population infected with TB (approximately 8 million), estimated 49,000 active cases.
  - The estimated incidence of TB in Cambodia: 302 per 100,000 populations.
  - Rates of MDR-TB were estimated at 1.8 % of new TB cases, and 8.2% of cases presenting for retreatment.
  - 580 (2%) HIV patients were diagnosed with active TB.

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

[27] Programmatic Management of Drug-resistant TB in Cambodia Technical and Operational Guidelines 2013

[28] WHO Cambodia TB Profile 2019 available at https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1

- 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%.[29]

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.
- A non-HIV infected person infected with TB has a lifetime reactivation risk of 5-10%, while for PLHIV it is 30-50%, or 10 to 20% 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** [30] for a comprehensive overview.

13.4 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 Drug Susceptible Tuberculosis (DS TB), due to inadequate regimen or poor adherence.
- DR-TB is therefore more common after treatment failure, relapse, return after default, and poor adherence or absorption of TB drugs.

13.4.1 Classification of DR- TB[31]

- Mono-resistant: resistance to one of the first line TB drugs
- Poly drug-resistant: resistant to $\geq$ 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).
- Pre-XDR: resistant to H and R and to either fluoroquinolone or to injectable drugs.
- 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).

13.4.2 Diagnosis of DS and DR TB

- Cambodia still uses microscopy as tools to diagnose and move toward universal rapid diagnosis by GeneXpert. At presence, GeneXpert is mainly used for high risk group include close contacts to TB patients, MDR-suspects, PLHIV, children, elderlies ≥55 years old and all presumptive TB patients seeking care at hospitals. In addition, GeneXpert will be used to test all smear positive TB cases. Presumptive TB patients are clinically diagnosed by on the clinical signs and symptoms, Chest X Ray, TST, etc.

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

[30] 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

[31] Treatment of Tuberculosis guidelines 4th Edition, WHO 2010

- 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. It detects MTB DNA and rifampicine resistance associated with specific genome mutation. In case of Rif resistance detected by GeneXpert, sample will be sent for 2nd line Line Probe Assay (LPA) test and culture and DST for confirmation.

13.4.3 Management of DR TB

- If DR-TB: standard treatment is likely to make the drug resistance worse.
- DR-TB needs prolonged multidrug therapy, and particular measures for contact tracing and infection control.[32]

13.5 Three Is Strategy in Cambodia

The 3 I's strategy in Cambodia aims to reduce the impact of HIV/TB coinfection by:[33]

1. Intensified TB case finding (lCF) among PLHIV and their household contacts
2. TPT include 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 TPT (see Chapter 6: Screening for TB amd assessment for TB Preventive Therapy, *page 47*)
3. TB infection control includes:
   - Early diagnosis and treatment of active TB disease
   - Separation of patients known of or presumptive TB
   - Coughing patients to wear surgical masks
   - Maximise ventilation, and natural light.

13.6 Clinical presentation of TB in PLHIV

- Clinical presentation of TB in PLHIV is different depending on early or late stage HIV.
- Contact with a known case of PTB is a strong predictor of TB.

[32] Programmatic Management of Drug-resistant TB in Cambodia Technical and Operational Guidelines 2013

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

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

As the CD4 reduces, 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
- Anemia
- Microscopy is less sensitive.

Rates of EPTB become relatively higher (although PTB is still more common) see chapter 13: sub-title: 13.7 Extra Pulmonary TB, *page 85.*

13.7 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 Annex 3: TB/HIV Algorithms, *page 187.*

13.7.1 Pulmonary Tuberculosis

Diagnostic work up:

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

- Sputum testing (includes GeneXpert is recommended, if not available, smear microscopy is less preferable) *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 DR-TB with 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 to inform about 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 another sputum for 2nd line Line Probe Assay (LPA). Once the result is confirmed, patients will be put on treatment based on the LPA result.

2. If GeneXpert MTB/RIF is not available at the site, sputum specimen is transported to Xpert site or 3 specimens should be examined by microscopy, but this is not encouraged.

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 extrapulmonary), especially in TB meningitis, for which definitive diagnosis is often difficult.
- **MTB positive cultures should be forwarded to CENAT for (DST)** in 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/mm^3: typical cavity TB or upper lobe consolidation
- As CD4 progresses to < 200 cells/mm^3: 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 26: Differential diagnosis of respiratory presentations, *page 94.*

If sputum test is negative for MTB
- 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 times daily or if allergic erythromycin 500mg 4 x daily with repeat clinical evaluation, +/- CXR and/or AFBs after completion of the antibiotic course.

13.7.2 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/mm^3 compared with 20% of cases in PLHIV with CD4 > 200 cells/mm^3.

Clinical presentation and diagnosis
Most often EPTB presents with unilateral lymphadenopathy. However, EPTB can be found in any organ, the most common EPTB forms are:
- CNS abscess or meningitis
- Spinal TB (Pott's disease), other joint or bone swelling or deformity
- Serosity (pleural, pericardial, and/or peritoneal)

- Abdominal mass or ascites
- Hepatitis or enteritis
- Renal TB; urinary obstruction or enlargement of kidneys
- Cutaneous lesions.

See Chapter 13: Tuberculosis, sub-title 13.7: Extra Pulmonary TB, *page 85*.

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 23: Clinical features and diagnosis of common extra-pulmonary tuberculosis

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

	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	• Fever, sweats, malaise ++ • Gradual onset and progression of headache • Confusion • Decreased consciousness, convulsions • +/-Neck stiffness • Focal neurological deficits e.g. Cranial nerve palsy	• ≥ 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	• Fever, sweats, malaise +++ • Very unwell • Hepatosplenomegaly • Diffuse large LN • Choroidal tubercles on fundoscopic examination	• Spine: Local pain, followed by deformity +/- neurological deficits • Joint: swelling of hip /knee/elbow, pain usually not severe. • +/- Fever, sweats, malaise	• Fever, sweats, malaise • Local features: • Pulmonary (chest pain, shortness of breath) • Abdominal (pain, distention) • Pericardial (chest pain and left (short of breath) and right ventricular failure (peripheral oedema)
Diagnosis	• Lumbar puncture, • If signs of ↑ intra-cranial pressure (papilledema, ↓ consciousness) LP dangerous, start treatment and LP when improves	• Needle aspirate of LN if node is fluctuant. • Ultrasound (intra-abdominal lymph nodes)	• CXR • Mycobacterial blood culture (if available)	• X-ray • Tissue biopsy	• Physical examination • CXR • Ultrasound • Echocardiogram • Aspirate effusion
Results	• CSF opening pressure ↑ • CSF mild ↑ white blood cell count, predominantly lymphocytes • Protein level ↑ • Glucose ↓ • AFB smear rarely positive. • GeneXpert	• Caseation • AFB may be seen. • GeneXpert	• CXR diffuse, small milliary shadows • CBC +/- pancytopenia • Liver function tests +/- abnormal • AFB smear on sputum, CSF or bone marrow aspirate may be positive (GeneXpert cannot be used for blood)	• AFB may be seen • Granulomatous reaction seen on histology	• CXR- pleural effusion, or large globular heart shadow seen • Ultrasound: ascites and intra-abdominal LN • Pleural biopsy: AFB and/or granulomas seen • Aspirate: • Usually AFB negative • TB culture takes 4-6 weeks • Exudate: Protein > 30 g/l • If aspirate clots likely to be exudate

13.8 Management of PTB and EPTB

Drug treatment of TB

- All TB in PLHIV should be treated according to the Cambodian Standard guidelines.[34]
- Check for any **potential drug interactions** with TB meds (esp. Rifampicin – e.g. warfarin (needs ↑ dose), contraceptives (↓ efficacy), fluconazole (↓ levels) and some ART)[35]
- Add **pyridoxine** (vitamin B6) 25 mg daily to reduce the risk of peripheral neuropathy.
- TB meningitis: add Prednisolone 60mg/day for 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 for 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 17: Timing of ART initiation in setting of active OIs.
- Check for drug interactions between ART and TB drugs according to Table 25: Drug interactions between ART and TB **drugs**, *page 90*.

Monitor

- Symptoms – cough, sweats, appetite, energy level, weight.
- Sputum smears (microscopy) at 2 and 5 months and at the end of treatment all (PTB) and for MDR-TB a sputum culture need to be done every month for 6 months.
- If the sputum does not convert at month 2 or 3, sputum, it needs to refer for GeneXpert testing for Rif testing.
- Monitor for side effects of the TB and ART regimens (see sub-title 13.8: side effects of TB therapy combine with ART, *page 89*).

If not improving:

- Repeat microscopy (not GeneXpert MTB/RIF), perform culture and DST and consider:
  - Poor Adherence, malabsorption
  - Drug resistant TB
  - Paradoxical IRIS (see Chapter 9: Immune Reconstitution Inflammatory Syndrome (IRIS), *page 62*)
  - Other infections, cancers and cardiac failure (see Table 26: Differential diagnosis of respiratory presentations, *page 94*).
  - Drug related adverse events.

[34] 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.

[35] www.hivdruginteractions.org/

- 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.

13.8.1 Side effects of TB therapy combined with ART

Table 24: 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; ddI	INH
Rash	NVP; EFV	Rifampicin; INH; Pyrazinamide

13.8.2 TB – HIV drug interactions

Table 25: Drug interactions between ART and TB drugs[36]

Drug	Interaction with ART and fluconazole
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, use DTG 50mg BID Abacavir: slight ↓ in concentration Nevirapine: contraindicated as ↓↓ concentration Efavirenz: ↓conc but effective with dose of EFV 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. DTG 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

[36] http://www.hiv-druginteractions.org/

Drug	Interaction with ART and fluconazole
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, use DTG 50mg BID Abacavir: slight ↓ in concentration Nevirapine: contraindicated as ↓↓ concentration Efavirenz: ↓conc but effective with dose of EFV 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
Kanamycin	Kanamycin and TDF both nephrotoxic. Monitor renal as 3TC dose may need to be adjusted.

Drug	Interaction with ART and fluconazole
Bedaquiline	Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Bedaquiline is metabolised by CYP3A4 and mainly eliminated in faeces. Concentrations are unlikely to be affected by DTG. There are no clinical data on the safety and efficacy of Bedaquiline when co-administered with antiretroviral agents.
Delaminid	There are no clinical data on the safety and efficacy of Delaminid when co-administered with antiretroviral agents.
Linezolid	Co-administration has not been studied but based on metabolism and clearance, a clinically significant interaction is unlikely. Linezolid undergoes non-CYP mediated metabolism.

Respiratory conditions

CHAPTER 14: RESPIRATORY TRACT INFECTIONS

- Both upper (e.g. sinusitis) and lower respiratory tract infections are common in PLHIV.
- Often multiple infections may be present at 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 26: Differential diagnosis of respiratory presentations for guidance as to clinical presentations and management of common respiratory infections, *page 94*.
- Figure 10: Algorithm: Respiratory presentation, *page 97.*
- Chapter 15: Pneumocystis pneumonia (PJP), *page 95*.
- Chapter 13: Tuberculosis, Sub title 13.7.1 Pulmonary Tuberculosis, *page 85.*

1. Signs of severe respiratory distress:
It is important to recognize the severely ill patient with pneumonia, 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 GeneXpert (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).

- Consider **Pneumocystis Pneumonia** (see next section)

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

Table 26: Differential diagnosis of respiratory presentations

Diagnosis	Typical features	Typical CXR changes	Management
Infections			
Pulmonary TB (any CD4)	Sub acute, cough +/- productive, night sweats, +/- pain	Lobar consolidation, Cavitation (upper zones) Pleural effusion, lymphadenopathy	See Chapter 13
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: Amoxi oral 1g 8 hourly or erythromycin 500mg oral 6 hourly, Hospital: IVI penicillin / ampicillin or IVI ceftriaxone
PJP (*Pneumocystis jiroveci* pneumonia) (CD4< 200)	Usually subacute, Prominent dyspnoea, dry cough	Bilateral diffuse interstitial "ground glass" shadowing Pneumothorax No air bronchograms	See Chapter 15
Less common infections:	Fungal (e.g. Cryptococcus, penicilliosis), MAC, Nocardia.	Variable	Guide by microbiology.
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 Amoxicillin /clavulinique 2 times/ day, or clindamycin 450mg 3 times / day. Duration 3-4 weeks.
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 crepitations, gallop rhythm, oedema	
Reactive airway disease (asthma)		Chronic, intermittent symptoms; expiratory wheezes; known triggers	
Chronic obstructive pulmonary disease (COPD)		Risk factor (smoking); chronic symptoms	

CHAPTER 15: PNEUMOCYSTIS PNEUMONIA (PJP)

Pneumocystis jiroveci (formally *Pneumocystis carinii PCP)* pneumonia is a common fungal infection in PLHIV with CD4 <200 cells/mm^3. PJP is a WHO Stage 4 illness.
PJP infection may coexist with other respiratory infections, including TB.

Prevention: early ART, cotrimoxazole prophylaxis.

15.1 Clinical presentation

Symptoms: Subacute onset (1 -2 weeks) Dyspnoea (shortness of breath). Initially dyspnea is just with exertion but later at rest. Non-productive cough may develop, +/- Fever.
Examination: tachypnea, chest may be clear or fine crepitation's, +/- cyanosis, pulse oxymeter – low $\%O_2$.

15.2 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, effusion), bacterial pneumonia (focal consolidation, effusion).
Other investigations – bronchoscopy and lavage, laboratory (PCR and silver stain).

15.3 Standard treatment

- Cotrimoxazole 15-20g/kg/ day divided into 3-4 doses daily for 21 days[37]
- Keep well hydrated.
- Add folic acid 5mg daily (cotrimoxazole depletes body of folic acid).

Table 27: Weight based cotrimoxazole dosing for treatment of PCP

Weight	Total dose/day	Dose in DS tablets (TMP160/SMX800mg)
30 - 40 kg	450 – 800 mg/day	2DS tablets 2 times/day
> 40 - 50 kg	600 – 1000 mg/day	2DS morning, 1DS midi, 2 DS evening *or* 2 DS tablets 3 times/day
> 50 - 60 kg	750 – 1200 mg/day	2 DS tablets 3 times/day
> 60 kg	900 - 1200mg/day	2 DS tablets 3 – 4 times/day

If hypoxemia with signs of respiratory distress or cyanosis add:

- Prednisolone: 40mg twice daily for 5 days, 40 mg daily for 5 days, the 20 mg daily for 11 days.
- High dose/prolonged courses of steroids along with the immunodeficiency associated with HIV, increases the risk of disseminated strongyloidiasis and septic shock.

[37] Sandford guide. Antimicrobial therapy 2015

Treat empirically with albendazole 400mg orally with fatty food 12 hourly for 7 days[38].

Alternative treatment

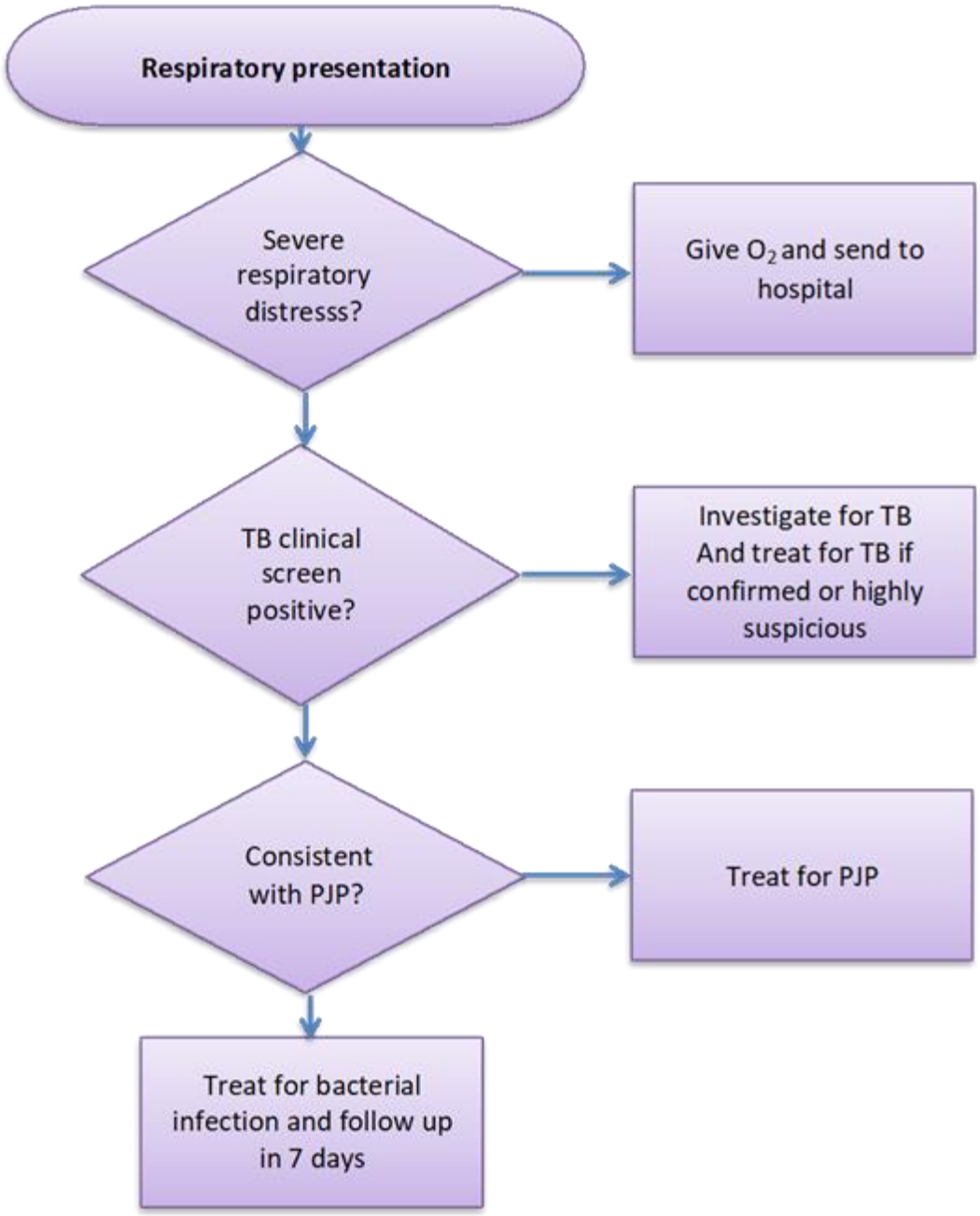
- Trimethoprim 300mg/day + dapsone 100 mg/day orally for 21 days, or
- Clindamycin 600mg 4 times daily + primaquine 15-30 mg daily for 21 days.

Monitor

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

Figure 10: Algorithm: Respiratory presentation

[38] Sanford Guide to Antimicrobial therapy 2015



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: Cryptococcus TB, or bacterial, (*Streptococcus pneumonia* (most common), *Neisseria meningitis*, *H. influenza B)*. Viruses include HIV itself or HSV, or syphilis.
Prevention: early ART, TB screening and IPT, Cryptococcal Ag screening.

16.1 Clinical presentation

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

****Bacterial infection typically presents acutely and is a <u>medical emergency</u>. If patient is suspected, give ceftriaxone 2g as soon as LP performed or prior to LP if you expect a delay of LP is more than 1 hour** and the treatment should be continued until completion****

Differential diagnosis: also consider 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 investigation: consider CXR and sputum for GeneXpert/microscopy, CBC, Malaria test, RPR.

16.2.1 Lumbar puncture

Table 28: Lumbar Puncture technique and CSF analysis

Lumbar Puncture technique and CSF analysis
• 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 H_20 • 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 ml CSF. • Check CSF glucose and protein • CSF microscopy - leucocytes • Cryptococcus India (China) ink stain for microscopy, Cryptococcal antigen (CrAg) • Bacterial stain and culture • TB stain for microscopy, GeneXpert, TB culture

16.2.2 Differential diagnosis of meningitis

Table 29: 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 (*S. pneumonia*), Gram –ve (*N. meningitides*) 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 Chapter 17: Cryptococcal meningitis (CM), *page 103*, and for TB meningitis sub-title: 13.8 Management of PTB and EPTB, *page 91*.

16.3.1 Bacterial meningitis treatment

- Ceftriaxone 2gm IVI, 12 hourly for 10 days.

16.3.2 Neurosyphilis meningitis treatment

- Benzypenicillin 1.8 g (3 million units), 4 hourly for 15 days

16.3.3 Herpes simplex encephalitis

- Acyclovir 10mg/kg IVI, 8 hourly for 10 days.

CHAPTER 17: CRYPTOCOCCAL MENINGITIS (CM)

17.1 Key points

- *Cryptococcus neoformans* is the most common life-threatening fungal infection in patients with AIDS. Mortality is as high.
- Risk of developing CM is highest when PLHIV have a CD4 < 100 cells/mm^3
- Early diagnosis and treatment are key to improving mortality from CM, and so it is important to have a low threshold for suspecting CM and performing an LP.
- CM often has a sub-acute presentation; severe headache is the most common symptom.
- 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.
- All patients with CM need to be hospitalized for treatment.
- IRIS is a particular concern in CM, and therefore ART commencement should be delayed until 4 – 6 weeks after commencement of treatment for CCM.

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 (look similar to molluscum contagiosum).

Differential diagnosis: bacterial meningitis, TB meningitis, bacterial sinusitis (see Table 29: Distinguishing between different causes of meningitis, *page 100*).

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 28: Lumbar Puncture technique and CSF analysis, and Figure 6: Cryptococcal antigen screening)

- If your facility does not perform lumbar puncture or CSF studies, and CM is suspected.
  - Start fluconazole 1,200mg daily AND
  - Promptly transfer the patient to a higher level of care where LP is available for proper management.

- 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 Cryptococal microscopy 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 sure of current infection in the context of possible relapse or recurrence is to do fungal culture.

17.4 Treatment of cryptococcal meningitis[39]

- 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:

A. Recommended Option:

A short-course (one-week) induction regimen with Amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for adolescents, up to a maximum dose of 800mg daily), is the preferred option.

B. Alternative options:

- Two weeks of fluconazole (1200 mg daily for adults, 12 mg/kg/day for adolescents + flucytosine (100 mg/kg/day, divided into four doses per day) or
- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for adolescents up to a maximum of 800 mg 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 times daily) lumbar punctures can be performed.

Monitoring response to treatment:

- Clinical monitoring of symptoms and clinical signs.

[39] Guideline for diagnosis, prevention and management for Cryptocuscal disease in HIV infected adults, adolescence and children, WHO March 2018.

- There is no need for routine LP at the end of treatment, however if the patient is still symptomatic after 14 days 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 resistance and investigate for the presence of other causes (including additional infectious causes).

Consolidation phase therapy
Fluconazole (800 mg daily for adults, 6–12 mg/kg/day for adolescents up to a maximum of 800 mg daily) is recommended (for eight weeks following the induction phase).

Maintenance treatment (secondary prophylaxis)
Fluconazole 200mg daily 6 mg/kg/day for adolescents) is recommended.

Discontinuation of maintenance treatment
- Patients may cease after ≥ 12 months of ART provided they are
  - Stable and adherent to fluconazole and ART, AND:
  - 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 positive (IPCA)
Note: be ensured that active CM is excluded by clinical screening or LP.

Induction phase: Fluconazole 800mg daily for 2 weeks, followed by 400mg/day for 8 weeks and followed by fluconazole 200mg/day **maintenance phase.**

Table 30: Amphotericin: Administration, toxicity prevention, monitoring and management

Administration of Amphotericin – toxicity prevention, monitoring and management[40]
Pre-emptive hydration and electrolyte supplementation • One liter of normal saline solution with one ampoule (20 mmol) of KCL over 2-4 hours before each infusion of amphotericin B (with one liter of 5% dextrose) • One to two 8mEq KCL tablets orally twice daily. • An additional one 8mEq KCL tablet twice daily may be added during the second week. • If available, add two 250mg tablets of magnesium trisilicate twice daily. • Potassium replacement should be avoided if renal impairment or hyperkalaemia. • A test dose for amphotericin B is not recommended

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

Administration of Amphotericin B

- Amphotericin powder (50mg vials) refrigerate at 2-8^{0}C and protect from light. Reconstitute each 50mg vial into 10ml sterile water and injected into 1liter bag of 5% dextrose and shaken. **(Never use saline).**
- Use within 24 hours of reconstitution
- Infuse through peripheral IV cannula over ≥ 4 hours. After infusion remove the infusion bag and flush line with normal saline. Monitor the IV cannula for phlebitis and change, as necessary.

Monitoring during the infusion

- Pulse, BP, temperature every 30 mins during the first 2 hours then every hour.
- In case of fever and shivers - hydrocortisone 50mg
- If BP < 70mmHg cease the infusion and give IVI fluids, clinical assessment

Monitoring for toxicities

- 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 *daily weight*

Management of toxicities

- If K <3.3mmol/l, increase potassium supplementation to two KCL ampoules (40 mmol), or one or two 8mEq KCL tablets three times 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 fold from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one liter 8 hourly. Once improved, restart at 0.7 mg/kg/day and 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 31: 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
Flucytocine	

17.4.3 Fluconazole; renal impairment and liver toxicity[41]

[41] MIMS Fluconazole. 2015. http://www.mims.com.au

- **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

- **Fluconazole and the liver**: Few patients need to cease fluconazole due to adverse events, however fluconazole can cause mild elevations in transaminases, and rarely clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. The risk is higher in patients also taking following medications: 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 (↑Biliribun and liver tenderness on examination are signs of severity).
- Review medications for drug interactions.
- Advise to stop drinking alcohol and 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 and pregnant/breast feeding women[42]

- **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 ART commencement, 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).

[42] Johns Hopkins ABX Guide. 200 – 2015. The Johns Hopkins University.

- 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 for 7 days[43].

[43] Sanford Guide to Antimicrobial therapy 2015

CHAPTER 18: CEREBRAL TOXOPLASMOSIS

- Cerebral toxoplasmosis is caused by reactivation of the protozoa *Toxoplasma gondii* cysts which have been 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 presentations

- Headache, +/- fever.
- Focal neurological symptoms and signs (hemiplegia, ataxia etc.).
- Encephalitis like symptoms: reduced consciousness and confusion.
- Fundoscopy: +/- retinochorioditis, +/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 or MRI is 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 already on 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 10: Cotrimoxzazole desensitization protocol (adults and adolescents, *page 44*).

18.5 Monitoring for response

- Clinical and radiological response is expected within 2 to 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.

CHAPTER 19: CYTOMEGALOVIRUS (CMV)

- CMV is a common virus, which reactivates to cause disseminated or local disease in PLHIV with advanced immunodeficiency: CD4 < 100 cells/mm^3, (particularly CD4< 50).
- CMV most commonly causes retinitis but also frequently GIT (oesophagitis, 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 presentation 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 hemorrhage.

19.2 Management

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

CHAPTER 20: HIV ENCEPHALOPATHY/DEMENTIA

20.1 Clinical condition

- Term *HIV-associated neurocognitive disorder* (HAND) encompasses a spectrum from mild 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 hypertension.
- 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 32: Clinical features of HIV associated dementia

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

20.2 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.

20.3 Clinical evaluation

- Screen for depression, as severe depression may mimic dementia (see Chapter 42: Mental Health, sub-title 42.1: Depression, *page 169*).

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 33: The International HIV dementia scale (IHDS)[44]

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

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

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

20.4 Investigations

- Treponema tests: Treponema Paledium Haemagglutination assay (TPHA), the trepon (TPPA), fluorescent treponemal antibody absorption (FTA-ABS) test, Rapid Plasma Reagent (RPR),
- Diabetes check – Baseline (BSL).
- Thyroid function tests
- Vitamin B12
- Consider lumber puncture, and CT scan (if available) to exclude other CNS pathology.

20.5 Management

- Commence ART as soon as possible.
    - 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.
    - Response to ART is often quite good.
- 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 to minimize alcohol consumption.

CHAPTER 21: PERIPHERAL NEUROPATHY

Peripheral Neuropathy (PN) frequently affects PLHA particularly if CD4 <200 cells/µl.

21.1 Causes of PN

The 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 to 1000mg 4 times a day
  - Ibuprofen (take care if abnormal renal, liver, GIT or HTN)
  - Amitriptyline: start with 25mg 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 which belongs to the hepadna virus 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 3 to 5% of the population HBV infected for the detail information please see the detail HBV Guideline 2019.

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.

Table 34: HBV transmission and prevention

Transmission of Hepatitis B	Prevention of Hepatitis B transmission
• Perinatal (30 – 90% transmission risk) • Parenteral – Injecting drug use (IDU): very high risk – Health care setting: • Transfusion, • Medical procedures • Needle stick (~ 30% risk) – Household: • child to child • Toothbrush, razors, etc. • Piercing, tattoos • Sexual (including oral)	• Vaccination – 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.

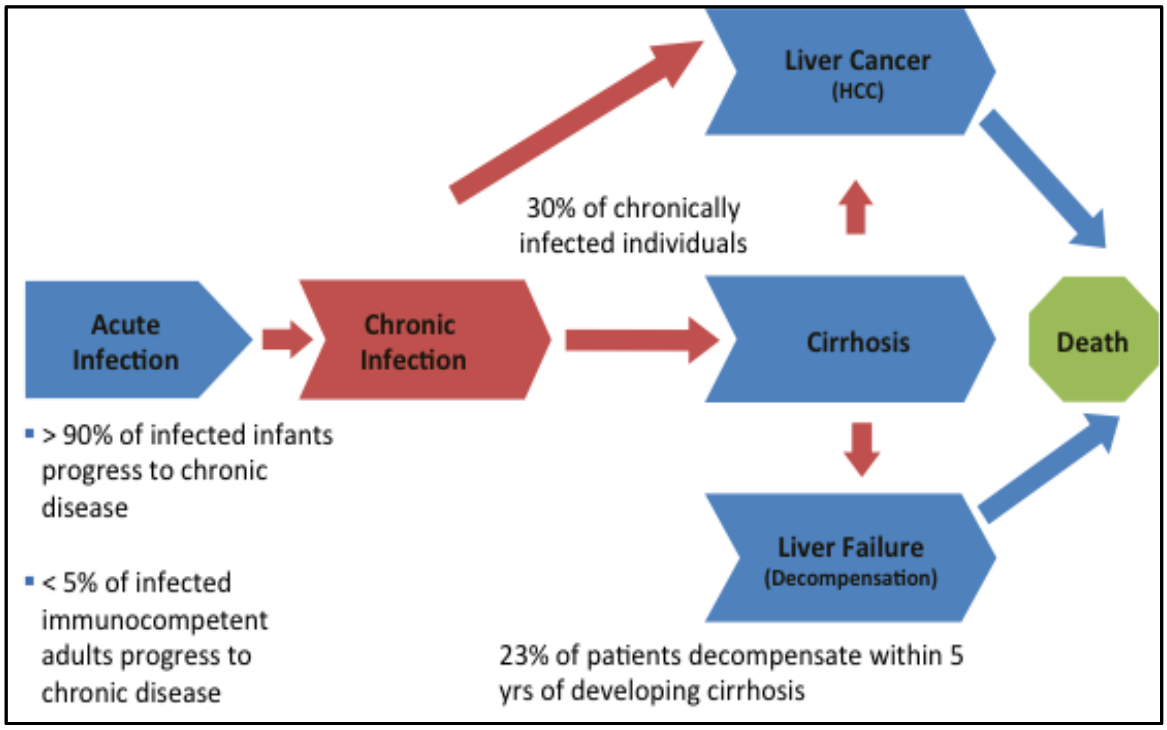
- HBcAb is positive either due to previous exposure, or if with HBsAg positive is due to persistent infection.

- 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 deciding when to initiate HBV antiviral therapy in HBV mono infected patients.

22.4 HBV clinical disease and natural history

Incubation period: 10 weeks (range from 4 to 26 weeks).

Figure 11: Natural History of untreated HBV monoinfection



The four phases of chronic HBV infection [45]

1. Immune tolerance: No immune 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% per year, HBeAg seroconversion → HBe Ab, associated with ↓ HBV DNA x 5
3. Immune control: Non-replicative (latent) infection.
   - HBeAg negative, low, or undetectable HBV DNA, normal ALT levels
   - Term "carrier" may be misleading as may fluctuate

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

4. Immune escape: Reactivation
    - Spontaneous reactivation in 20% in immune control phase
    - HBeAg negative, positive HBcAb, detectable (often high) HBV DNA VL, persistently or intermittently elevated ALT levels.

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 HBV and Pregnancy

- Mother to child transmission: rate 10% - 90% (dependent on HBV DNA VL):
    - First-dose of HBV vaccine to infant within 24 hours of birth reduces transmission by 70% but they need to be vaccinated by two or three additional doses (6, 10 and 14 weeks of life).
    - Further reduction in transmission is expected if highly viremic women received preventive antiviral therapy during the third trimester of pregnancy.
    - No indication for caesarian section.
    - 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 (if not on antiviral therapy).

22.6 Management of HBV HIV co-infection

- In mono infected HBV patients, antiviral medication is only indicated in the immune clearance, and immune escape phases as these are when there is a risk of progression to cirrhosis and HCC. Patients not in these phases are monitored 6-12 monthly.
- This assessment is difficult as most of the required tests are not available readily in Cambodia, particularly HBV DNA viral load.
- However, it is different in the HIV infected patient as some ARV used to treat HIV are also indicated for HBV (TDF and 3TC/FTC), and now all HIV patients will be commenced on ART, this will include treatment for HBV co-infection.
- It is important that all patients with HIV/HBV coinfection are commenced on TDF + 3TC/FTC containing ART, and they must continue TDF even if they change to 2nd line ART.
- If just one of these drugs (particularly 3TC/FTC) are used, drug resistance will develop. Standard 2nd line ART for HBV/HIV co-infected patients will therefore include AZT + 3TC + TDF + DTG or ATV/r.
- HBsAg is ideally measured prior to starting ART, however it is not necessary for this to be routinely required whilst the preferred 1st line ART contains both TDF and 3TC.
- HBsAg must be tested 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 Chapter 24: Chronic liver disease, *page 119.*

CHAPTER 23: HEPATITIS C

Hepatitis C (HCV) is a single stranded RNA virus belonging to the flavivirus family.
HCV genotypes 1 to 6 have a slightly different clinical course and responses to treatment. There is more detail information in the HCV Guideline 2019.

23.1 HIV-HCV relationship

- Hepatitis C is mostly transmitted via the parenteral route and is common in intra-venous drug users (IVDU). However, the risk of sexual and perinatal transmission seems higher in PLHIV than in non-PLHIV, specifically if HIV viral load is not controlled.
- HIV co-infection results in higher rates of progression of HCV to cirrhosis and hepatocellular carcinoma (HCC).
- HCV results in higher risk of liver toxicity with ART and other drugs.

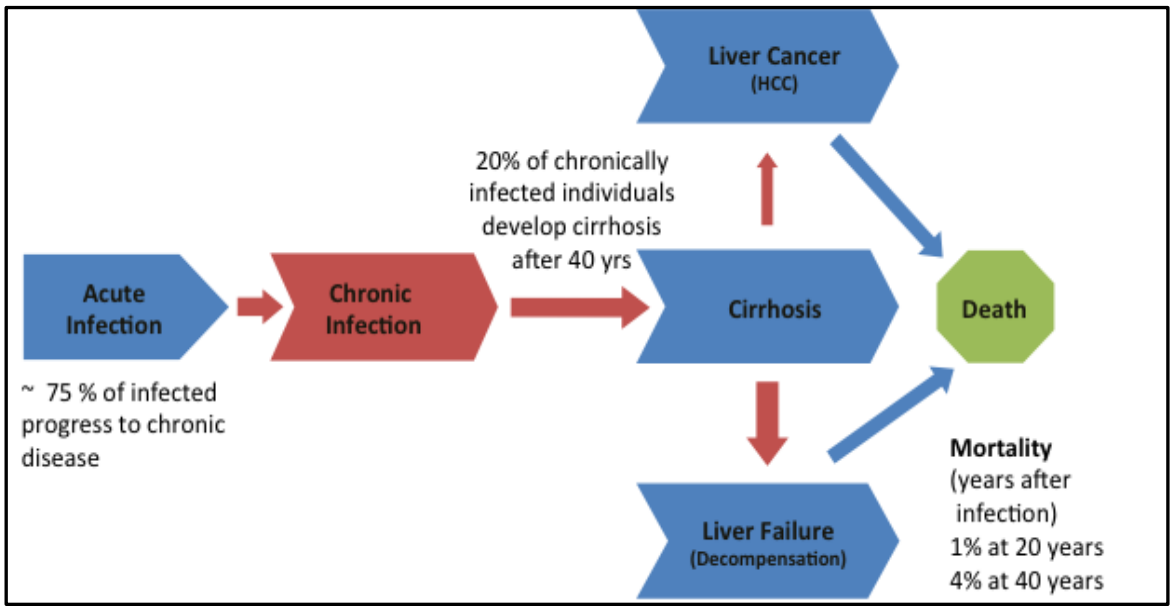
23.2 HCV Transmission and prevention

- 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 from 2 to 21 weeks).

Figure 12: 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.

Extrahepatic manifestations of chronic HCV infection include diabetes, dermatological conditions such as porphyria cutanea tarda, and vasculitic rashes associated with cryoglobulinaemia, 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 HCV infection, and to monitor therapy. This test is available in Cambodia.

23.5 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, well tolerated, including fixed dose combination oral regimens and it requires 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 coinfection.
- Many DAA are becoming available globally, including protease inhibitors Simepravir, and Paritaprevir NS5A inhibitors Ledipasvir, Ombitasvir, Daclatasvir, and NS5B inhibitors Sofosbuvir, and dasabuvir.
- It is expected that preferential pricing arrangements for LMIC will enable access to DAA and viral load testing for HCV treatment.

See also Chapter 24: Chronic liver disease, *page119* and HCV National Management Guidelines.

CHAPTER 24: CHRONIC LIVER DISEASE

24.1 Clinical assessment

- History: symptoms of acute and chronic liver disease, and extra hepatic manifestations. Obesity, insulin resistance, type 2 diabetes mellitus, and dyslipidemia history.
- 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.

24.3 Management of chronic liver disease

Table 35: Management of complications of chronic liver disease

General management of complications of chronic liver disease due to any cause (including HBV, HCV an 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 7: Recommendations for prevention and management of NCD, *page 32*.
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:
  - 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 often but with ↓ intravascular volume, so there is a risk of renal failure, especially with diuresis, and drainage.

Management of Spontaneous bacterial peritonitis (SBP)

- Usually associated with severe hepatic dysfunction
- Suspect if ascites ↑, fever, abdominal pain and tenderness, worsening encephalopathy.
- Investigation: ascitic tap - WBC > 500/mm^3 +/or neutrophil >250/mm^3
- Causative organisms mostly enteric Gram-negative bacilli e.g. E coli, + if on prophylaxis; streptococcal or enterococcus
- Treatment: ceftriaxone 1g IV daily, + if on antibiotic prophylaxis add amoxi/ampicillin 1 g IV, 6-hourly.
- Prophylaxis: trimethoprim + sulphamethoxazole 1 DS daily if:
  - GIT bleeding
  - Low ascitic protein (<10g / l)
  - Previous episode of SBP

Management of portal hypertension

- 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)

Management of portal systemic encephalopathy

- Look for underlying cause: HCC, SBP, renal failure etc.
- If severe (grade 3 or 4)
  - 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

Patients with type 2 diabetes and/or obesity must be screened for Non-alcoholic fatty liver disease (NAFLD) using liver ultrasound to identify liver steatosis. Lifestyle modification consisting of diet, exercise, and weight loss is the main treatment for NAFLD.

Oro-gastro-intestinal conditions

CHAPTER 25: ORAL DISEASE

- Oral health is important to enable adequate nutritional intake, 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 oesophageal candidiasis, HSV >1 month and oral Kaposi Sarcoma (KS).

- PLHIV should be advised regarding oral hygiene:
  - Regular teeth brushing (do not share toothbrushes), and flossing.
  - Mouthwashes (1 teaspoon baking soda, 1 teaspoon salt, 250 cc warm water) can be used for symptomatic relief and hygiene.
  - Dental checkup when gum disease or cavities is present.

25.1 Most common oral disease in PLHIV

25.1.1 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 and metronidazole 500mg three times daily, or clindamycin 450mg three times daily, for 7 days or amoxicillin/clavulate 875/125mg 12 hourly. Tooth abscess should be drained, and severe necrotizing infections (Vincent's Angina, Norma, Cancrum oris), require surgical debridement of necrotic tissue.

25.1.2 Oral candidiasis

Persistent oral candidiasis = WHO stage 3

Clinical features

- Symptoms: pain, difficulty eating.
- Examinations: White patches anywhere in the mouth; some material 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 1 time/day or
- Nystatin pessary, 100 000 IU, oral 4 times/day or
- Nystatin oral solution 1 – 2 ml swirl around mouth 5 times/day or
- Nystatin tablets or amphotericin lozenges sucked 4 times daily.

Alternative treatment

Fluconazole 100mg once daily for seven days (if severe or not responding).

25.1.3 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.

25.1.4 Kaposi's sarcoma

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.

25.1.5 Angular stomatis

Caused by candida or bacteria, presents as painful cracking of the corners of the mouth.

Management: antifungal cream or gel twice daily for 10 days, +/- topical antibacterial.

25.1.6 Oral ulcers

HSV: shallow painful ulcers, often multiple.

If extensive/recurrent treat with acyclovir 400mg 3 times daily

Syphilis chancre, often not painful. Check RPR but may take time to rise, so if consistent clinical picture and presentation treat empirically with Benzathine Penicillin 2.4 million units IMI single dose (Alternate doxycycline 100mg BID for 14 days).

Syphilis mucous patches: may be seen in the mouth in secondary syphilis. RPR high, treat as for primary syphilis.

Oral ulcers: Apthous ulcers

It is often very painful, and cause is unknown.

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

CHAPTER 26: ODYNOPHAGIA (PAINFUL SWALLOWING)

Odynophagia = pain in the throat and retrosternal space on swallowing food
Dysphagia = difficulty swallowing.

Odynophagia and dysphagia both affect the PLHIV's ability to maintain adequate nutritional intake and adhere to medications.
Oesophageal candidiasis 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 based on 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/ mm^3).

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

Drug treatment for esophagitis

- Candida: loading dose of Fluconazole 400mg on day 1, followed by Fluconazole 200 mg, once daily for 14 – 21 days.
- HSV: Acyclovir 800mg 3 times daily for 14 - 21 days.

26.2 Management

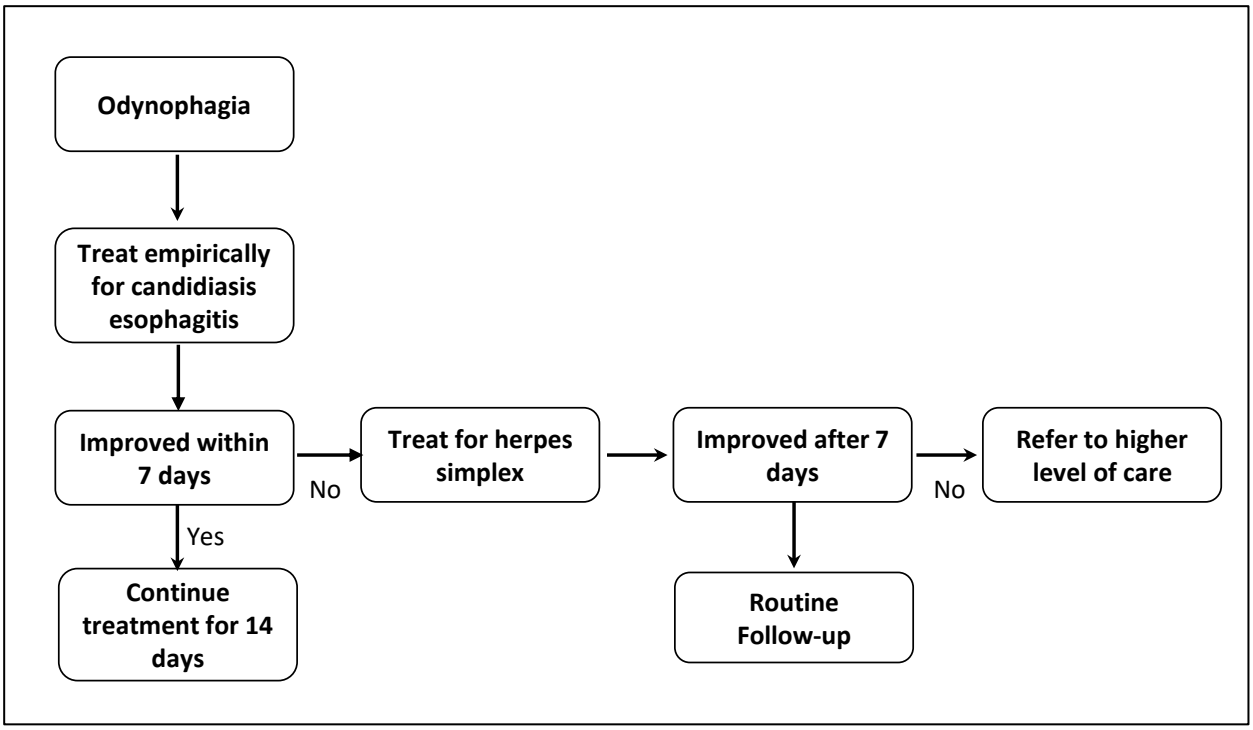
- For patients with likely diagnosis of candidiasis (based on typical symptoms, CD4 > 200 cells /mm^3 and oral candidiasis): treat empirically for candidiasis and follow up in 7 days.
- If patients do not respond, treatment for HSV can be trialed.
- If the patient has herpetic mouth lesions, treat for HSV first, then for candida if they do not respond adequately (both infections may be present concurrently).
- Reflux esophagitis: try proton pump inhibitor or ranitidine
  - However, check for drug interactions[46]: omeprazole is contraindicated with ATV/r, and cimetidine or ranitidine should be avoided if possible, as the absorption of ATV/r is reduced. If unavoidable use the lowest possible dose of ranitidine/cimetidine, and

[46] http://www.hiv-druginteractions.org/

space as far apart from the ATV/r dose as possible.

- If no response, refer for endoscopy if available.

Figure 13: Algorithm for Syndromic management of odynophagia



26.3 Antifungal agents and pregnancy/breast feeding[47]

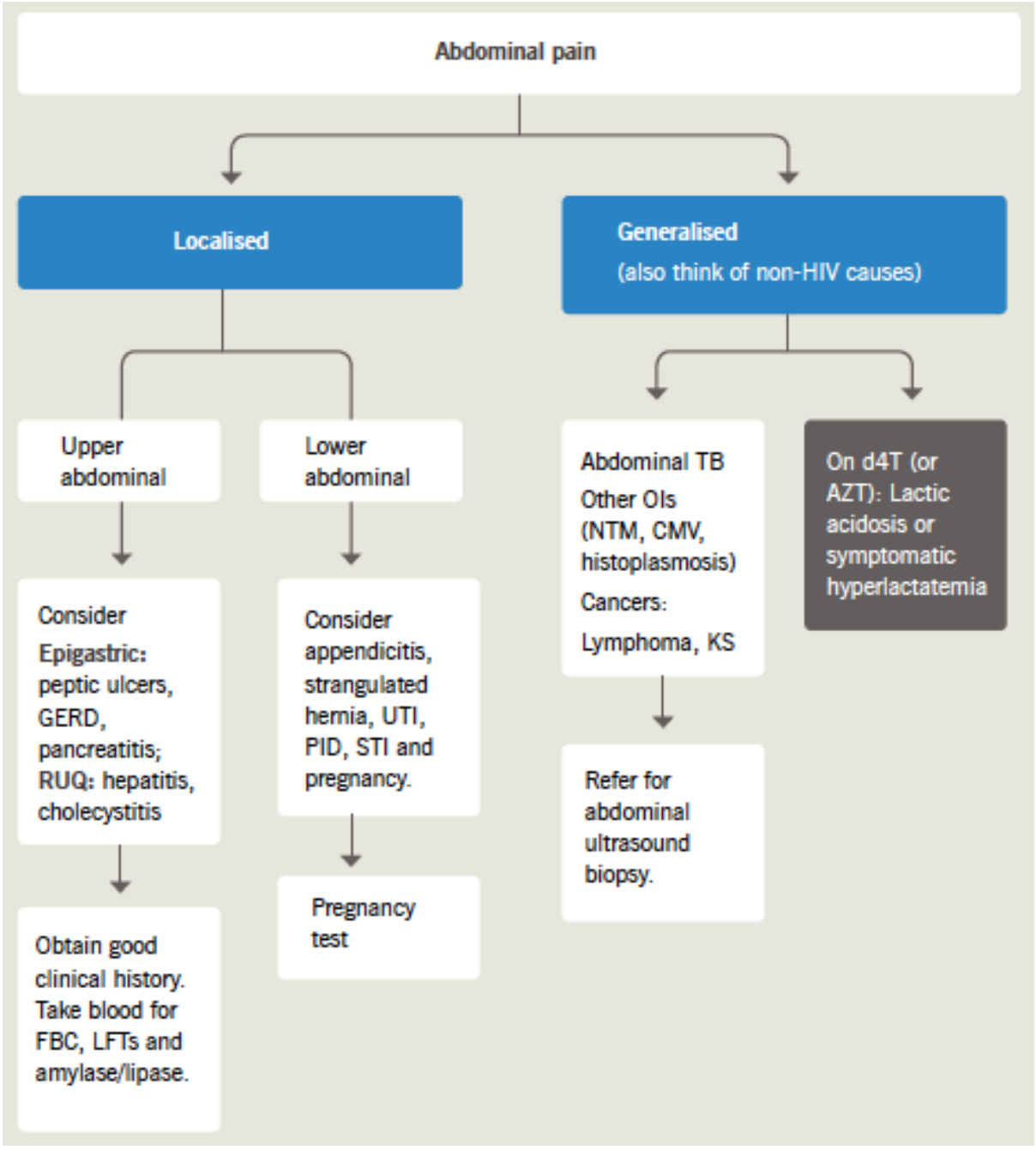
Fluconazole should generally be avoided in first trimester of pregnancy. However, the overall risk benefit needs to be assessed. (See sub-title: 17.4.4 Antifungal treatment of Cryptococcal Meningitis and pregnant/breast feeding women, *page 105*).

[47] 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 14: Algorithm for an approach to abdominal pain[48]



[48] Copied directly from MSF HIV/TB clinical guide 2015, p214.

CHAPTER 28: DIARRHEA

PLHIV are vulnerable to both acute and chronic diarrhea, including 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**: diarrhea ≤ 14 days duration,
- **Persistent diarrhea**: > 14 days and ≤30 days duration
- **Chronic diarrhea**: > 30 days duration diarrhea.

28.2 Acute diarrhea

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

28.2.1 Causes

They include viruses (norovirus), and bacterial (e.g. *E. coli, Salmonella, Shigella, Campylobacter*) and parasites (e.g. *Entamoeba histolytica*).
Non-infectious causes include side effects of medications.

28.2.2 Management of acute diarrhea

- The mainstay of treatment of acute diarrhea is the assessment and management of dehydration according to Table 36: Assessment and management of dehydration in patients with diarrhea.

- **Antimicrobial management**
  If acute diarrhea does not improve within few days, and the person has frequent stools (>6 per day), together with a high temperature and/or bad cramps, then give:

  - Cotrimoxazole DS 1 tablets twice daily for 5 days, AND metronidazole 500 mg three times daily 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 twice daily for 5 days.

Table 36: Assessment and management of dehydration in patients with diarrhea[49]

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	• Rehydrate with IV (or nasogastric tube). • Consider causes and treat. • Report cases.	• Give fluid and food. • Immediately advise when to return. • Follow up in 5 days if not improving.	• Treat at home. • Advise when to return. • Follow up in 5 days if not improving.

Rehydration:

- Drink as much fluid as possible, and 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.

28.3 Chronic diarrhea

Advanced HIV itself can cause chronic diarrhea, also PLHIV with low CD4 counts are vulnerable to chronic infections with:

- Protozoa: Microsporidium, cryptosporidium, Isospora belli, Giadia lamblia, Entamoeba histoytica,
- Bacteria: Salmonella, mycobacterium avium complex, MTB, and viruses CMV.
- Non-infectious causes: include gut neoplasms including lymphoma and Karposi's sarcoma, pancreatic insufficiency, or drug side effects (e.g. LPV/r).

28.3.1 Diagnosis

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

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

Stool microscopy: for WBC, RBC, parasites (increased sensitivity with 3 specimens).
Abdominal ultrasound: examine for enlarged LN and hepato splenomegaly (TB, MAC).

28.3.2 Management [50]

- Assess and manage dehydration and nutritional status. according to Table 36: Assessment and management of dehydration in patients with diarrhea, *page 128* and Chapter 33: Nutrition and weight management in HIV infected Adults and Adolescents, *page 148.*

- Treat any identified and treatable infections
  - Isosporiasis: cotrimoxazole DS 4 times daily for 10 days then 2 times daily for 3 weeks
  - Strongyloides stercoralis: Albendazole 400mg twice daily for 7 days
  - Giardiasis: Metronidazole 500mg three times daily for 7 days
  - TB: refer to CENAT treatment guideline for standard treatment

- Otherwise trial empiric antimicrobial therapy (although ensure TB is excluded prior to prescribing ciprofloxacin).

- Cotrimoxazole DS 1 tablet twice daily for 5 days, AND metronidazole 500 mg three times daily for 5 days.
- If fails, try albendazole 400mg twice daily for 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 to 8 tablets per day.
  - Codeine phosphate from 30 to 60 mg up to 4 times per day.

- Ensure the patient is established on ART as soon as possible.

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

CHAPTER 29: ENTERIC FEVERS (INCLUDING SALMONELLA)

Enteric fevers are caused by salmonella typhi, non typhoidal salmonella species, and other gram-negative bacteria including Shigella and toxin producing E. Coli, Campylobacter.
Recurrent septicemia, including non-typhoidal salmonella is classified as WHO stage 4.

Prevention: early ART, cotrimoxazole prophylaxis (partially protective), food/drinking water hygiene (see sub-title: 33.9 Food handling and safety, *page 154*).

29.1 Clinical features of enteric fever

Symptoms: fever, rigors, nausea, abdominal pain, GIT may include profuse bloody or non-bloody diarrhea, 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 test.

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

29.3 Standard treatment[51]

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 bacteremia is confirmed, or highly suspected, please 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/mm^3) treatment with ciprofloxacin can be extended from 2 to 6 weeks.

29.4 Secondary prophylaxis

- Cotrimoxazole prophylaxis according to standard regimen.

[51] 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.

Skin conditions and STI

CHAPTER 30: SKIN DISEASE

30.1 Key points

- Skin lesions are common and often early manifestation of PLHIV
- Skin lesions may have 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. Kaposis sarcoma)

- Prompt diagnosis and treatment of cutaneous manifestations is important for symptom relief and to treat potentially life-threatening disease (e.g. infection, or severe drug reaction).

30.2 Adverse drug reactions

- All drugs have potential side effects, which often manifest on the skin. They range from mild to life-threatening.
- If a patient presents with rash, +/- fever and constitutional symptoms – always consider drug reactions in the differential diagnosis.
- In HIV and TB settings, the following drugs are commonly implicated:
  - ARVs: nevirapine, efavirenz, abacavir (as part of abacavir hypersensitivity syndrome), and less commonly 3TC, AZT
  - Cotrimoxazole
  - TB drugs
  - Others: anti-epileptics (e.g. carbamazepine, phenobarbitone), NSAIDS, allopurinol, etc.

30.3 Clinical presentation

Key syndromes:

1. **Maculopapular (also mobilliform, or exanthematous) drug eruptions** are the most common type of adverse drug reaction. They are diffuse symmetrical eruptions of macules +/or 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.
   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 and Toxic Epidermal Necrolysis (TEN)**
   They involve epidermal necrosis to varying degrees from less than 10% to more than 30% body surface area, involving at least 2 or more mucous membranes, e.g. eyes, mouth, or genitalia. Usually starts as an abrupt onset of dusky purple macules areas with pain on shedding of skin secondary to pressure.

Key features of some drug eruptions

1. **Fixed-drug eruptions** (e.g. NSAIDS, tetracyclines):
   May present as localized or extensive coin-shaped hyperpigmented areas +/- blistering, which often recur in the same place when the drug is repeated.

2. **Lichenoid drug eruptions and photodermatitis** (e.g. thiazides, TB drugs, chloroquine, cotrimoxazole):
   Lichenoid pigmentation (slate grey/blue color) of skin, sometimes in more sun exposed areas but can be generalized.

30.4 Management

- For any severe drug rash, particularly with extensive skin involvement +/or systemic symptoms, + /or DRESS, 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 later.
- For more information regarding management of specific drug reactions see:
  - Abacavir hypersensitivity: Chapter 10, sub-title: 10.2.2 Abacavir hypersensitivity, *page 65.*
  - Cotrimoxazole: Chapter 5, sub-title 5.8: Cotrimoxazole hypersensitivity, *page 42.*
  - ARV drug rashes: Chapter 10, sub-title 10.3.4: ARV drug rash, *page 68.*

30.5 Disseminated infections with dermatological manifestations

- Bacterial infections: Staphylococcus aureus, Bacilliary 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 cryptococal infection), Histoplasmosis, Sporotrichosis, Penicillium.

30.5.1 Invasive fungal diseases

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

30.5.2 Penicilliosis

Penicilliosis is caused by infection with *Talaromyces* (formally *Penicillium) marneffei* 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

- Clinical diagnosis however 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 200 mg/day until CD4>100 for 6 months.[52]
- 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/mm^3

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.

Histoplasmosis has been rarely reported in Cambodia. Some patients may present with reactivation disease as their immunity decreases with HIV and not with primary infection.

[52] Sanford Guide to Antimicrobial therapy 2015

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: 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, diagnosis will not be able to be established. Consult an expert if diagnosis is being considered for advice re investigation and management.
- 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.
- 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 37: Bacterial skin and soft tissue infections

Bacterial skin infection	Causative organism	Description	Treatment
Folliculitis	*Staphylococcus aureus*	Inflammation, infection of the hair follicles	- Warm compress - Cleansing with topical gentian violet - Cloxacillin in severe cases
Cellulitis	*Streptococcus, Staphylococcus aureus, Haemophilus influenzae*	Inflammation of skin and subcutaneous tissues, characterized by edema, erythema, and pain +/- fever	- Cloxacillin 500 mg 4 times daily for 10 days. - Severe cases require IV antibiotic (cloxacillin or ceftriaxone)
Boils, soft tissue abscess	*Staphylococcus aureus, Haemophilus influenzae*	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	*Staphylococcus aureus, Streptococcus*	Yellow colored crusting or irritating blisters	- Soak crusts with warm water. - Topical antibiotic or antibiotic/salicylic acid preparation - Cloxacillin for disseminated lesions
Paronychia	*Staphylococcus aureus*	Infection involving the folds of tissue surrounding the fingernail or toenail	- Surgical drainage if pus under nail. - Cloxacillin for 5-7 days

Pyomyositis	*Staphylococcus aureus*	Deep abscess formation within muscle. Likely systemically unwell, fever, pain.	- Surgical drainage most important. - Cloxacillin 1-2 grams IV 4 times daily or ceftriaxone 2 grams daily for 10 days
Bacillary angiomatosis "cat scratch disease"	*Bartonella henslae*	Disseminated vascular lesions that may mimic Kaposi's sarcoma	- Consult expert - Erythromycin 500 mg 4 times daily or doxycycline 100 mg 2 times daily for two months
Necrotising soft tissue infections including necrotizing fasciitis	*Streptococcus pyogenes, Clostridium perfringens (gas gangrene), of Vibrio species or polymicrobial mixed aerobe and anaerobic bacteria*	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. - Ex. ceftriaxone + metronidazole/ clindamycin, or meropenum + metronidazole/ clindamycin. - Narrow antibiotic spectrum if culture result available
Staphylococcal Scalded Skin Syndrome	*Staphylococcus aureus*	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	*Treponema pallidum*	1^0 Painless, indurated ulcer (chancre) at site of inoculation Diagnosis clinical (RPR takes 4 – 6 weeks to become positive)	- Benzathine penicillin 2.4 M IU single dose. - 2^{nd} line doxycycline 100mg 2 times daily for 14 days, 3^{rd} line erythromycin 500mg 4 times daily for 4 weeks
Syphilis	*Treponema pallidum*	Maculopapular rash, condylomata lata, fever, lymphadenopathy, oral mucus patches. Diagnosis high RPR	- Benzathine penicillin 2.4 M IU single dose - 2^{nd} line doxycycline 100mg 2 times daily for 14 days, 3^{rd} line erythromycin 500mg 4 times daily for 4 weeks

30.5.5 Viral skin infections

Table 38: Viral skin infections

Viral skin infection
Herpes simplex 1, 2. Orolabial lesions, Genital lesions Vesicles on an erythematous base on lips, nose, tongue, oropharynx, gingival and genital areas. Diagnosis clinical and Tzank test *Management:* Acyclovir 400mg 5 times daily for 7 days.

Gentian violet can help reduce superinfection.
Herpes Zoster, shingles Herpes Zoster virus(reactivation) *Signs and Symptoms:* Common in HIV patients. Dermatomal distribution painful vesicles – then crusting, rarely crosses midline. May cause ocular damage. Diagnosis clinical + Tzank. *Management:* Acyclovir 800mg 5 times daily 7-10 days. Gentian violet can help reduce superinfection. Calamine lotion for skin lesions.
Herpes Zoster, chicken pox Herpes Zoster virus (primary infection) *Signs and Symptoms:* Prodrome 3 days, generalized vesicular rash in "crops" may be complicated by pneumonitis, hepatitis, encephalitis. *Management*: Acyclovir 800mg 5 times daily 7-10 days. Gentian violet can help reduce superinfection. Calamine lotion.
Moluscum contagiosum Pox virus *Signs and Symptoms:* Umbilicated papules, patient not unwell. Must be differentiated from Cryptococcus or Penicillium or Histoplasmosis (usually systemically unwell) *Management:* Self-limiting. Open lesion with sterile needle and expressing contents, curettage, or liquid nitrogen cryotherapy.
Warts Human papilloma virus *Signs and Symptoms:* 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 (maxium). Protect unaffected skin vaseline or zinc ointment, then wash with water and soap after 1-4 hours. DO NOT ADMINSTER DURING PREGNANCY. Cryotherapy if available.

30.5.6 Fungal skin infections

Table 39: Fungal skin infections

Fungal skin infection
Tinea (ringworm) Tinea corporis, capitis, pedis. *Signs and Symptoms:* 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 tinea capitis treat with systemic fluconazole 150mg weekly for four weeks.
Tinea onychomycosis Tinea ungum *Signs and Symptoms:* Hyperkeratosis of undersurface of the nail plate. *Diagnosis:* fungal microscopy and culture. *Management:* Treat onychomycosis only if severe. Iitraconazole 200mg 2 times daily for first seven days of 4 consecutive months. Or Terbenafine if available. Check for interaction with ARV
Cutaneous candidiasis *Candida species* (usually *albicans*) *Signs and Symptoms:* 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 times per day until 48 hours after rash resolves.

30.5.7 Scabies

Table 40: Scabies

Scabies infestation
Scabies Sarcoptes Scabies var hominis *Signs and Symptoms:* 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.
Crusted (Norwegian) scabies Sarcoptes Scabies var hominis. *Signs and Symptoms:* 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.

30.5.8 Non infective skin lesions

Table 41: Non infective skin lesions

Non infective skin lesions
Seborrheic Dermatitis
Signs and Symptoms: 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.
Pruritic Papular Eruption
Most common in patients with CD4 < 200 cells/mm^3
Signs and Symptoms: 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.
Eosinophyilic folliculitis
Signs and Symptoms: Edematous, 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
Psoriasis
Extensive Psoriasis can be observed in severely immunosuppressed patients.
Signs and Symptoms: 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 times daily with coal tar shampoo (if scalp is involved), and potent topical steroids (betamenasone 0.1% or Diprosalic cream cream applied to lesions 1-2 times daily for 14 days.
Generally, psoriasis is refractory to treatment other than ART.
Kaposis Sarcoma (very rare in Asia)
Cancer due to HHV8 virus, WHO stage 4 illness.
Signs and Symptoms: 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: most important is prompt starting of ART, discuss with an expert re need for radio /chemotherapy.

Figure 15: Algorithm for rash with pain (MSF)

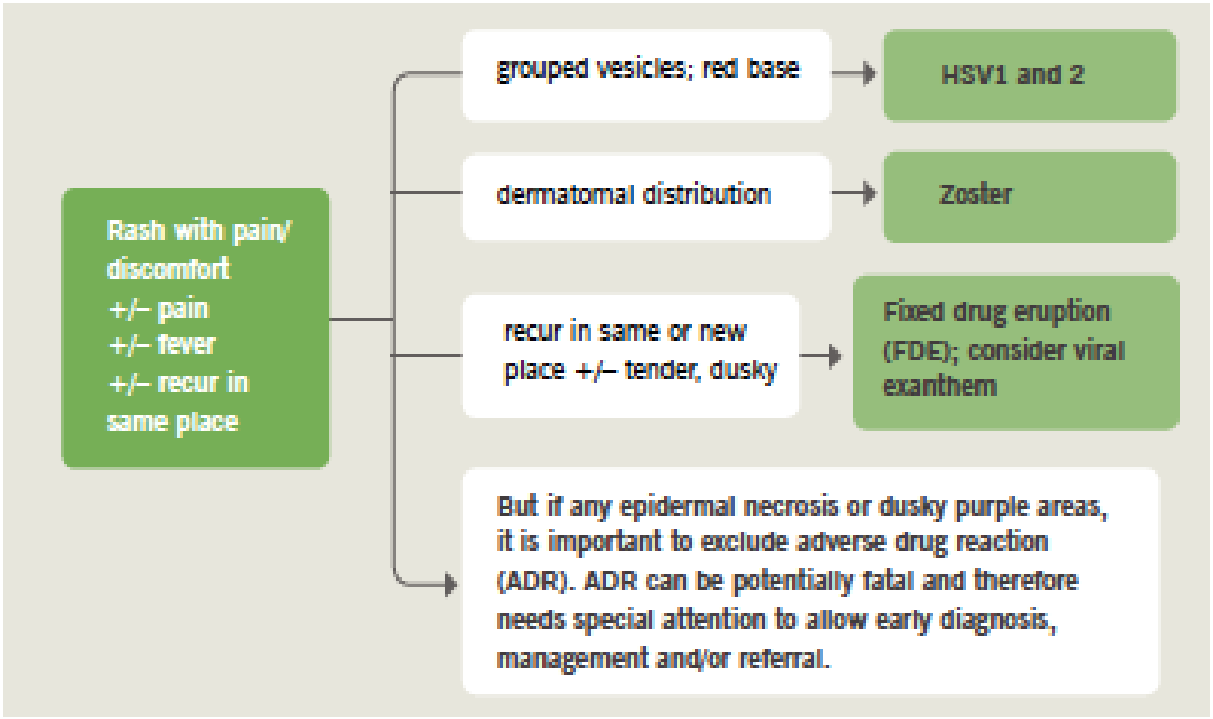


Figure 16: Algorithm for rash with no pain/itch (MSF)

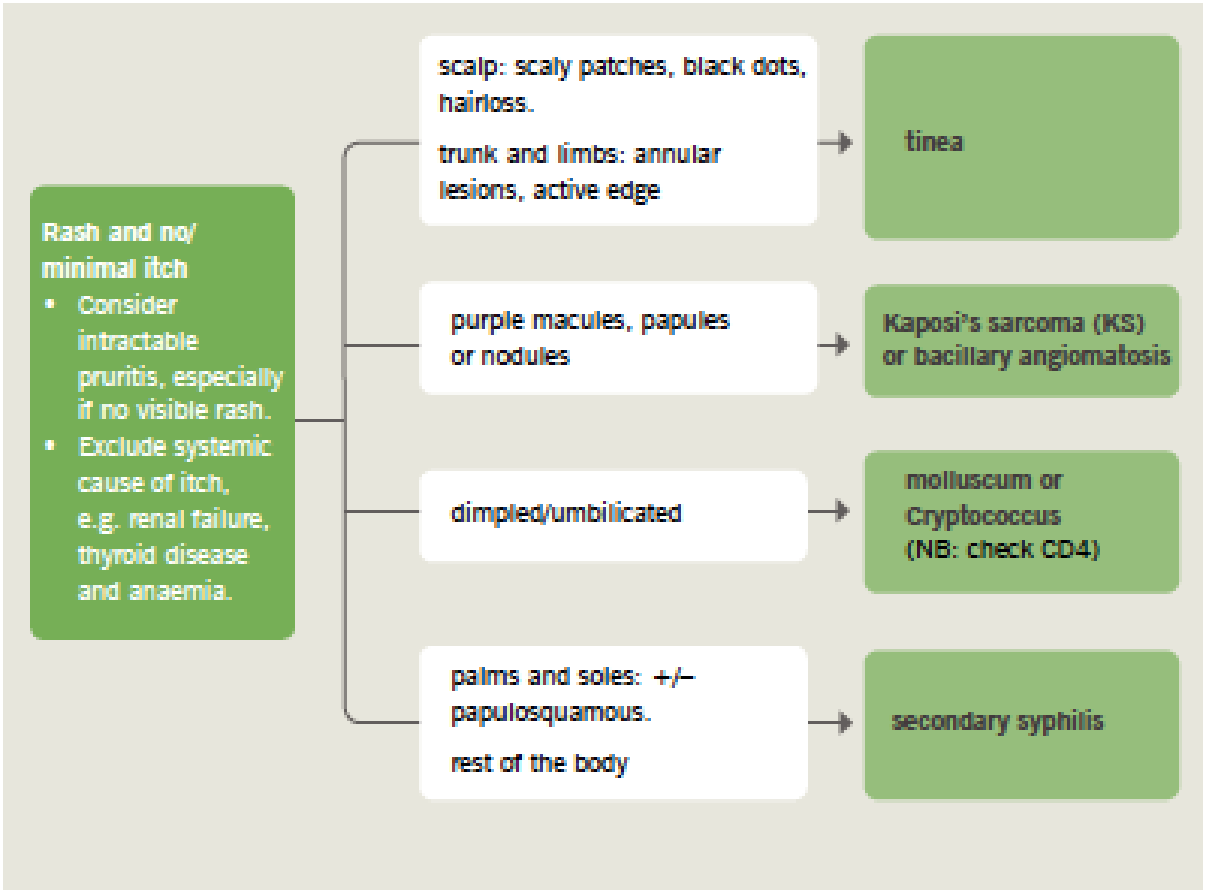


Figure 17: Algortithm for rash with itch (MSF)

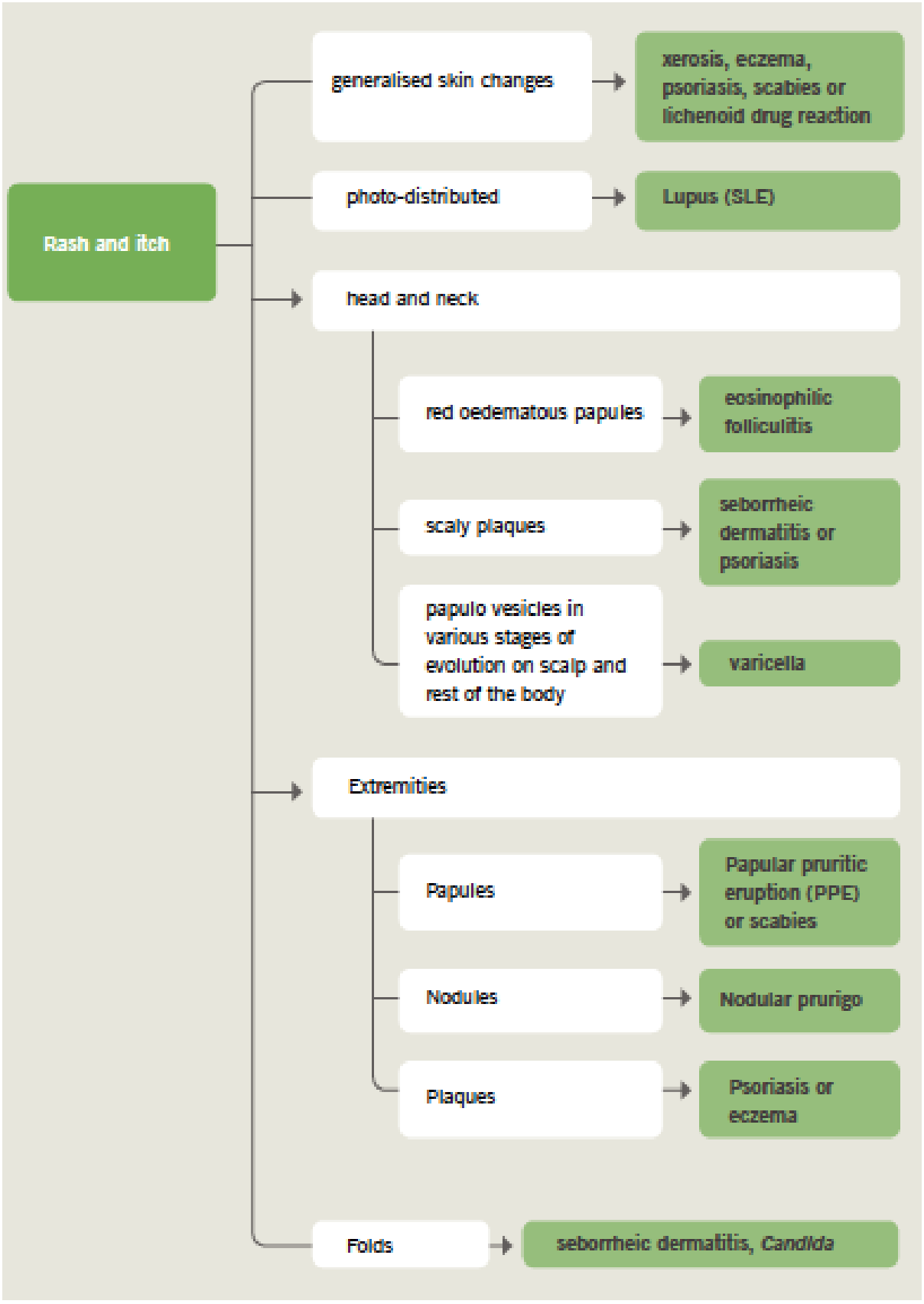
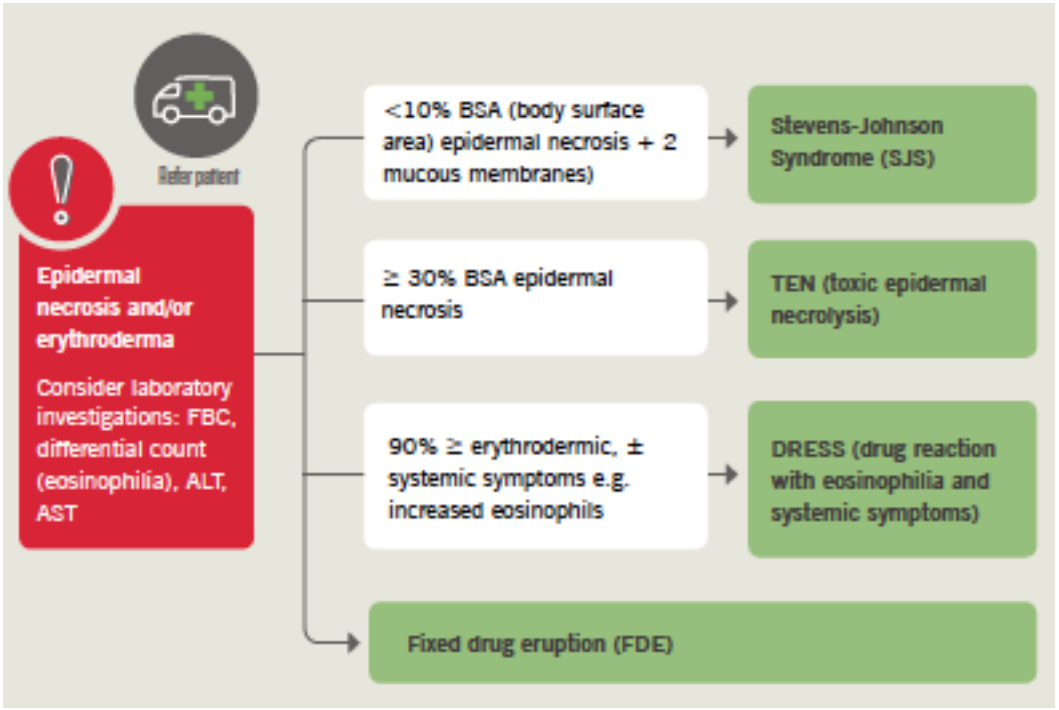


Figure 18: Algorithm for severe rash (MSF)



CHAPTER 31: REPRODUCTIVE AND SEXUALLY TRANSMITTED INFECTIONS

- It is important that PLHIV and their partners are treated for STIs for the health of the individuals, and as they increase the risk of transmission of HIV.
- Generally, the evaluation and treatment for STI are the same as for non-HIV infected individuals.
- See NCHADS STI management guidelines, in particular STI/RTI care and treatment for people living with HIV/AIDS[53].
- See sub-title 3.2 Contraception *page 34*, for discussion regarding family planning and contraception needs.

31.1 Vaginal candidiasis

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

31.1.1 Clinical findings

Symptoms: itching or burning sensation as well as white vaginal discharge.
Examination: White adherent vaginal discharge creamy white vaginal discharge with cheese-like plaques vulvo-vaginal area is erythematous, swollen, and painful.

31.1.2 Diagnosis

Clinical signs are based on symptoms and examination findings. Please consider other causes of vaginal discharge including bacterial vaginosis and cervicitis due to gonorrhea, chlamydia, and trichomonas. Particularly if clinical features are atypical or treatment is ineffective.

31.1.3 Standard treatment (any of the following)

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

31.1.4 Treatment of persistent or recurrent vaginal candida

- Fluconazole 150-200 mg take once time (more prolonged duration maybe considered in difficult case).

[53] Kingdom of Cambodia, Ministry of Health. National guidelines on sexually transmitted infections (STI) and reproductive tract infections (RTI) case management. 2010 module 6. chapter 6, p217 – 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 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 malignancy 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 Chapter 35: Smoking cessation, *page 156*).

32.1 Non-Hodgkin's lymphoma (NHL)

NHL is usually associated with very advanced HIV (CD4 < 50 cells/ mm^3), 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, and night sweats, splenomegaly, hepatomegaly, evidence of focal infiltrates, and cytopenias on CBC.

Table 42: Site dependent clinical presentations of NHL

Mediastinal or Pharyngeal tumor	**Abdominal tumor**
Dyspnea, Tachypnea, Stridor Localized decrease in breath sounds, cough	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 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 progress over time to develop cervical intraepithelial

dysplasia (CIN) and on to invasive cervical carcinoma. Invasive cervical cancer is listed as a WHO stage 4 AIDS defining illness. 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 oncogenic high-risk 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. Primary screening methods include cytology (Papanicolou or "pap" smear, or Liquid based cytology) or hr-HPV PCR testing (GeneXpert). In some resource limited settings, if hr-HPV test is positive, visual inspection methods (acetic acid (VIA) or Lugol's Iodine) could be used and be followed by cryotherapy or thermal ablation on positive lesions, as one stop screen and treat services.

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 abnormal presentation.

Treatment

Treatment options are limited in Cambodia, however if feasible refer to the Khmer Soviet Hospital or Calmette hospital for further investigation and treatment for cervical dysplasia with, loop electrical excision cauterization, or cone excision procedures or thermal ablation or cryotherapy. 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

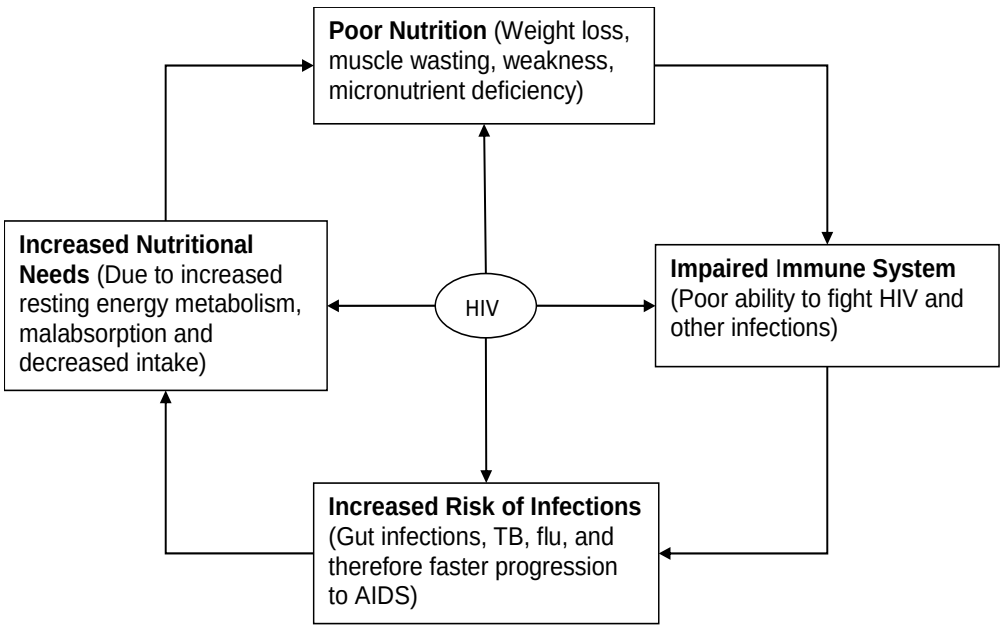
33.1 Key points

- 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 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 patient's 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 of infectious diseases."

Figure 19: Cycle of malnutrition and infection in HIV[54]



33.3 Nutrition Screening and weight management

33.3.1 Initial evaluation

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

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 - current weight)/BBW x 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 43: WHO BMI Classification of adult underweight, overweight and obesity.
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 ≥ 80cm
4. See the following sections according to if the patient is ***under***, ***normal*** or ***overweight***.

33.3.2 Weight evaluation every visit

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

At initial and follow up visits – see the following section relevant to the patient's needs:

- *Underweight* (WHO and BMI criteria): See sub-title:
- 33.4 Assessment and management of underweight or loss of weight, *page 152.*
- *Overweight* (BMI or waist circumference criteria): See sub-title: 33.5 Assessment and management of overweight, *page 154.*
- *Normal weight* sub-title: 33.6: Nomrmal weight at initial or follow up visits*, page 153.*

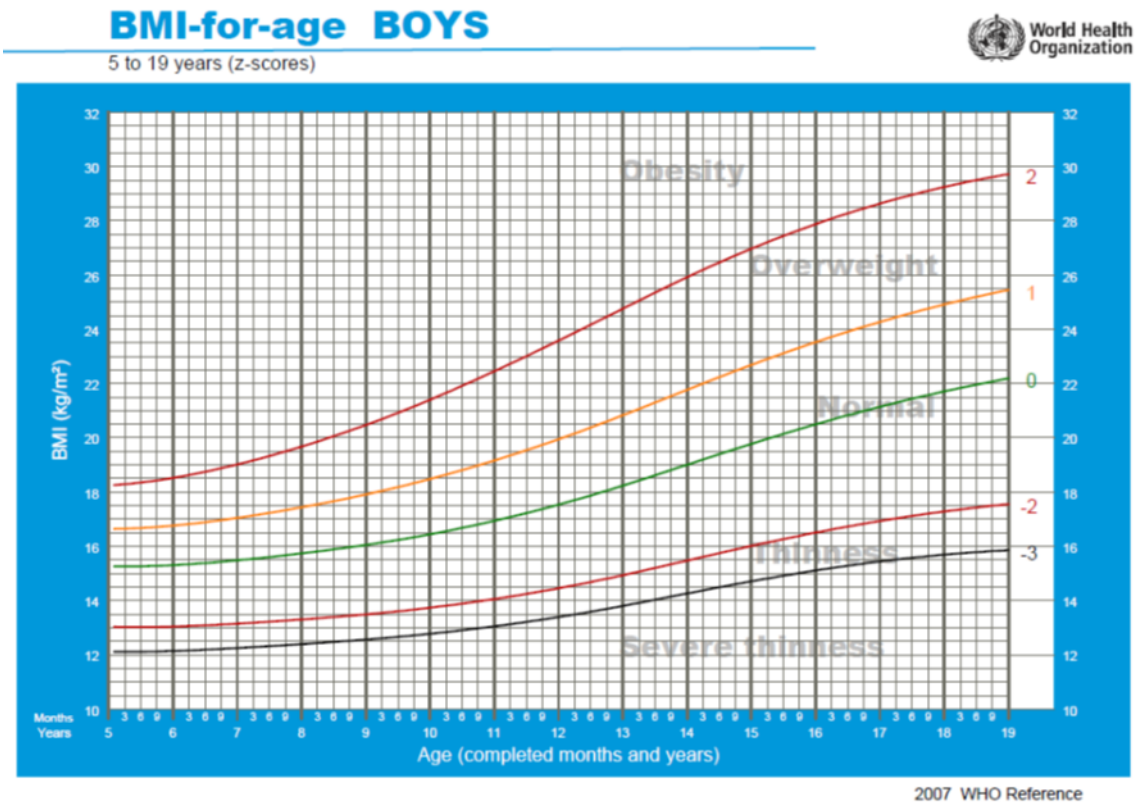
Table 43: WHO BMI Classification of adult underweight, overweight and obesity[55]

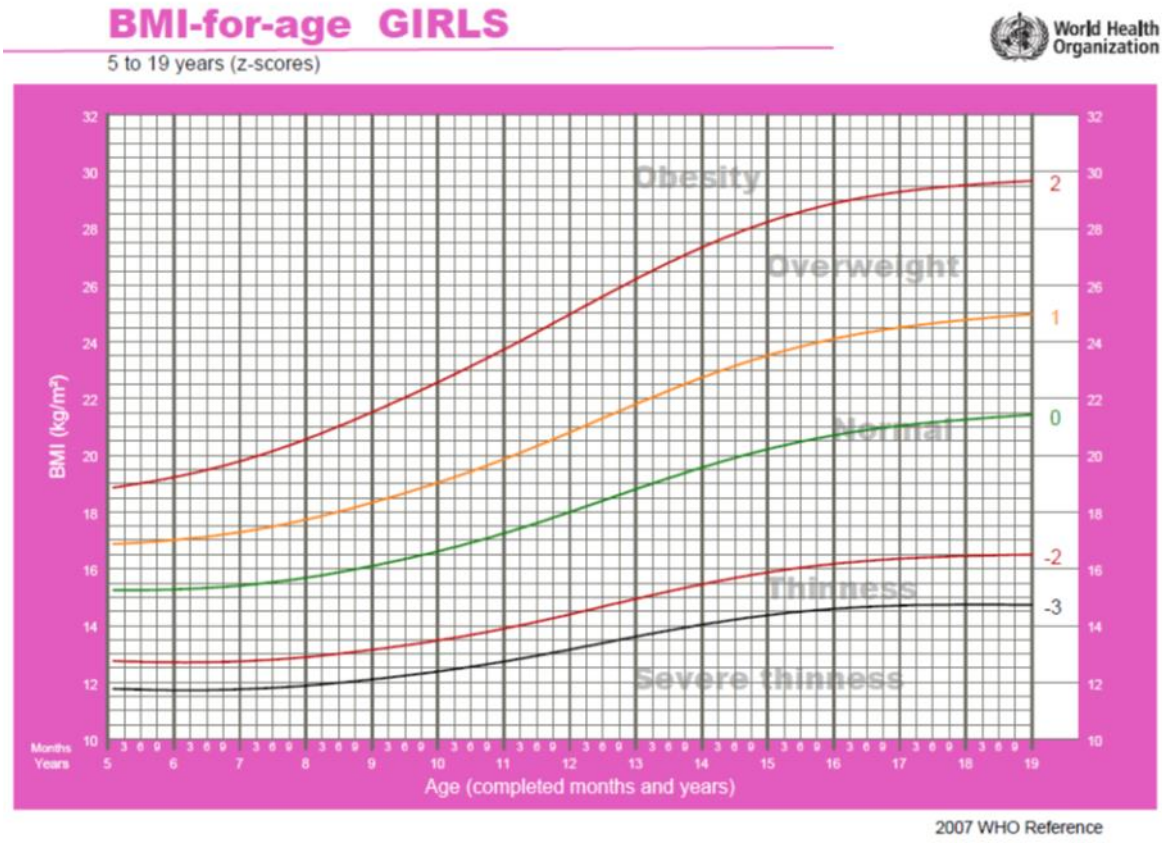
Classification	WHO Principal cut-off points	Cambodian cut-off points*
Underweight	**<18.5**	**<18.5**
Severe thinness	<16.0	<16.0
Moderate thinness	16.0 - 16.9	16.0 - 16.9
Mild thinness	17.0 - 18.4	17.0 - 18.4
Normal range	**18.5 - 24.9**	**18.5 - 22.9**
Overweight	**≥25.0**	**23.0- 24.9**
Pre-obese	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.[56]		

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

[56] 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 20: WHO BMI Classification of child/adolescent





33.4 Assessment and management of underweight or loss of weight

33.4.1 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 and water 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.
- Diarrhea (including evidence of malabsorption in stool – fat/food).

33.4.2 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 (see Table 45: Recommendations for prevention and management of NCD, *page 155*) 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 tables.
- Monitor weight, clinical findings and discuss nutrition at each visit.

Table 44: Symptom targeted management of poor food intake

Symptoms	Management [57]
Loss of appetite	• 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 flavor to drinks and food.
Mouth ulcer	• 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	• 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	• 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 odor • Drink plenty of liquids • Rest and relax after meals • Avoid lying down immediately after eating • Avoid coffee and alcohol.
Diarrhea	• 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, and/or 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	• Eat fiber-rich food • Take light exercise and activity • Drink plenty of water.

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

33.5 Assessment and management of overweight.

- Patients are more likely to become overweight once OI are successfully treated and HIV infection is controlled on ART.
- Overweight or 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.

33.5.1 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 if available.

33.5.2 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 21: WHO Counselling tool to assist individual to quit smoking, *page 155*)
- 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 45: recommendation for prevention and management of NCD, *page 155*)
- Undertake daily exercise – e.g. brisk walking at least 30 min/day

  If hypertension (>140/80) – see Chapter 36: Hypertension, *page 157*.
- If diabetes or glucose intolerant – see chapter 37, sub-title 37.4: Management of type 2 diabetes, *page 160.*
- 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 45: : Recommendations for prevention and management of NCD, *page 155*)
- Monitor weight at each visit
  - If undesired weight loss, refer to sub-title:
  - 33.4 Assessment and management of underweight or loss of weight
  - If undesired weight gain refer to sub-title: 33.5 Assessment and management of overweight.

33.7 Food and medications

Always check whether there are any requirements regarding the timing of food with each medication prescribed. (e.g. 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. The National Nutrition Program offers special 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.

CHAPTER 34: 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 them 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, non-alcoholic fatty liver disease (NAFLD) and cancers.
- It is important that the HIV clinician is aware of NCD, and regularly addresses issues of 1^0 and 2^{nd} prevention with PLHIV during consultations.
- In addition, PLHIV on long-term ART should be screened for NCD (according to these guidelines) 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. [58]

Table 45: Recommendations for prevention and management of NCD

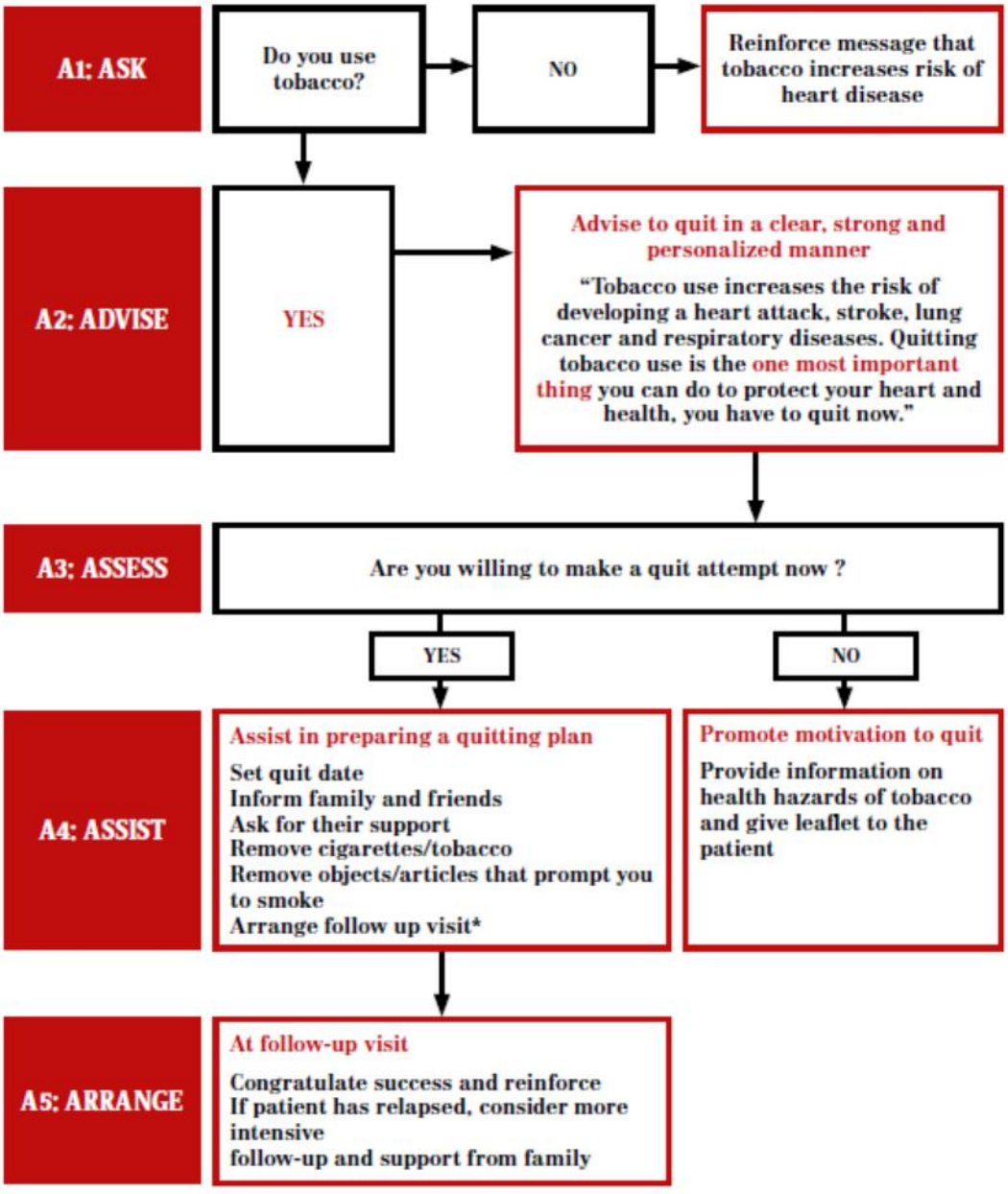
The emphasis on diet and lifestyle modification will vary depending on whether the patient is under/over/normal weight and other risk factors, HT, diabetes etc.
Diet: most people need to pay attention to eat • More protein (tofu, beans, chicken, fish) • More vegetables (5 x 400 – 500gm servings vegetables 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)

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

CHAPTER 35: SMOKING CESSATION

- Clinicians should encourage and provide practical advice to patients to quit smoking.
- The following tool (figure 21) can assist clinicians to help patients give up smoking.

Figure 21: WHO Counseling tool to assist individuals to quit smoking[59]



* 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.

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

CHAPTER 36: HYPERTENSION

The Cambodian Clinical Practice Guidelines detail the management of hypertension.[60]

36.1 Screening, and diagnosis hypertension in PLHIV

All patients should have blood pressure taken at each visit.
Hypertension is classified into 4 stages as following:

- STAGE 1 or Prehypertension is 120/80 to 139/89.
- STAGE 2 or Mild Hypertension is 140/90 to 159/99.
- STAGE 3 or Moderate Hypertension is 160/100 to 179/109.
- STAGE 4 or Severe Hypertension is 180/110 or higher.

If BP > 140/90 is more than one occasion, it is required for treatment.

36.2 Management of hypertension

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 45: , 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.

2. Evaluate for other conditions associated with hypertension
   - 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.

3. Pharmacological management
   - 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:

[60] 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, MINISTRY OF HEALTH, DEPARTMENT OF PREVENTIVE MEDICINE 2015.

- Thiazide diuretic + ACE I
- Thiazide diuretic + calcium channel blocker
- ACE I + calcium channel blocker

Table 46: 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	SBP < 140 mm Hg
	DBP ≥ 90 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

- Examples of drug doses:
  - ACE I: Enalopril – start 5mg OD - increase up to max 20mg OD
  - ACE I: Captopril – start 12.5mg BID – increase to max 150mg TID
  - Thiazide: Hydrochlorthiaide - 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: - Amilodipine start 2.5mg OD – increase to max 10mg.

- Follow up after starting antihypertensive medication 2 weekly, until stable.

36.3 Drug interactions with antihypertensive medicines and ART [61]

Table 47: Antihypertensive drug interactions with ARV

Drug	Interaction with ARV
ACEI: enalopril, captopril, ramipril;	No described interactions with NNRTI, NRTI or PI.
Calcium channel blockers: including amilodipine, nifedipine;	Levels of CCB are potentially *decreased* by NNRTI, and *increased* 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 *decreased* by NNRTI, and *increased* by PI → careful monitoring of BP and dose adjust

[61] http://www.hiv-druginteractions.org/

CHAPTER 37: TYPE 2 DIABETES

The Cambodian Clinical Practice Guidelines detail diagnosis and management of diabetes.[62]

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 ≥ 85cm and in women ≥ 80cm)
- Family history of diabetes
- Hypertension (BP > 140/90)
- Dyslipidaemia
- History of stroke or ischaemic heart disease
- Women with a history of gestational diabetes or given birth to a large baby (>3500g)
- 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 and every 12 months.

37.2 Diagnosis of type 2 diabetes and impaired glucose tolerance

Table 48: Diagnostic criteria for Diabetes and impaired glucose tolerance

	Glucose concentration, mmol/l (mg/dl)		
	Whole blood		Plasma venous
	Venous	Capillary	
Diabetes mellitus			
Fasting	≥ 6.1 (110)	≥ 6.1 (110)	≥ 7.0 (126)
or			
2-hour post glucose load	≥ 10.0 (180)	≥ 11.1 (200)	≥ 11.1 (200)
or both			
Impaired glucose tolerance			
Fasting concentration (if measured)	≤ 6.1 (110)	≤ 6.1 (110)	≤ 7.1 (126)
and			
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)	≤ 6.7 (120)	≤ 7.8 (140)	≤ 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

[62] 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

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.

37.3 Management of impaired glucose tolerance

- Weight loss if overweight
- Healthy diet and lifestyle as detailed in Table 45: Recommendations for prevention and management of NCD, *page 155.*
- Follow up testing in 12 months.

37.4 Management of type 2 diabetes

- See the National guidelines for comprehensive guidance on management of diabetes[63]
- 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 45: Recommendations for prevention and management of NCD, *page 155.*
   - Modification of the diet → diabetic diet. This mostly consists of reducing the portion size of carbohydrate, including rice. (see Figure 33: Food pyramid for Diabetes Type 2, *page 203.*

- Patients should be evaluated for other conditions associated with diabetes:
  - Weight, BMI, (see Table 43: WHO BMI Classification of adult underweight, overweight and obesity, *page 150*) and Waist circumference: overweight = men ≥85 cm, women ≥ 80cm
  - Hypertension > 140/90 or > 130/80 if 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

[63] 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

3. Drug interactions between diabetes medication and ART [64]

Table 49: Diabetes drug interactions with ARV

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

[64] http://www.hiv-druginteractions.org/

CHAPTER 38: 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 atazanavir/r compared to lopinavir/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. E.g. *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 after treatment failure), and monitored after 3 months and then 12 monthly, as PI drugs can cause hyperlipidaemia.
- PLHIV may have other indications for serum lipid levels – e.g. diabetes.

38.2 Management of hyperlipidaemia

Hyperlipidaemia requires both pharmacological and non-pharmacological management.

1. Non pharmacological management

- Follow Table 45: 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 – First Line

Change from LPV/r to ATV/r (unless contra-indicated)

- If predominantly raised LDL-C
  - Statin
- Predominantly raised TG (>10mmol/l), especially if with a low HDL-C
  - Fibrate +/or 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 50: Lipid lowering drugs interactions with ARV

Statins • **Simvastatin and lovastatin are *contraindicated* 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: - 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
• **Fibrates** - Gemfibrozil ▪ Drug levels may be lowered by PI ART ▪ Do not use in combination with a statin due to the risk of myositis - Fenofibrate ▪ Monitor ALT/CK if in combination with statins due to increased risk of side effects
• **Fish oils** are not known to interact 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

39.1 Definition

Osteoporosis is a skeletal disorder 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.

39.2 Risk factors for osteoporosis

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

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.[65]
- 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 45: , are all very important factors for prevention and management of osteoporosis, with an emphasis on stopping smoking, balanced diet including adequate calcium intake, adequate vitamin D intake, maintaining healthy weight range, and weight bearing exercise (e.g. walking), and minimizing alcohol intake.

- Avoid long courses of corticosteroids unless 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.

[65] 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

CHAPTER 40: KIDNEY DISEASE

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

40.1 Investigation of kidney disease

Table 51: Tests used in the investigation of kidney function

Urine tests
Urine dipstick, includes: • 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: - 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): • Elevated in diabetic nephropathy (often negative dipstick protein and creatinine +/- N).
Urine microscopy • Leukocytes, red blood cells, and organisms (UTI) - If available perform culture for identification and antimicrobial sensitivity • Red cell morphology. - Dysmorphic red blood cells; originate from kidney (nephritis) - Normal red blood cells; come from the lower urinary tract.
Blood tests
Serum Creatinine • Creatinine is a natural chemical excreted in the urine. • Serum creatinine rises when it is not cleared properly and usually indicates kidney injury.
• Creatinine clearance / estimated Glomerular Filtration Rate (eGFR) - A more accurate assessment of kidney function than serum creatinine. - The eGFR drops in kidney injury (Normal eGFR = > 90ml/min) - The creatinine clearance may be calculated by the Cockroft – Gault equation: eGFR ml/min = (140 – age) x weight (kg) / serum creatinine (µmol/l) (male) eGFR ml/min = (140 – age) x weight (kg) x 0.85 / serum creatinine (µmol/l) (female).
• Serum electrolytes: potassium, sodium, phosphate, bicarbonate, urate
• CBC: normocytic anaemia (MCV normal) is common in chronic kidney injury.
Renal tract ultrasound

- Chronic kidney disease usually → small kidneys (<9cm)
- Acute kidney disease may → large kidneys (>12 cm) e.g. HIVAN
- Renal tract obstruction
  - 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 31: Creatinine evaluation algorithm
- Figure 32: Urine dipstick algorithm.

40.2 Acute kidney injury

1. **Pre-renal acute kidney injury** usually results from an episode of hypotension, due to:
   - Sepsis
   - Volume loss e.g. dehydration due to diarrhea
   - Vascular – 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 does not improve quickly
    - Investigate for additional cause of renal impairment
    - Adjust renally excreted drug doses according to creatinine clearance (see Table 61: Drug dose adjustments in patients with renal failure, *page 198*)
    - Monitor the renal function for changes in eGFR which may require further dose adjustments.

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.

3. **Intrinsic kidney injury** – intrinsic causes of renal failure are many, drug reactions are important:
- Tenofovir (TDF) toxicity (see below)
- Cotrimoxazole and rifampin 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 and/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 nMCV)
- Small kidneys on ultrasound (if available).

- **Management:**
    - Stop smoking
    - Optimal treatment of diabetes and hypertension
    - Include ACE I in regimen e.g. enalopril 2.5mg BD - (check BP and potassium)
    - Avoid nephrotoxic drugs particularly NSAIDS
    - Adjust renally excreted drug doses according to creatinine clearance
    - (see Table 61: Drug dose adjustments in patients with renal failure, *page 198*)
    - 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:**
    - ≥ 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 enalopril 2.5mg BD - check BP and potassium
    - Monitor proteinuria and creatinine 3 monthly for 2 times, then 6 monthly
    - Avoid nephrotoxic drugs, and adjust renally excreted drugs according to eGFR (see Table 61: Drug dose adjustments in patients with renal failure, *page 198*)
    - Monitor the renal function for changes in eGFR which may require further dose adjustments.

CHAPTER 41: 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 56: Cambodian HIV prevalence estimates by demographic, *page 175*).
- 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, result in inadequate 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 available services for harm reduction services at community and methadone replacement therapy at Russian Friendship hospital.

CHAPTER 42: 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 6: Figure 34: Common Presentations of Mental Health conditions, *page 204.*
- 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 52: 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:

3. Have you ever thought about giving up?
4. 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 antidepressant.[66]

Table 53: 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 amitriptyline/SSRI/ haloperidol, All cause QT prolongation. Avoid if possible, otherwise use lower dose of amitriptyline/SSRI/ haloperidol and monitor ECG.
Amitriptyline	OK	OK	
SSRI – fluoxetine, sertraline	OK	OK	
SSRI – sertraline, venlafaxine, citralopram	OK	EFV potentially ↓ levels of SSRI	

42.2 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 54: Distinguishing medical from psychiatric illness[67]

	Delirium secondary to medical causes	Psychosis as symptom of psychiatric illness
Cause	***Medical:*** infection/hypoxia/hypoglycemia/ 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

[66] www.hiv-druginteractions.org/

[67] Adapted from MSF HIV/TB Clinical guide 2015.

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, cryotococcus).
- 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.

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.

Antipsychotic and sedative medication may be considered when non-pharmacological measures fail; for urgent management of agitation/aggression, e.g. while arranging transfer patient to hospital.

Consider drug interactions prior to drug administration (see Table 53: Psychiatric drug interactions with , *page 170*)

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 – 20mg orally, repeat every 2 – 6 hours according to clinical response up to a maximum of 120mg in 24 hours.
- 2nd line: Haloperidol 0.5 – 2mg orally, repeat every 2 hours according to clinical response, up to a maximum of 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 (PEP)

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 (ideally within 4 to 6 hours) 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 for which indication must be systematic.
- 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 55: Routes of HIV transmission, and average transmission risk per episode

Exposure from an HIV infected source	Estimated risk of HIV transmission per episode[68]
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

[68] Post-Exposure Prophylaxis after Non-Occupational andOccupational 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:
  - Sexual assault.
  - 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 56: Cambodian HIV prevalence estimates by demographic

Population / subpopulation	Prevalence	Source
General adult population	0.6%	AEM 2016
Injecting drug users (PWID)	15.2%	IBBS 2017
Non injecting drug users (PWUD)	5.7%	IBBS 2017
Entertainment worker	11.8%	IBBS 2016
Transgender M→ F	5.9%	IBBS 2016
MSM	2.3%	IBBS 2014

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

However, please note that:

- The real risk may increase due to biological factors outlined above that increase the risk
- 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 an HCW who has a needle stick injury from a person from the general adult population, HIV status unknown = 1/440 x 0.6% = 0.0014%
- The risk to a man who experienced condom breakage during vaginal sex with an entertainment worker = 1/2500 x 11.8% = 0.0047%
- 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 15.2% = 0.012%

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 45.7%) + (1/70 x 5.7%) = 0.0045% + 0.06% = 0.081%
- The risk to a woman who is vaginally raped by 5 PWUD = 5 x 1/1250 x 5.7% = 0.022%

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 $\rightarrow$ 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 that is known to have an undetectable viral load (e.g. condom breakage from HIV positive spouse), the risk is extremely low, and PEP is not indicated.

43.4 PEP regimen

- Adherence to the **full 28 days regimen** is critical to the effectiveness of the intervention
- **2 NRTI + Integrase Inhibitor ARV drug regimens are preferred**, at standard treatment doses.
  - **TDF 300mg + 3TC 300mg + DTG 50 mg, fix dose combination once daily for 28 days**[69]
- The NRTI backbone of TDF + 3TC is well tolerated, and an integrase inhibitor 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.

[69] Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016 from the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

- There is a theoretical risk of hepatic flare among people infected with HBV once TDF-, 3TC/ FTC-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/FTC-based PEP, but people known HBV infection should be clinically monitored for hepatic flare after discontinuation of TDF-, 3TC/ FTC-based PEP.

43.5 Post exposure prophylaxis care pathway

- **Assessment and immediate management**

- **First aid**
  - 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)
  - 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

- **Counselling re risks and options re PEP**

- Explain the estimated risk of transmission (see above)
- Explain the risks and benefits of PEP:
  - 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

- **Initiate PEP as soon as possible following exposure, TAKE THE FIRST DOSE NOW!**

- 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:
  - **TDF 300mg + 3TC 300mg + DTG 50 mg once daily x 28 days**
  - Take the first dose straight away.
  - Give initial prescription / supply for 4 days

- **Assess and provide emergency contraception and STI treatment in the context of sexual exposure.**

  - 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 [70]**

  - See also NCHADS STI guidelines which detail management of sexual assault[71]

- **Complete documentation:**

  - See table 63: NCHADS PEP Clinic visit and report form, *page 205*.

[70] Responding to intimate partner violence and sexual violence against women: who clinical and policy guidelines. Geneva: World Health Organization; 2013

[71] National Guidelines on Sexually Transmitted Infections (STI) and Reproductive Tract Infections (RTI) case management. 2010 module 6 charter 5, page 212

• **Follow up on PEP**
- Return to the clinic in 3 to 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.

CHAPTER 44: PRE-EXPOSURE PROPHYLAXIS (PREP)

PrEP offers a complementary bio-medical approach to prevent the acquisition of HIV infection and the consequent morbidity and mortality, human suffering, cost to society and stop onward transmission. For some, hopefully many, PrEP will be a positive attraction to come to clinics to access ARV and agree to HIV screening where in the past they may have avoided because of stigma associated with their risk behaviors or the possibility of being HIV infected.

In Cambodia, NCHADS plans to initially offer PrEP as a service for individuals at high risk for HIV infection attending Chhouk Sar Clinic and an ART clinic in Phnom Penh. EW, MSM and TG will be the primary target populations. A regimen of daily TDF+3TC (300/300mg) will be given. Recommended by WHO as an alternative to TDF/FTC (Truvada), this fixed-dose combination with either Nevirapine or Efavirenz, is already in use in Cambodia. Following a one-year implementation period, close monitoring, and evaluation, the intent is to scale PrEP service to other public, private, and NGOs clinics in the country.
The purpose of introducing PrEP is to reduce the spread of HIV infection among key-populations.

41.1 PrEP eligibility criteria

44.1.1 Behavioral Risk Criteria

HIV-uninfected individuals of 18 years and older with substantial risk for HIV infection are eligible and will benefit most from PrEP. Common substantial risks include but are not limited to:

- Being an HIV uninfected sexual partner of a PLHIV who is not virally suppressed, or results of viral load testing are unknown (i.e., HIV discordant couples) and where condoms are not consistently used.
- Had condomless anal/vaginal/neovaginal sex in the past 6 months with more than one partner.
- History of any new sexually transmitted infection (STI) in the past 6 months.
- Used drugs for sexual pleasure during the past 6 months and there is condomless sex

or inadequate access to sterile injecting equipment.

- Injected drugs in the past 6 months where injecting equipment shared or there is inadequate access to sterile injecting equipment.
- Received post-exposure prophylaxis (PEP) one or more times in the past 12 months.
- If the sexual partner of the person has one or more of the HIV risk factors listed above.

44.1.2 Clinical criteria

Even though PrEP has a good safety profile, there are several contra-indications for prescribing PrEP. Therefore, the following individuals may take PrEP:

- Must be HIV negative. So, someone being known to be HIV infected or suspected to be HIV infected or in the HIV window period where no HIV antibodies can be detected by 4th generation antibody tests cannot take PrEP. PCR, if available can reduce the window period to a few days but cannot eliminate it.
- Must be free of symptoms of acute retroviral syndrome (ARS).
- Must have good renal function (creatinine clearance (> 60 ml/mn).
- Must be free of any ARV drug allergy (either to TDF or its companion drug 3TC).
- Must have enough body weight (>35 kg).
- Clients with chronic or acute hepatitis B infection may take PrEP but with caution under the guidance of an experienced physician. For someone on PrEP, he/she should be warned that stopping may cause suppressed HBV infection to flare.

PrEP has no or minimal drug interactions with commonly prescribed medicines nor significant side-effects and has proven to be safe in many randomized controlled trials. PrEP can be used safely by most people including:

- Pregnant or breastfeeding women.
- Women using hormonal drugs for contraception.
- Transgender persons on gender-affirmative hormone therapy.

44.2 Prescription of PrEP

44.2.1 Clinical assessment

Prior to prescribing PrEP, medical history and a physical exam should be performed. Acute HIV infection should be suspected in persons with a recent high-risk exposure. Most common symptoms include fever, headache, coughing and malaise, whereas abnormalities are related to head, ears, nose and eyes, lymphadenopathy and tachycardia (12). Individuals presenting with symptoms or signs of acute HIV infection should not be started on PrEP until HIV infection has been excluded.

44.2.2 Counseling

Counseling for potential PrEP clients should focus on increasing awareness of PrEP as an additional HIV prevention method (i.e., should be applied in combination with other prevention methods including condom use, reduction in number of sexual partners), whether

PrEP is the right prevention method given the risk behavior profile of the client and that PrEP provides optimal but not 100% protection from HIV infection.

44.2.3 Dosing, duration, follow-up and adherence of PrEP

PrEP can also be effective if taken daily for short periods of time or around single events of possible HIV exposure. This event-based strategy has been evaluated only for MSM. However, daily continuous PrEP use is believed to facilitate adherence because of its routine character and the unpredictability of HIV risk in many situations and persons. Dosing, duration, follow-up and adherence to PrEP, are recommended as follows:

- For daily PrEP dosing, oral co-formulated TDF/3TC should be taken daily and continuously during periods of high risk for HIV infection.
- For event-driven PrEP dosing, the first dose (2 tablets) is taken 2 to 24 hours before the first sexual intercourse then one tablet daily for until 48 hours after the last sexual intercourse.
- Clinicians and health care workers (counselors) should help their clients deciding when to initiate and discontinue PrEP (more detail see NCHADS' PreP SOP)
- When to stop PrEP: How you stop PrEP depends on which dosing you use.
- Daily dosing: Continue daily PrEP for seven days after the last time you had sex.
- On-demand dosing: If you had a recent risk, continue taking PrEP at your regular time for another 48 hours. This means taking two doses, one for each of the two days after your last risk. If in the future your circumstances change again, it is easy to restart PrEP.

44.3 Client monitoring

Pre-PrEP evaluation procedures, clinical follow-up and laboratory and adherence monitoring of PrEP clients are listed in **Table 57** below. After PrEP initiation, clients should return to the clinic for follow-up and laboratory monitoring every three months during the first year and every six months thereafter. In some cases, clinicians may want to see their clients after one month for HIV re-testing, assessment of early side-effects and adherence evaluation and to address any question or difficulty. A one-month clinic visit may also be considered for more controlled refill prescriptions following PrEP initiation.

Table 57: Pre-PrEP evaluation, clinical follow-up, laboratory and adherence monitoring of PrEP clients

Test/procedure	Visits			
	Month 0	Month 3	Every 3 months until month	Every 3 months
HIV serology	Y	Y	Y	Y
Evaluation for ARS	Y	Y	Y	Y
Medical history and physical exam	Y	Y	Y	Y
Creatinine clearance[72]	Y	Y	N	Every 6 months

[72] Biomedic has been contacted and agreed to perform creatinine clearance test at a 20% reduced cost.

HBV serology and management	Y	N	N	N
HCV serology	Y	N	N	Every 12 months
STI evaluation and management	Y	Y	Y	Y
Drug dispensing	Y	Y	Y	Y
Adherence evaluation		Y	Y	Y
Risk evaluation	Y	Y	Y	Y

ARS, acute retroviral syndrome; BMD, bone mineral density; HCV, hepatitis C virus; HBV, hepatitis B virus; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Annexes

CHAPTER 45: ANNEXES

ANNEX 1: WHO STAGING SYSTEM

Table 58: WHO staging system adults and adolescents (≥ 15 years)[73]

Clinical stage 1	Clinical stage 2
• Asymptomatic • Persistent generalized lymphadenopathy	• Moderate unexplained weight loss (under 10% of presumed or measured body weight) • Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulcerations • Papular pruritic eruptions • Seborrhoeic dermatitis • Fungal nail infections
Clinical stage 3	**Clinical stage 4**
• Unexplained severe weight loss (over 10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month) • Persistent oral candidiasis • Oral hair y 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 109/l) and/or chronic • thrombocytopenia (below 50 x 109/l).	• 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.

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

ANNEX 2: ROUTINE CLINICAL CONSULTATION VISIT GUIDE

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

Table 59: Initial clinical visit guide

Follow the National forms for assessment checklist and documentation.	• 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 TPT	• Past history TB (Drug-sensitive or resistant?) • Recent/current contact with a TB case? • TB screening (fever, cough, night sweats, weight loss) • Any positive (any visit) → Clinical exam, 1 x sputum for GenXpert, CXR • All negative, check ALT/AST → TPT 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.)
Points to include in the National Adult Initial visit form	
Reproductive health and STI	• Check for history of STI and current symptoms • Ask about reproductive wishes and plans?
TB Screening	• TB screening (fever, cough, night sweats, weight loss) • Any positive (any visit) → Clinical exam, 1 x sputum for GeneXpert, CXR • All negative, check ALT/AST → TPT prophylaxis
Current medical history	History of depression / other mental illness, history suggestive of cognitive impairment.
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[74], waist circumference. Examination; including mental status, neurological – central + peripheral, skin/mouth, CVS, Respiratory, Abdomen.

[74] BMI = weight (kg) / Height $(m)^2$

WHO clinical staging	Take history specific to HIV staging, including weight loss, recurrent infections, herpes zoster etc.
Investigations	Order investigations according to • Routine investigation - • Further investigation as clinically indicated
Management -Information and counseling	• Give information re HIV including OI prophylaxis and ART on same day if eligible. • Advise re nutrition, substance use, healthy lifestyle. • Refer for adherence counseling • MMM, psychosocial support or other services as required[75]
Management - medical	• Treat current illnesses as clinically indicated. • Refer to other medical services if required.
Medication	Initiate OI prophylaxis according to schedule**Error! Reference ource not found.**
Follow up	Schedule for 1 week.

Table 60: 2nd and subsequent clinical visit guide

Follow the National forms for assessment checklist.	• National Adult Patient Visit form • Adult updated information form
Points to include in the initial assessment and documented in visit forms:	
History	• New symptoms? • Review active medical problems
TB screening every visit If eligible start INH prophylaxis at 1M after start ART	• Recent/current contact with a TB case? *(Drug-sensitive or resistant?)* • TB – screening (fever, cough, night sweats, weight loss) • Any positive → Clinical exam, 1 sputum for GeneXpert, CXR • All negative and ALT/AST < 3 x ULN → eligible for TPT prophylaxis.
OI Prophylaxis	Adherence, side effects.
ARV	Ready to start? if started, review adherence, side effects.
Reproductive health and STI	• Review pregnancy status and reproductive plans? • Condom + contraception use • STI symptoms
Mental health	• New symptoms? • Review current mental health issues.
Recreation substance use	Support stop smoking, and harm reduction
HIV disclosure	Review, Support disclosure
Examination	• 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, Ix results.

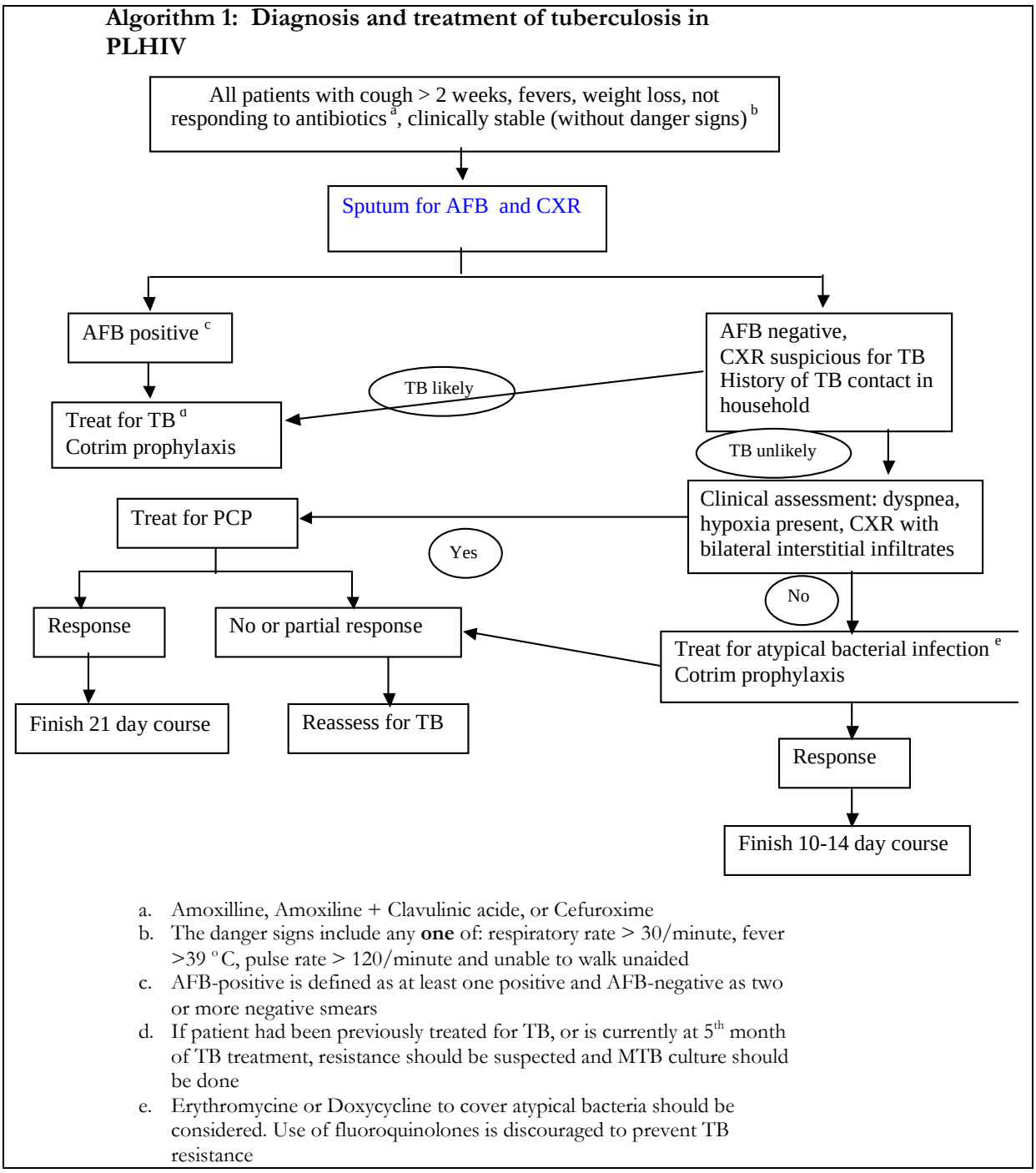
[75] See 'Continuum of Care for people living with HIV/AIDS – Operational Framework' for ways to link ART into the comprehensive care approach

Investigations	• Follow up results of routine and clinically indicated investigation. • Further investigation as clinically indicated
Medications	• Update medication list • Review adverse effects and adherence • Check drug – drug doses, and interactions
Drug allergies	Update
WHO clinical staging	Review WHO stage $\rightarrow$ correct/ advance if necessary
Management - information and counseling	• Reinforce information re HIV OI prophylaxis and ART. • Advise re nutrition, substance abuse, healthy lifestyle. • Refer for adherence support, MMM, psychosocial support or other services as required
Management - medical	• 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.
Follow up	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 months

ANNEX 3: TB/HIV ALGORITHMS

The following algorithms are copied directly from the National TB HIV guidelines[76]

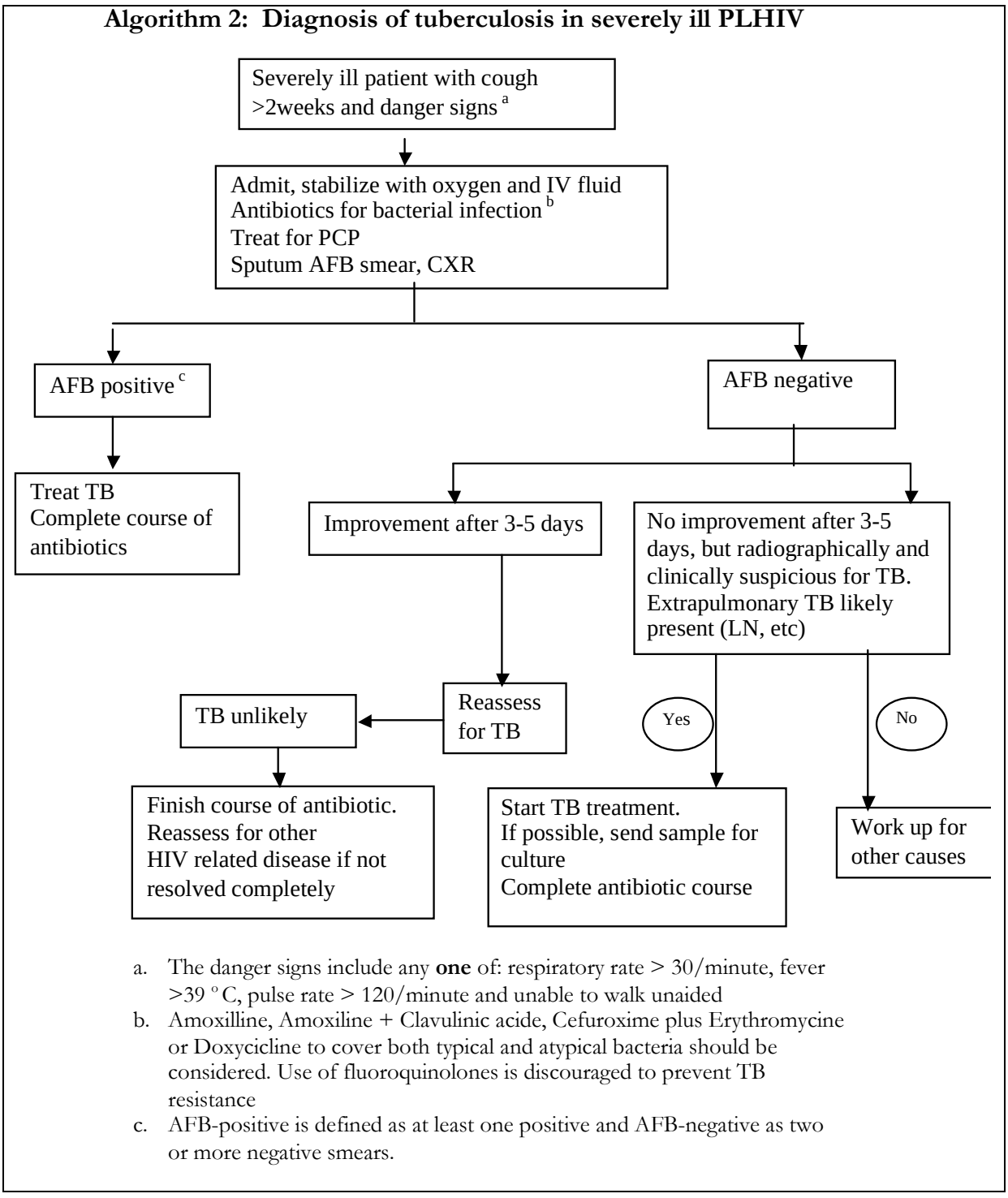
Figure 22: Algorithm 1 Diagnosis and Treatment of TB in PLHIV



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

[76] 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 23: 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 + Clavulinic acide, Cefuroxime plus Erythromycine or Doxycicline 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 24: Algorithm 3 Clinical management of lymphadenopathy in PLHIV

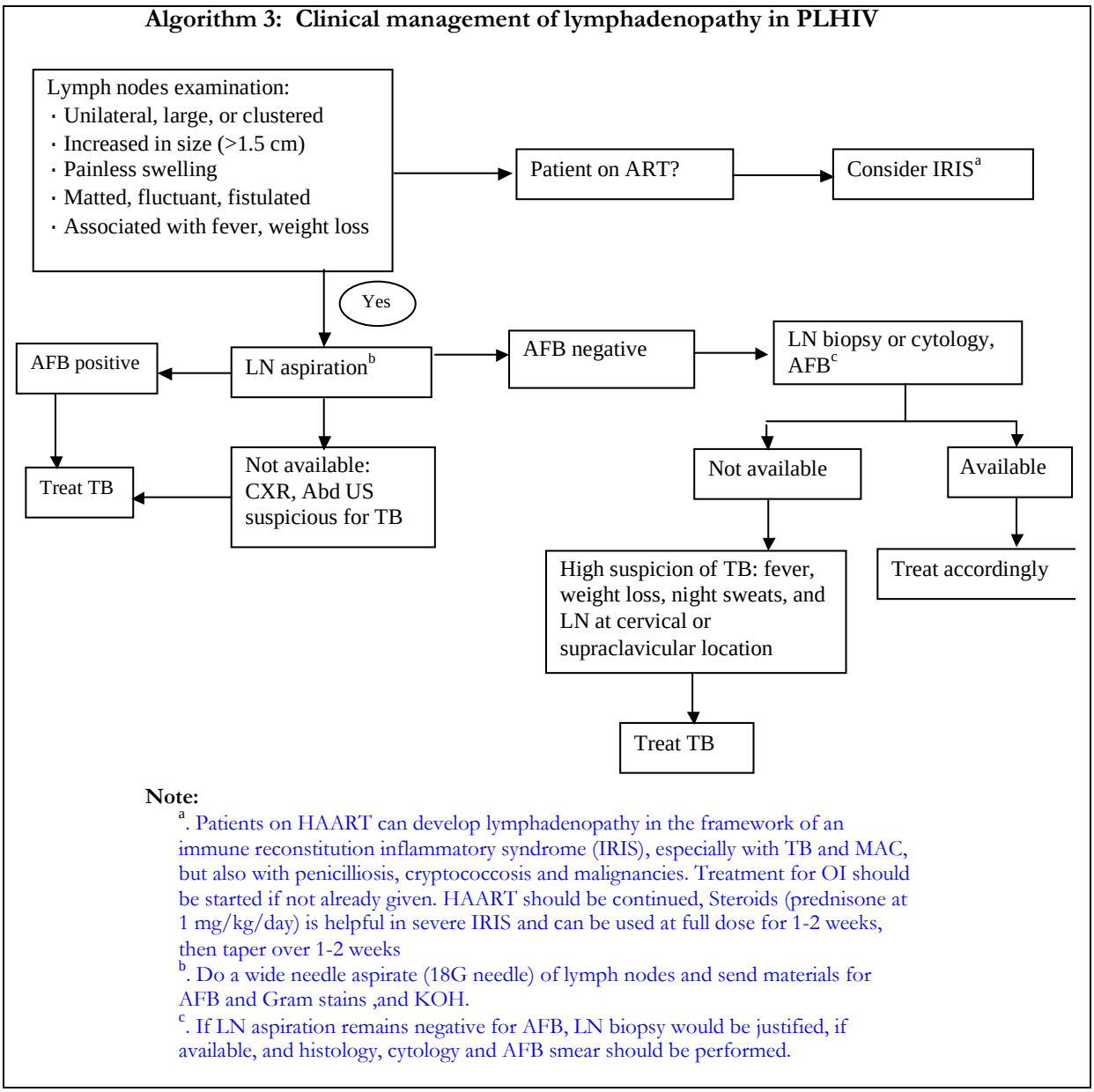


Figure 25: Algorithm 4 Management of abdominal lymphadenopathy

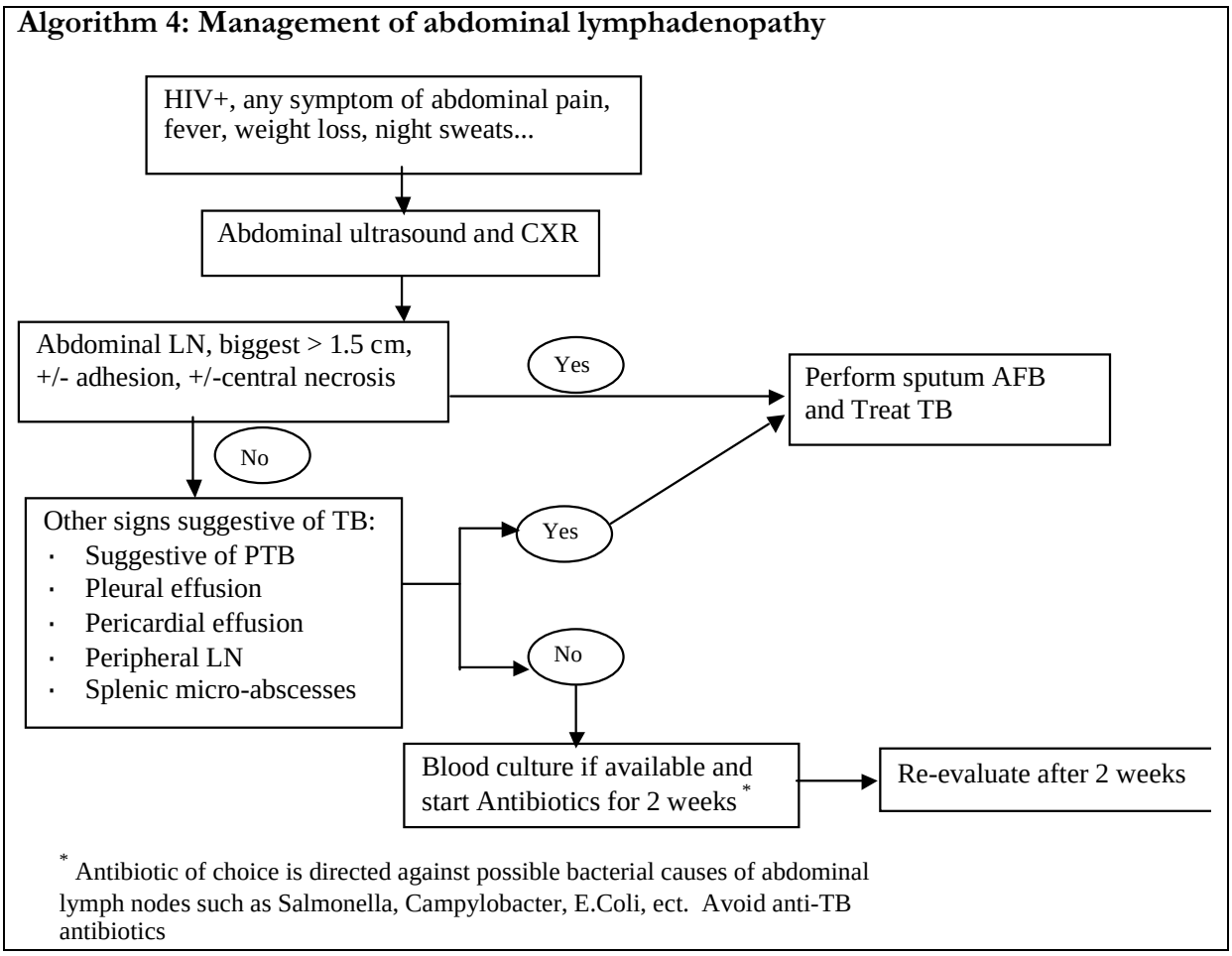


Figure 26: Algorithm 5 Management of pleural effusion in PLHIV

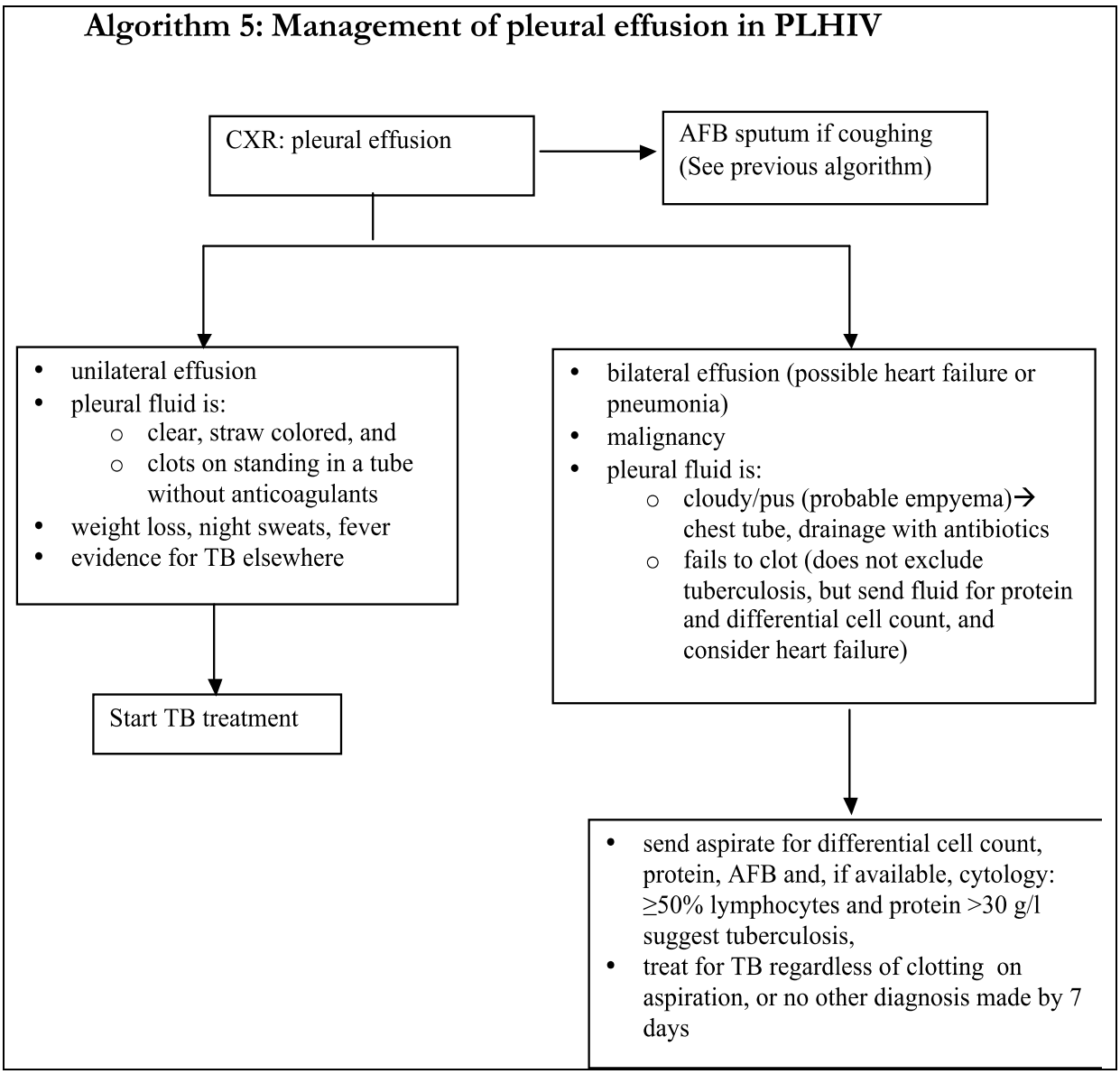


Figure 27: Algorithm 6 Management of pericardial effusion in PLHIV

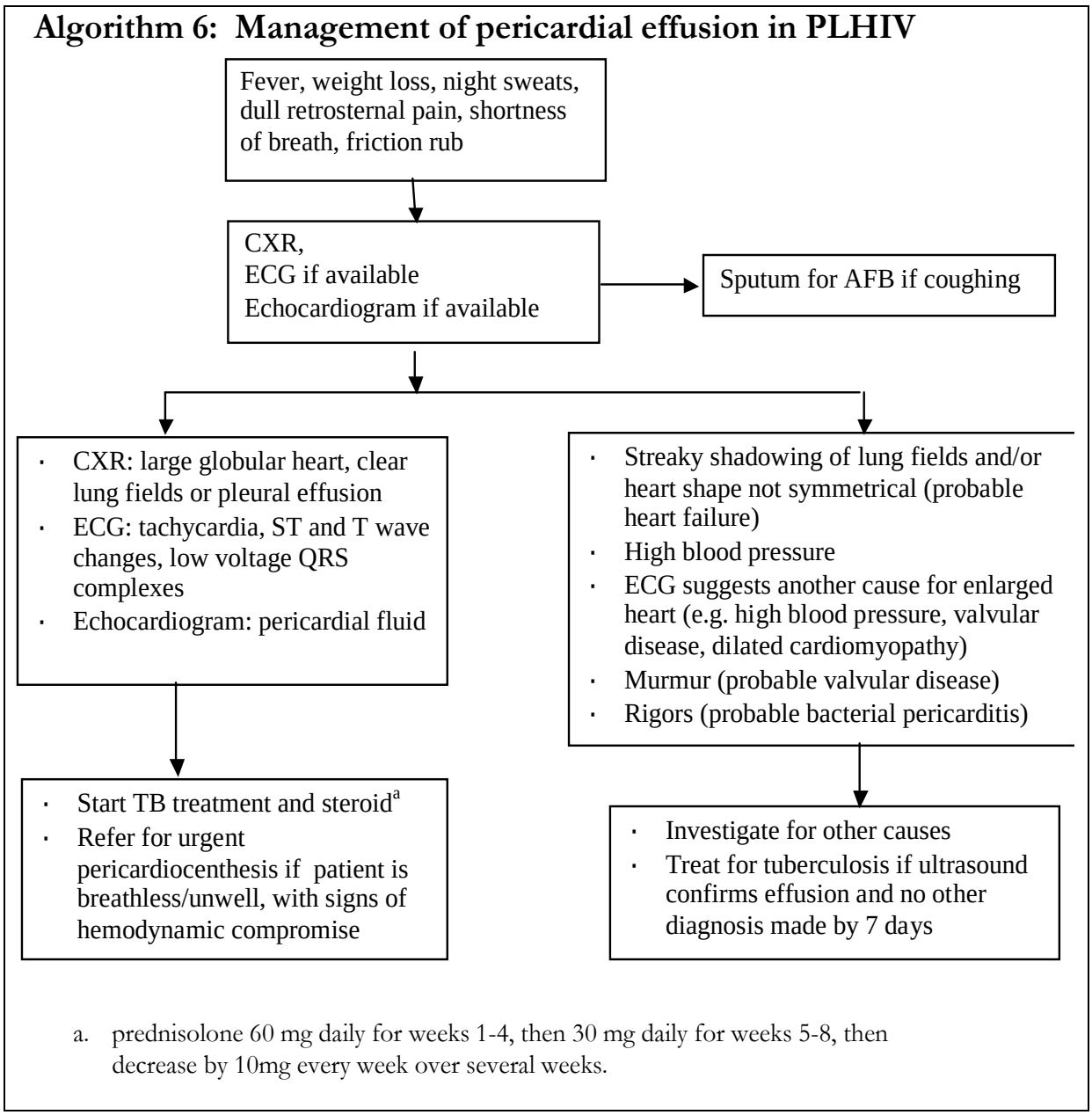
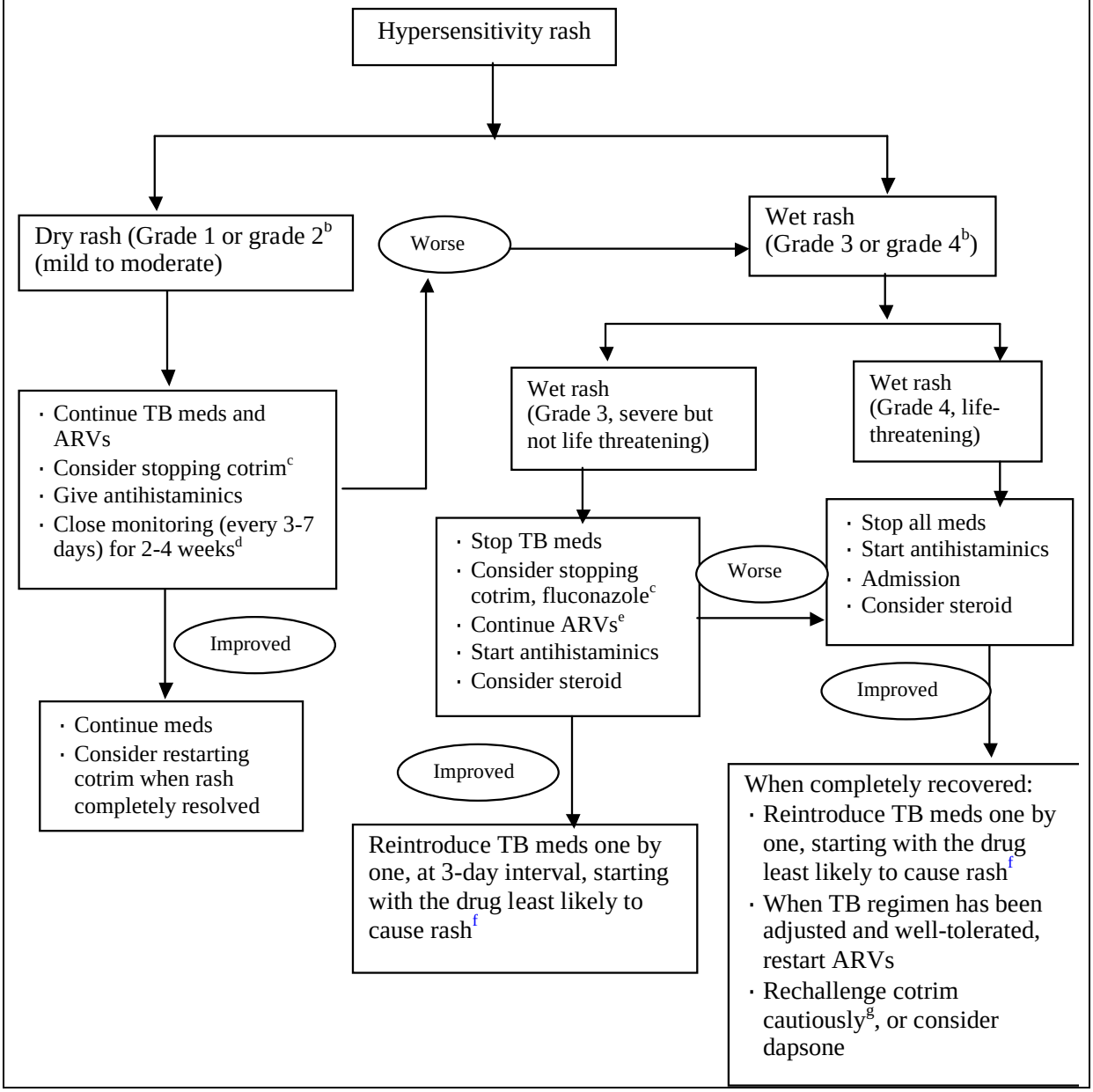


Figure 28: Algorithm 7 Management of skin rash in patients on ART starting anti – TB medications

Algorithm 7: Management of skin rash in patients on ART starting anti-TB medications[a]



Notice:
Patient already received ART for 6 weeks or more than 6 weeks before starting TB treatment
Defining level of skin rash:

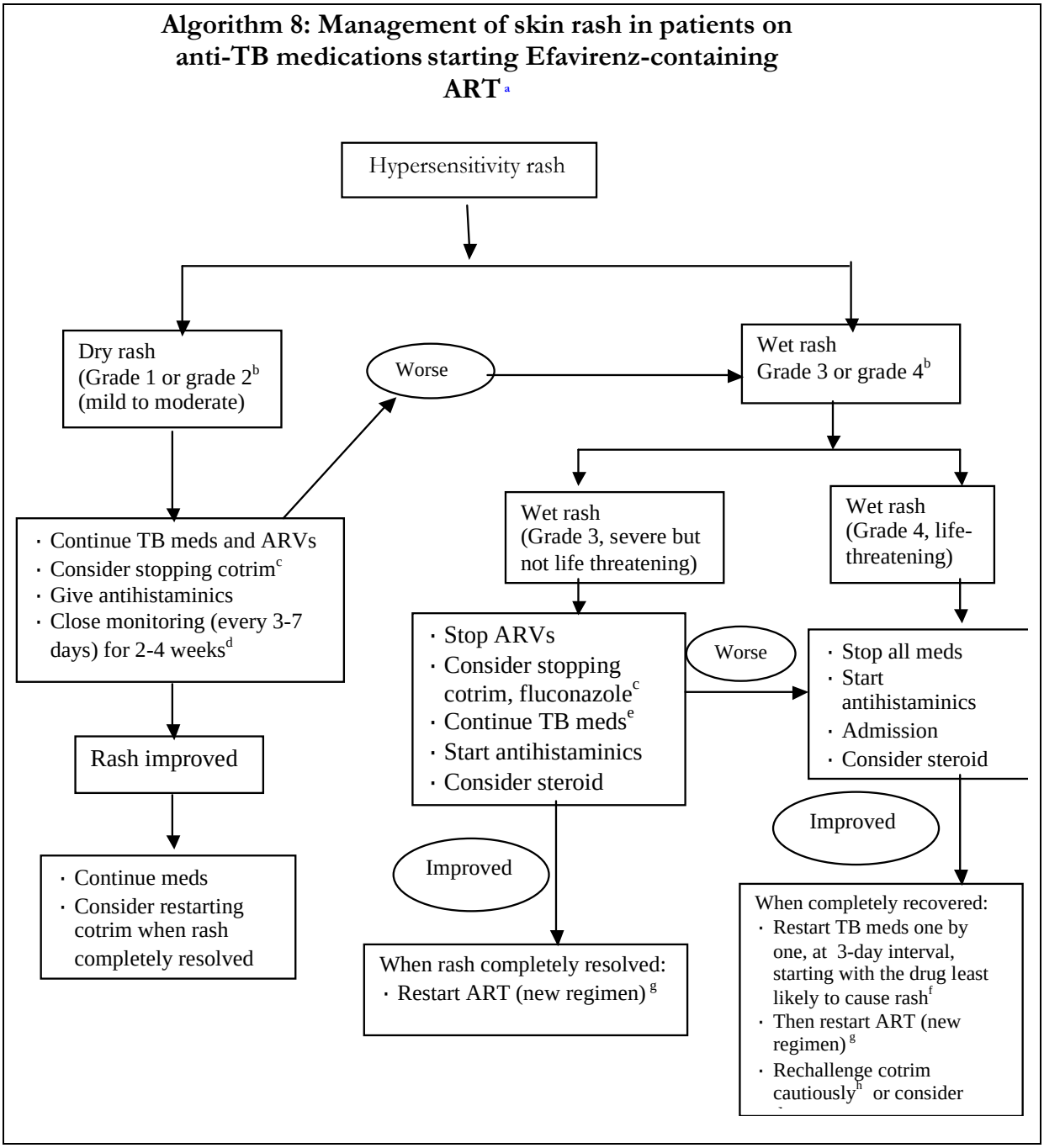
- Level 1 (mild): erythema, pruritus
- Level 2 (moderate): diffuse maculopapular rash, or dry desquamation
- Level 3 (severe): vesiculation (moist desquamation) or ulcer > 50 % of body
- Level 4 (life threatening): have any signs of the below: extensive rash with desquamation angioedema, serum sickness-like reaction, rash with systemic symptoms such as fever blistering, conjunctivitis, oral lesions, exfoliative dermatitis, Stevens Johnson syndrome, toxic epidermal necrolysis (TEN) (WHO)

a) Consider stop cotrim, fluconazole if rash has just recently started within the last 6 weeks)
b) Closely monitor and follow up the skin rash evolution. Tell patient to come back soonest when the skin rash is worsening
c) ARV can be continued if it was already used for more than 6 weeks
d) Restarting TB drug, after drug reaction, shall be followed the table:

Drug	Drug reaction possibility	Challenging dose		
	Less likely	Day 1	Day 2	Day 3
Isoniazid		50mg	300mg	300mg
Rifampicine		75mg	300mg	Full dose
Pyrazinamide		250mg	1000mg	Full dose
Ethambutol		100mg	500mg	Full dose
Streptomycin	Most Like	125mg	500mg	Full dose

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

Figure 29: Algorithm 8 Management of skin rash in patients on anti – TB medications starting Efavirenz-containing ART



Notice:

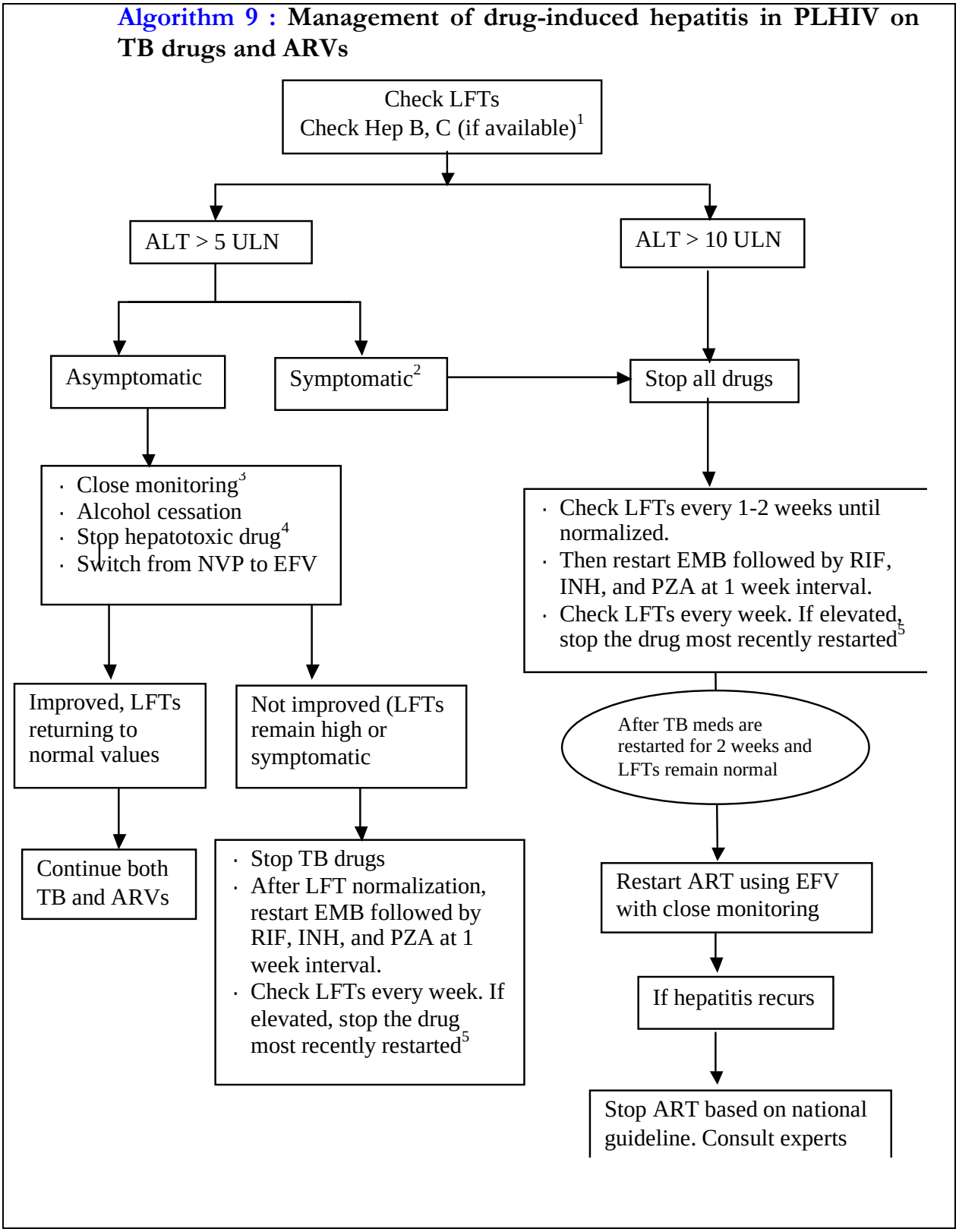
a) Patient already received TB treatment for 6 weeks or more than 6 weeks before initiating ARV. If ART started before this time frame and developed skin rash due to any drug, discuss with expert
b) Defining level of skin rash (see previous algorithm)
c) Consider stop cotrimoxazole or fluconazole if 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 2 NRTIs 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:

- Pl containing formula: Pl 2NRTIs, however, Rifampicin will reduce Pl 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 Isoniazid and Ethambutol. Pl dose not needs 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 1 and 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 1 SS for 3 days and 1 DS in next day.
- If cotrimoxazole suspension is not available, use 80/400mg (480 mg 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 30: Algorithm 9 Management of drug induced hepatitis in PLHIV on TB drugs and ARVs



ANNEX 4: KIDNEY DISEASE

Table 61: Drug dose adjustments in patients with renal failure[77]

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

Drug	reatinine 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
gliben-clamide	2.5–5 mg bd		AVOID		AVOID
metformin	500–1000 mg bd		25%		AVOID

[77] 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			
amoxycillin	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
clarithromy-cin	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
metoclopra-mide	10 mg tds	75%	50%
omeprazole	20–40 mg daily	No adjustment needed	No adjustment needed
ranitidine	150–300 mg nocte	50%	25%

Table 62: TB drug adustment for Cr Clearence < 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 31: Creatinine evaluation algorithm

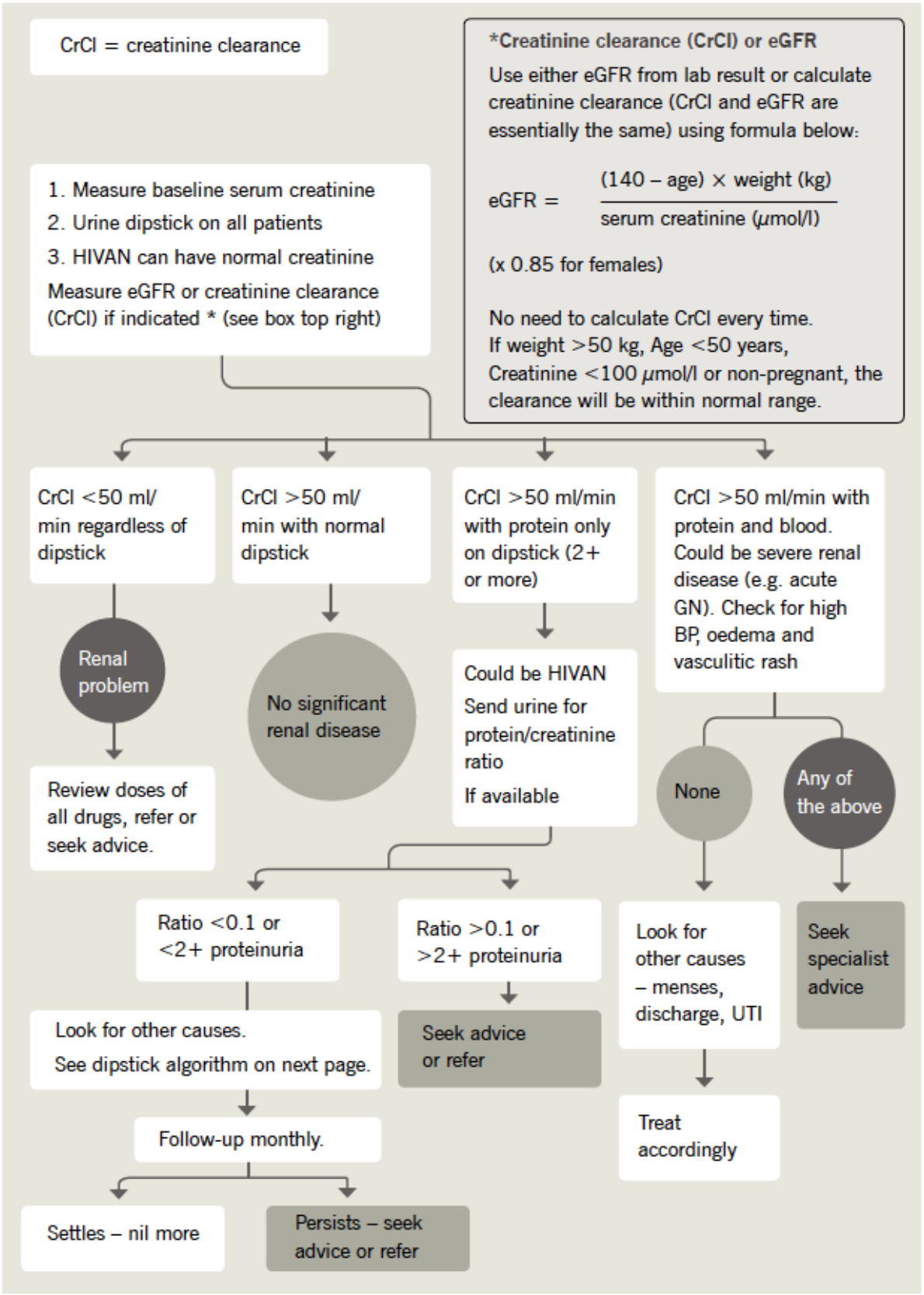
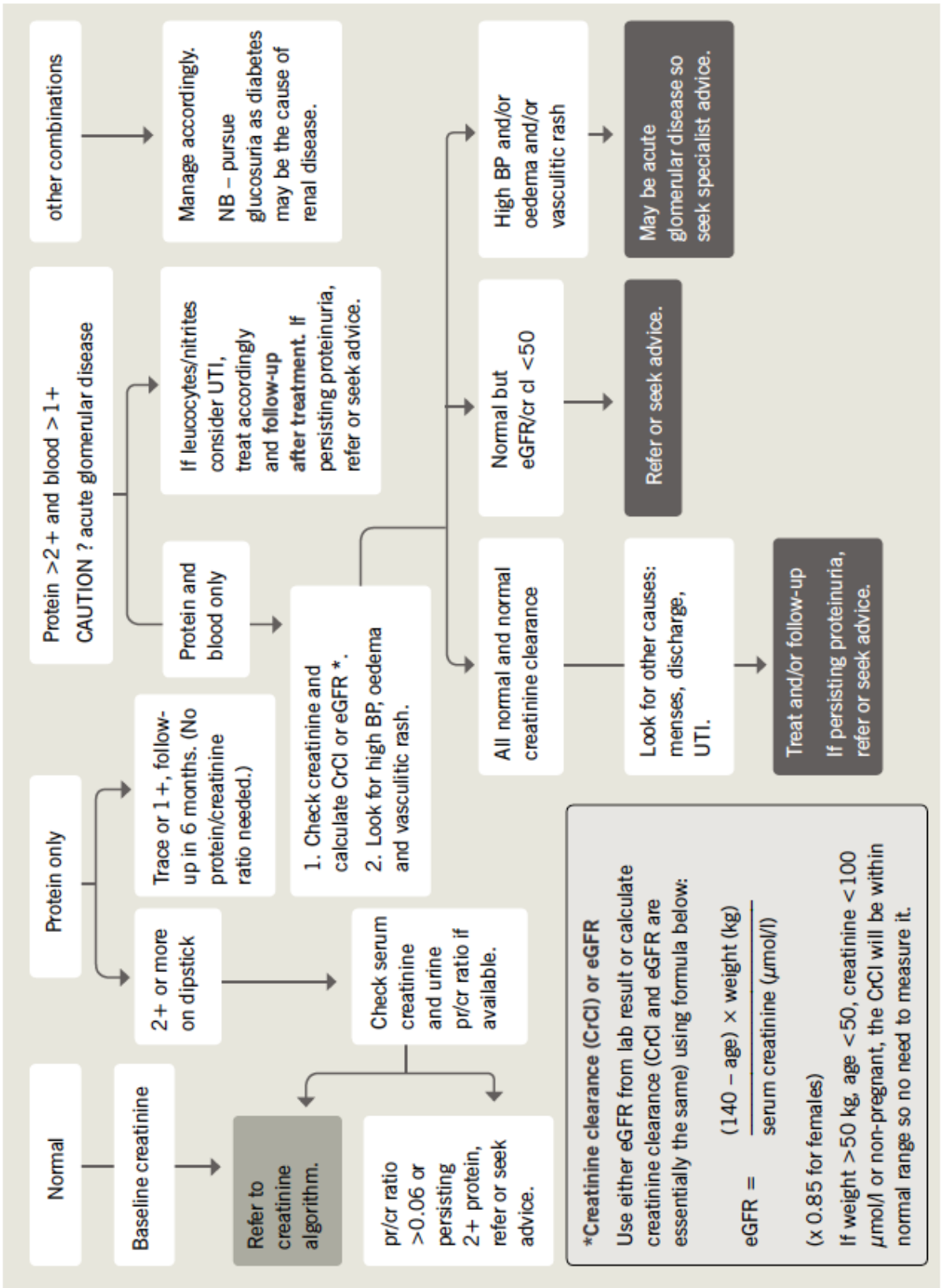


Figure 32: Urine dipstick algorithm



ANNEX 5: DIABETES

Figure 33: Food pyramid for Diabetes Type 2

ANNEX 6: MENTAL HEALTH [78]

Figure 34: Common Presentations of Mental Health conditions

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
➤ 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
➤ 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
➤ Convulsive movement or fits/seizures ➤ During the convulsion: – 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
➤ 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 Children and adolescents	DEV
➤ 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 Children and adolescents	BEH
➤ 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 Older people	DEM
➤ 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
➤ 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
➤ 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

[78] · mhGAP Intervention Guide. World Health Organization 2010

ANNEX 7: PEP REPORTING FORM

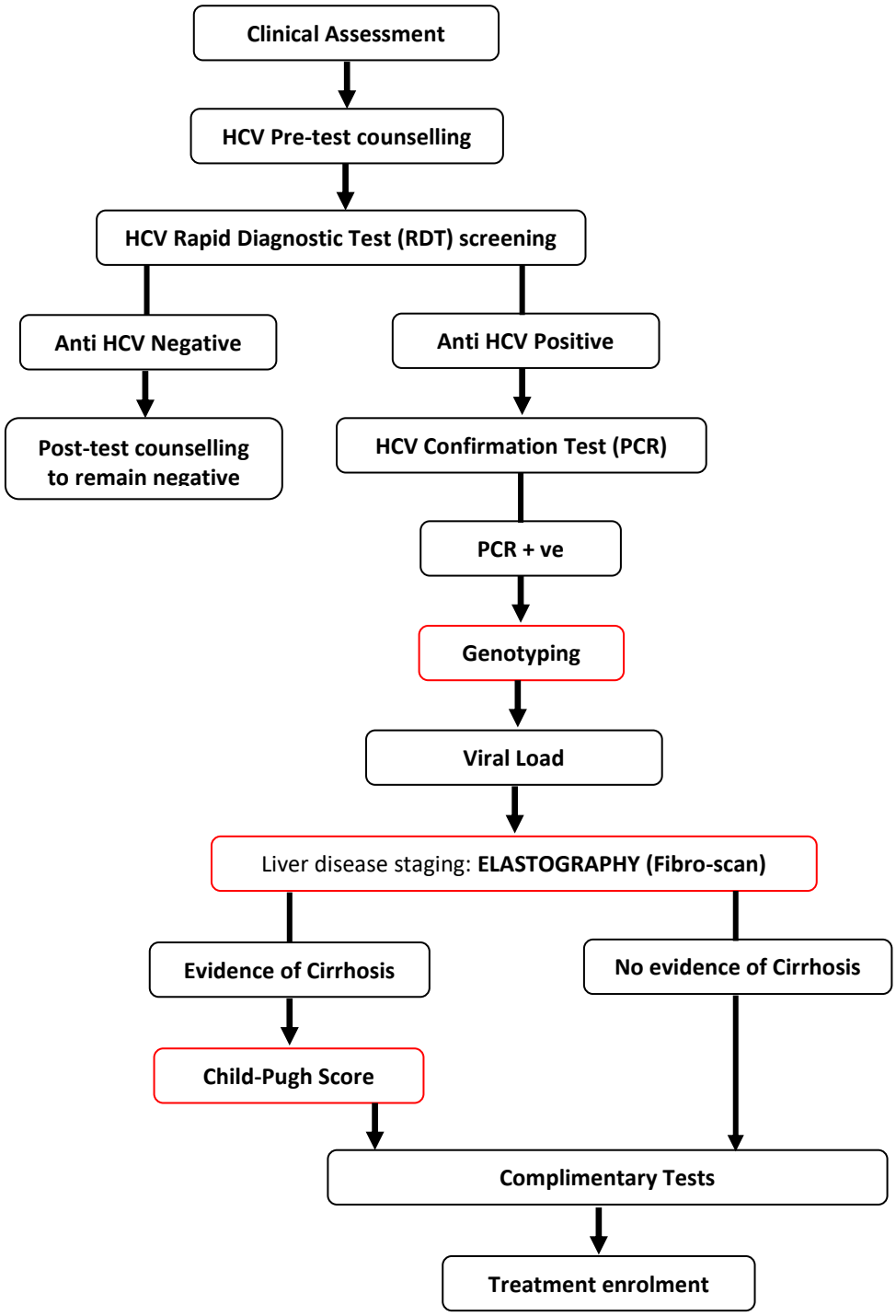
Table 63: NCHADS PEP Clinic visits and reporting form

See PEP guideline, and follow PEP care pathway for steps in PEP management.	
Demographic details Name _____ DOB ___/___/_____ Age	 Phone no:_____ Sex Clinic number Date of first visit ___/___/_____
Category of exposure Occupational ☐ Discordant couple ☐ Victim of sexual assault ☐	**Timing of exposure** Date of exposure ___/___/_____ 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____UK____ If PLHIV are they on ART? Yes____ No_____UK____ 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____UK_____ Date___/___/_____	
Exposed person's HIV status (If HIV positive do not start/or discontinue PEP when known) At time of presentation: Pos___ Neg____UK____ Ever had HIV test? Yes___ No___ Date ___/___/_____ HIV test at baseline: Pos____ Neg___UK_____ Date ___/___/_____ HIV test 3M post exposure: Pos___ _Neg___UK_____ Date ___/___/_____	
1. Nature of exposure: Occupational Health care facility Deep injection of contaminated hollow bore needle: ☐ Other parenteral exposure to blood or body fluids ☐ Mucus membrane exposure: ☐ Describe exposure	
2. Nature of exposure: Discordant couple Receptive vaginal ☐ Receptive anal. ☐ Receptive oral with ejaculation ☐ Insertive vaginal ☐ Insertive anal ☐ Condom used? Yes___ No___ UK____ Condom broke? Yes___ No___ UK____ Exposed male circumcised? Yes___ No___ Evidence of trauma; bleeding or mucosal tear? Yes___ No___ UK____ Describe exposure	
3. Nature of exposure: Victim of sexual assault Receptive vaginal ☐ Receptive anal. ☐ Receptive oral with ejaculation ☐ Condom used? Yes___ No___ UK____ Condom broke? Yes___ No___ UK____	

Evidence of trauma; bleeding or mucosal tear? Yes___ No___ UK____ 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 ☐ 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___ UK____ Recipient? Yes___ No___ UK____ Source HCV+ Yes___ No___ UK____ Recipient? Yes___ No___ UK____ Tetanus vaccination indicated? Yes___ No___ given? ☐
Explained need for secondary prevention ☐
Follow up appointment (stress the importance of this): Date ___/___/_____
Doctor to sign
Follow up consultation (3 – 4 days) Date ___/___/_____ Attend? ☐ 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? ☐ Result_____ (if HIV negative, discontinue PEP) Blood test from exposed checked? ☐ 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? ☐ 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 ☐ (complete results section on front page) STI screen ☐ HBV Ab ☐ HCV Ab ☐ Pregnancy test ☐ Follow up required? Yes___ No___ Describe:
Doctor to sign

ANNEX 8: HCV DIAGNOSTIC ALGORITHM

Figure 35: HCV diagnosis and assessment 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.

ANNEX 9: WHO DRUG INTERACTION TABLE

Table 64: 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 children)
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use alternative antihistamine agent
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	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 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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