

Kingdom of Cambodia  
Nation Religion King



Ministry of Health

**National Guidelines**  
**for the Prevention and Treatment**  
**of Opportunistic Infection among**  
**HIV-Exposed and HIV-Infected**  
**Adults and Adolescents**

1<sup>st</sup> Edition  
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National Center for HIV/AIDS, Dermatology and STD control

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## Preface

The national guidelines for the prevention and treatment of opportunistic infection among HIV-exposed and HIV-infected adults and adolescents is an important part of the National Center for HIV/AIDS, Dermatology and STD (NCHADS) strategy to increase the quality of Adults and Adolescent HIV/AIDS care and treatment in Cambodia. NCHADS Strategic Plan for HIV/AIDS and STI Prevention and Care identifies the continuous development and revision of policies and guidelines as a key strategy for achieving the objective of “improving and maintaining the quality and accessibility of care for PLHIV through integrating of health facility based care services nationwide.”

This document represents comprehensive guidelines for the prevention and treatment of HIV-related illnesses in both HIV-exposed and HIV-infected adults and adolescents greater than 14 years of age in Cambodia.

This adult and adolescent guideline is the result of significant contribution from national and international experts in incorporating with recent development in adults and adolescent HIV/AIDS care, and practical recommendations based on limited diagnostic capabilities across various health care settings in Cambodia.

The Ministry of Health Cambodia has reviewed and approved to official use this National Guidelines at all relevant health care service, and hope that health care providers who provide care and treatment to adults and adolescents with HIV/AIDS will use this guidelines in order to enhance their care and treatment capacity with quality.

Phnom Penh, 27/01/2012  
Minister for Health 



  
**Dr. MAM BUNHENG**  
**MINISTER OF HEALTH**

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The finalization of the guidelines represents a great achievement that incorporates the latest advances in adult HIV/AIDS care in Cambodian context.

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Phnom Penh, 25 January 2012



**Dr. Mean Chhi Vun**

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## Abbreviations

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
AZT	Zidovudine
BMI	Body mass index
CBC	Complete Blood Count
CD4	CD4+ T-lymphocyte
CMV	Cytomegalovirus
CNS	Central Nervous System
CrCl	Creatinine clearance
CSF	Cerebral Spinal Fluid
CTX	Cotrimoxazole
CXR	Chest x-ray
D4T	Stavudine
ddl	Didanosine
DOT	Directly observed therapy
DST	Drug Susceptibility Testing
E	Ethambutol
EBV	Epstein Barr Virus
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
H	Isoniazid
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
INH	Isoniazid
ITP	Immune thrombocytopenia
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
KS	Kaposi's Sarcoma
LDH	Lactate dehydrogenase
LFT	Liver function test
LN	Lymph node
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MAC	<i>Mycobacterium avium</i> complex
MDR-TB	Multi drug resistant tuberculosis
MTB	<i>Mycobacterium tuberculosis</i>
NCHADS	National center for HIV/AIDS dermatology and STIs
NHL	Non-Hodgkin's lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor



NVP	Nevirapine
OHL	Oral hairy leukoplakia
OI	Opportunistic infection
ORS	Oral rehydration solution
PCP	<i>Pneumocystis jiroveci</i> pneumonia
PPE	Pruritic papular eruption
PI	Protease inhibitor
PLHIV	People living with HIV
PMN	Polymorphonuclear leukocyte
PPD	Purified protein derivative
PTB	Pulmonary tuberculosis
R	Rifampicin
RBC	Red blood cell
RIF	Rifampicin
RPR	Rapid plasma reagin
RTV	Ritonavir
SJS	Stevens Johnson syndrome
SMX	Sulfamethoxazole
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TMP	Trimethoprim
TPHA	Treponemal pallidum particle agglutination
TST	Tuberculin skin test
US	Ultrasound
WBC	White blood cell
WHO	World Health Organization
XDR	Extensively drug-resistant
Z	Pyrazinamide

# **National Guidelines for the Prevention and Treatment of Opportunistic Infection among HIV-Exposed and HIV-Infected Adults and Adolescents**

## **Introduction**

Cambodia is one among the successful countries in the Western Pacific Region in successful response to the HIV epidemic by reducing HIV prevalence among people aged 15-49 from 2% in 1998 to 0.8 % in 2010. It is estimated that there are 56,200 people who are living with HIV, of whom 46,200 people are in need for antiretroviral therapy,

The Comprehensive Continuum of Care (CoC) Framework for PLHIV started to implement in Cambodia in 2003. In 2010, Cambodia has achieved the universal access target for HIV treatment, with over 90 percent of adults and children in need receiving antiretroviral therapy (ART), in 51 Adult OI/ART sites for adults and 33 sites for children.

In order to better meet the needs of adults and adolescents greater than 14, herein referred to as “adults” with HIV infection, NCHADS convened a series of meetings of key stakeholders consisting of medical doctors from government, private, NGOs, and academic institutions to develop a comprehensive guidelines on the treatment of opportunistic infections among HIV-exposed and HIV-infected adults and adolescents in Cambodia.

The National Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Adults and Adolescents is the first edition and an important document to ensure the high standard and high quality of treatment and care of HIV-infected patients across referral hospital in Cambodia. The guidelines includes recommendations for the prevention and treatment of common HIV-associated diseases and was developed by the authors based on day-to-day experience caring for adults in Cambodia, supported by the latest information from regional and international guidelines.

In addition, a concerted effort has been made to make these guidelines feasible across health care settings with different levels of resources, in particular different access to diagnostic capability. Based on the results of direct survey to a number of the referral hospitals level II and provincial hospitals to estimate the availability of diagnostic services, the survey was necessary to guide the development of clinical algorithms for the approach to different clinical presentations among PLHIV that providers will encounter.

This national guideline should be used as a simple reference to assist providers in caring for adults and adolescents who are at risk for opportunistic infections.

# 1. HIV Basics, Transmission, and Primary Infection

## Key points:

- HIV is an RNA virus that is converted to DNA and incorporated into the host genome
- HIV cannot be cured and must be managed as a chronic illness
- Transmission mode in Cambodia most commonly occurs through unsafe sexual behavior.

### 1.1 Basics of HIV infection

HIV is an RNA virus that is able to enter 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. When the virus infects CD4 cells, it is converted to DNA by viral reverse transcriptase and inserted into the host genome, at which time the infection becomes incurable. New virus particles are made by the host cells, which are then packaged and released. Because CD4 cells are necessary for the immune system to function, the level of CD4 cells in the blood serves as a marker for the degree of functioning of the immune system. As more cells are infected the immune system becomes weaker and eventually illness occurs.

**Table 1: CD4 count and degree of immunosuppression in adults and adolescents**

Level of Immunosuppression	CD4 cells
No significant immunosuppression	>500 cells/mm <sup>3</sup>
Mild immunosuppression	350-500 cells/mm <sup>3</sup>
Advanced immunosuppression	200-349 cells/mm <sup>3</sup>
Severe immunosuppression	<200 cells/mm <sup>3</sup>

### 1.2 HIV transmission and risk factors

Patients with certain risk factors are more likely to contract HIV; in particular, patients with the following history are more likely to be infected with HIV:

- Present or past STD infection and genital ulcerations
- Present or past use of blood or blood products
- Present or past use of intravenous or subcutaneous (“skin-popping”) drug abuse
- Present or past high risk sexual behavior:
  - Multiple sexual partners
  - Having sex with sex workers
  - Sex partners with known AIDS or HIV infection
  - Sex partners with high-risk behavior (many women with only one regular sex partner are often at high risk)
  - Men who have sex with men
- Other injections, tattooing, scarification, ear piercing or body piercing using non-sterile instruments.

**Table 2: How HIV is transmitted**

Modes of HIV Transmission
HIV can be spread by sexual intercourse via blood, semen or vaginal fluids
HIV can also be transmitted by blood transfusion, reusing needles or from mother to child during pregnancy, labor or breast feeding

HIV can be spread to healthcare workers through penetration of skin by infected needles or prolonged or large quantity exposure of contaminated blood to mucosal surfaces and non-intact skin
Untreated individuals with acute primary HIV are at significant risk for transmitting HIV due to high circulating virus
Someone can be infected with HIV and be well for many years but still transmit HIV
HIV cannot be transmitted by normal social contact, kissing, sharing food or by insects

### **1.3 Clinical manifestations suggestive of primary HIV infection**

There are a number of other conditions that can be seen in HIV-infected and non-HIV infected adults that when associated with possible HIV exposure, can suggest HIV infection. Clinical manifestations include:

- Acute Primary HIV Syndrome which is characterized by a constellation of signs and symptoms of fever, malaise, muscle pain, lymphadenopathy, pharyngitis, and rash in an otherwise previously healthy adult that can easily be confused with influenza or infectious mononucleosis.
- Weight loss > 10% of base line body weight
- Fever (continuous or intermittent) more than one month
- Diarrhea (continuous or intermittent) more than one month
- Generalized lymphadenopathy
- Oral candidiasis (thrush) or recurrent vaginal candidiasis
- Skin conditions
  1. Fungal infections:
    - fungal skin infection
  2. Viral infections:
    - herpes zoster (shingles)
    - genital herpes (recurrent)
    - molluscum contagiosum
    - condyloma (genital warts)
  3. Bacterial infections:
    - folliculitis
  4. Other skin conditions:
    - seborrheic dermatitis
    - papular pruritic eruption (PPE)
    - psoriasis
    - diffuse skin dryness.
- Respiratory manifestations:
  - cough more than two weeks
  - dyspnea
  - tuberculosis
  - recurrent bacteria infections and bouts of pneumonia
  - chronic or recurrent sinusitis
- Neurological manifestations:
  - worsening headache (continuous and unexplained)
  - febrile convulsion
  - declining cognitive function

#### **1.4 Conditions and Infections that warrant immediate testing**

Certain conditions and infections are not common in non-HIV infected adults. These conditions are highly suggestive of HIV infection and warrant immediate HIV testing:

- Recurrent septicemia
- Pneumocystis jiroveci pneumonia (PCP)
- Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Disseminated nontuberculous mycobacteria infection
- Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)
- Central nervous system toxoplasmosis
- Encephalopathy or focal neurological deficit without a clear source
- Cryptococcosis including meningitis
- Disseminated histoplasmosis
- Disseminated penicillium
- Lymphoma (cerebral or B cell non-Hodgkin)
- Kaposi sarcoma
- Cervical dysplasia in an adolescent female
- Invasive cervical carcinoma.

#### **1.5 HIV Testing**

When providers suspect a patient is infected with HIV, they should immediately follow provider initiated testing and counseling (PITC) guidelines and provide information on the importance of HIV testing and refer patients for testing (please see national Policy Strategy and Guidelines for HIV Counseling and Testing, 2007). In addition, clients should receive the information on behavior changes and HIV education while patients accept to do HIV test with confirmatory rapid antibody testing to identify infection or not. For those who have HIV positive results should refer to an appropriate OI/ART care and treatment site and early initiation of ART.

## **2. Prevention of Opportunistic Infections in PLHIV**

### **Key points**

- Primary prophylaxis prevents HIV associated opportunistic infection with PCP and Toxoplasmosis and improves outcomes with any form of TB
- Serious adverse are rare with cotrimoxazole desensitization
- Primary prophylaxis with fluconazole is not recommend for other HIV associated conditions including penicillosis and recurrent candida infections
- Duration of prophylaxis varies depending on disease and immune status of the patient

Prophylaxis of opportunistic infection is an integrated part of a package of comprehensive care for PLHIV. All PLHIV should have access to information and educational materials regarding prophylactic therapy including isoniazid, cotrimoxazole, and fluconazole prophylaxis (please refer to table 3 below).

**Table 3: Summary of OI prophylaxis for PLHIV**

Prophylaxis	Eligibility	Recommended Dosing and Duration
Isoniazid / Pyridoxine (vitamin B6)	All patients with HIV without active TB regardless of CD4 count including pregnant women regardless of trimester*	INH 5 mg/kg to a maximum of 300 mg/day (Patient weighing < 40 kg should be given 200 mg) <b>and</b> Pyridoxine (vitamin B6) 50 mg/day for 6 months
Cotrimoxazole	All PLHIV with CD4 count less than 200 cells/mm <sup>3</sup> OR with Stage 3 or 4 HIV disease regardless of CD4 count including pregnant women regardless of trimester.	1 double strength (DS; TMP-160mg, SMX-800mg) tablet daily or 2 single (SS; TMP-80mg, SMX-400mg) tablets daily. Adults should receive cotrimoxazole prophylaxis until asymptomatic and CD4 counts are above 200 on 2 separate measurements at least >6 months apart .
Fluconazole	All PLHIV with CD4 count of less than 100 cells/mm <sup>3</sup> . Except pregnant women in first trimester.	100 mg orally once per day (200 mg per day if previous cryptococcal infection). Adults should receive fluconazole prophylaxis until CD4 counts are above 100 cells/mm <sup>3</sup> on 2 separate measurements at least >6 months apart.

\* Please refer to SOP on 3I's for eligibility for INH in areas where tuberculosis skin testing is available. If patient's test is positive, should be eligible for 36 months of INH prophylaxis. If patients test is negative, should not be eligible for INH prophylaxis.

### 2.1 Isoniazid prophylaxis

- Isoniazid can be an integrated part of a package of comprehensive care for PLHIV (see policy statement on Standard Operating Procedure (SOP) for Prompt Testing of TB-HIV and Rapid Access to Treatment and Care Services, 2006 and Standard Operating Procedures (SOP) for implementing the 3Is in Continuum of Care Setting, 2009).
- All PLHIV should have access to information and educational materials regarding TB and preventive therapy. IPT can be offered to PLHIV who agree, who do not have active TB at screening, AST/ALT<3 x ULN, and who can be adequately monitored for isoniazid side effects and active TB (Please refer to National Policy on SOP of 3I's and TB).
- Please also refer the annex 8 of the National Policy on SOP of 3I's and TB regarding for eligibility for INH in areas where tuberculosis skin testing (TST) is available. In these areas, if patient's TST is positive, they are eligible for 36 months of INH prophylaxis if there are no contraindications to INH. If patients' TST is negative, there are not eligible for INH prophylaxis.

### Recommended regimen

- Isoniazid at a dose of 5 mg/kg to a maximum of 300 mg/day should be used (200 mg/day if less than 40kg). Pyridoxine (vitamin B6) 50 mg/day should be given at the same time to reduce the risk of peripheral neuropathy.
- The duration of IPT should be 6 months in areas without TST or 36 months for eligible patients based on positive TST results in areas with TST on the condition that there no contraindications to INH and there are adequate systems in place for monitoring and supporting of adherence.

### When to start INH (IPT)?

- PLHIV should be offered IPT as early as possible because active TB can occur at any CD4 count and once present leads to further weakening of the immune system and increased risk of other opportunistic infections. PLHIV with symptoms of TB such as cough or fever should not commence IPT until a cause for these symptoms is found. IPT should not be given to PLHIV with AST/ALT>3 x ULN.

### Screening for active TB

- Adequate systems must be in place to screen for active TB prior to commencement of an IPT program as described in the National SOP for implementing 3Is in Continuum of Care Setting (see Table 4 and Algorithm 1). This must include the capacity to diagnose all forms of TB, including smear negative pulmonary TB and extrapulmonary TB, using history taking, careful physical examination, chest X-rays and sputum examination.

**Table 4: TB screening per 3I's Strategy**

TB Symptom Screening	Responses	Management
In the last 4 weeks: 1) fever, anytime of any duration 2) cough, anytime of any duration 3) Two weeks or more of drenching night sweats	No Symptoms	Start INH prophylaxis*
	1 or more symptoms	TB clinical assessment, AFB smears x 3 (plus culture if available), CXR.

\* Do not start INH until confirm that AST/ALT<3 ULN, no active alcohol consumption, and no previous adverse reaction to INH. Place TST at this visit if available (see Standard Operating Procedures (SOP) for Implementing the 3Is in Continuum of Care Setting, 2010).

During the upcoming years, CENAT will likely make available GeneXpert, a MTB/RIF assay that can be used to examine sputum rapidly in the OI/ART setting and detect 90% of positive AFB smear cases and 80% of negative AFB smear cases for MTB.

### Monitoring

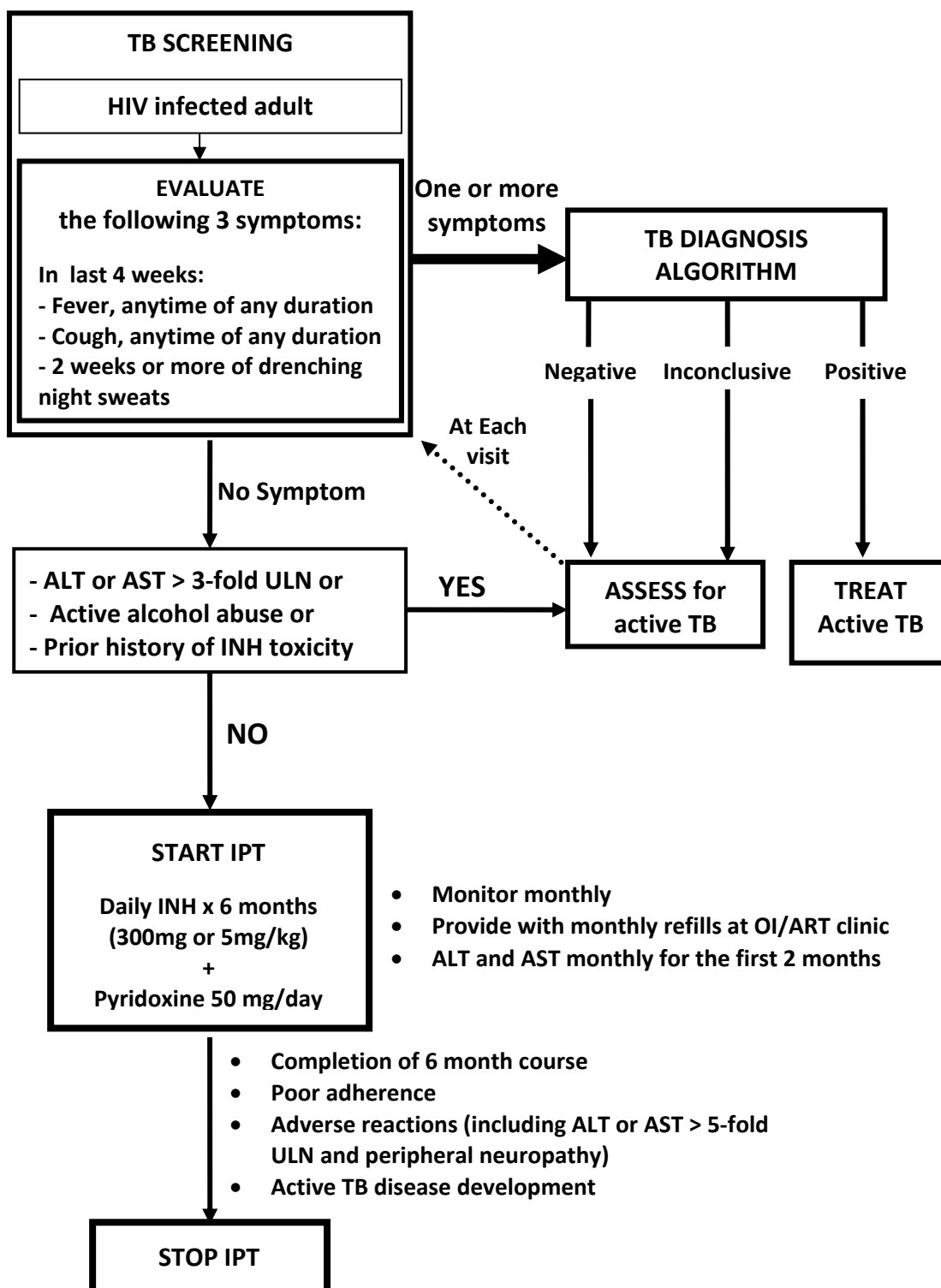
- PLHIV taking IPT should meet with a specifically trained health care worker at least monthly and medication dispensed monthly. The appointment could be taken place at OI/ART site of the referral hospital. Patients should be evaluated for any clinical evidence of isoniazid toxicity and receive information and adherence support.
- The main side effects of isoniazid are gastro-intestinal including nausea and vomiting, hepatitis and peripheral neuropathy. The risk of hepatitis is approximately 0.3% in young healthy adults and increases to 2.6% in the elderly. The risk of neuropathy is largely prevented with the use of pyridoxine. PLHIV taking IPT should be warned of the symptoms of hepatitis: nausea, vomiting, abdominal pain, lethargy, jaundice and dark urine. They should be advised that if any of these symptoms occur to cease isoniazid and consult their health care professional expert.
- 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 Hepatitis B or C, then check LFT's monthly for the first 4 months.

- o If AST or ALT are not  $< 3 \times$  ULN, at 4 months, repeat only if Symptomatic,
  - o If AST or ALT still  $> 3 \times$  ULN, continue monthly LFT monitoring,
  - o If AST or ALT  $> 5 \times$  ULN or if lower elevations are associated with symptoms, then discontinue isoniazid.
- PLHIV taking IPT should also be evaluated for active TB or other opportunistic infections at each visit, for example with screening questions and follow up investigations such as sputum smears if coughing. Measures should be taken to avoid contact between PLHIV taking isoniazid and people with TB in order to prevent TB transmission.



**Algorithm 1: SOP for IPT for Adults**  
(In the areas where there is no TST<sup>1</sup>)



- Adherence should be assessed at each visit and any problems addressed. Resources to support adherence should be utilized, such as home care teams and peer support groups.

## 2.2 Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis should be offered as an integrated part of comprehensive care service for PLHIV. The primary aim of cotrimoxazole prophylaxis is to prevent PCP and toxoplasmosis, with the prevention of major bacterial illness. It 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).

***Although pregnant women living with HIV widely use co-trimoxazole, there is no evidence of an increase in co-trimoxazole-related adverse events among pregnant women versus non-pregnant women regardless of pregnancy trimester.***

### When to start cotrimoxazole?

- Cotrimoxazole should be offered to adult PLHIV who have:
  - CD4 count less than 200 cells/mm<sup>3</sup> OR
  - Advanced symptomatic HIV disease (WHO clinical stage 3 including any form of TB or stage 4) regardless of CD4 count  
*(In the absence of CD4 results, providers may use a total lymphocyte count less than 1200 cells/mm<sup>3</sup>).*

### When to stop?

- Cotrimoxazole prophylaxis should be stopped in:
  - Adults treated with ARV and who are asymptomatic regardless of previous WHO clinical stage and have a CD4 count consistently above 200 cells/mm<sup>3</sup> on 2 measurements at least 6 months apart. If the CD4 count drops below 200 cells/mm<sup>3</sup> then cotrimoxazole prophylaxis should recommence until the CD4 count is again consistently above 200 cells/mm<sup>3</sup> on 2 measurements at least 6 months apart.
  - Patients with CD4 counts >200 cells/mm<sup>3</sup> and completed TB treatment.

### When to continue

- If patient has CD4 <200 cells/mm<sup>3</sup>
- If a patient has a history of PCP above a CD4 count of 200 cells/mm<sup>3</sup>, continue cotrimoxazole secondary prophylaxis indefinitely.

### Drugs and Dosing

Cotrimoxazole (TMP/SMX) should be given as follows:

- Adults: 1 double strength (DS; TMP-160mg, SMX-800mg) tablet daily or 2 single (SS; TMP-80mg, SMX-400mg) tablets daily.
- An alternative for PLHIV unable to tolerate cotrimoxazole for the prevention of PCP is Dapsone 100mg orally once a day.

### Initiation

Adults and adolescents with a history of severe adverse reaction (GRADE 4 – see Annex 1) to cotrimoxazole or other sulfa drugs should not be prescribed cotrimoxazole prophylaxis. Cotrimoxazole prophylaxis should be initiated by clinicians at OI/ART sites of the referral

hospital. All PLHIV commencing cotrimoxazole should be given the opportunity to learn about cotrimoxazole and counseled about possible benefits, side effects and the importance of regular administration.

### Monitoring

Once cotrimoxazole prophylaxis is commenced it is important that its use be monitored within a continuum of care. Ongoing support, explanation, encouragement as well as monitoring for side effects nausea, vomiting or jaundice and provision of medicine should be coordinated between care services. For example, home care teams can play a critical role in the support and monitoring of PLHIV and should receive appropriate training and supervision to facilitate this. Referral mechanisms for PLHIV with side effects or possible 'breakthrough' OI should be developed and clearly understood by all involved. Simple side effects could be managed at health centers and more marked symptoms such a severe rash, hepatitis, or bleeding from thrombocytopenia could be referred to a referral hospital. Follow-up by a health care worker should be at least monthly until stable and can then be reduced to three monthly. Otherwise, there is no need for routine laboratory studies, unless indicated, for cotrimoxazole.

### Side effect management

The main side effects of cotrimoxazole are rash, bone marrow suppression and hepatitis. They are more likely to occur soon after initiation of cotrimoxazole. Minor rashes are common and can usually be managed with careful observation and continuing cotrimoxazole. More severe rashes including Stevens Johnson syndrome and clinical hepatitis are possible and must lead to immediate cessation of cotrimoxazole (see Table 5). Supportive management including hospital admission is sometimes necessary. Reductions in hemoglobin or white cell count can be managed by dose reduction if not severe.

**Table 5: Management of cotrimoxazole-related rash**

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

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

Dapsone.

### **Desensitization to Cotrimoxazole for re-started treatment**

- Desensitization can be attempted two weeks after a non-severe (grade 3 or less) Cotrimoxazole reaction that has resulted in a temporary interruption of Cotrimoxazole.
- Cotrimoxazole desensitization has been shown to be successful in 40-80 % of individuals with previous hypersensitivity and rarely causes serious reactions.
- **Desensitization should not be attempted in individuals with a history of grade 4 reaction to previous Cotrimoxazole or other sulfa drugs.**
- It is recommended to commence an antihistamine regimen of choice one day prior to starting the regimen and to continue daily until completing the dose escalation. On the first day of the regimen, the step 1 dose of Cotrimoxazole is given and subsequently increased one step each day. If a severe reaction occurs, the desensitization regimen is terminated. If a minor reaction occurs, repeat the same step for an additional day. If the reaction subsides, advance to the next step; if the reaction worsens, the desensitization regimen is terminated.

### **SERIOUS REACTIONS DURING DESENSITIZATION ARE RARE**

Below is an outpatient and inpatient protocol for oral Cotrimoxazole desensitization among adults and adolescents:

#### **Outpatient Step Dose\***

DAY 1 80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspension)

DAY 2 160 mg sulfamethoxazole + 32 mg trimethoprim (4 ml of oral suspension)

DAY 3 240 mg sulfamethoxazole + 48 mg trimethoprim (6 ml of oral suspension)

DAY 4 320 mg sulfamethoxazole + 64 mg trimethoprim (8 ml of oral suspension)

DAY 5 One single-strength sulfamethoxazole-trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim)

DAY 6 AND ONWARDS.

#### **Inpatient Step Dose\***

Over 6 hours, give hourly doses (TMP/SMX in mg): 0.004/0.02, 0.04/0.2, 0.4/2.0, 4.0/20, 40/200 and 160/800.

\*Two single-strength sulfamethoxazole (400mg)-trimethoprim (80mg) tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim). Cotrimoxazole oral suspension is 40 mg trimethoprim + 200 mg Sulfamethoxazole per 5 ml.

- If desensitization fails Dapsone should be given (See 'Drugs and Dosing' above).

### **2.3 Fluconazole prophylaxis**

Fluconazole prophylaxis is an important component of comprehensive care service for PLHIV in Cambodia. If resources are sufficient to supply Fluconazoles and staff have received appropriate training. Initiation to treatment should be at an OI/ART site. Health centers and home care teams can assist in follow-up and monitoring.

#### **Primary prophylaxis of cryptococcosis**

- Primary prophylaxis of cryptococcosis including cryptococcal meningitis, should be offered to PLHIV with CD4 count of less than 100 cells/mm<sup>3</sup>. Fluconazole 100mg orally

once per day is recommended. Fluconazole should not be given during first trimester of pregnancy.

- Fluconazole should not be administered if AST/ALT are greater than 3x ULN.
- 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 Hepatitis B or C, then check LFT's monthly for the first 4 months.
  - o If AST or ALT are not  $< 3 \times$  ULN, at 4 months, repeat only if symptomatic,
  - o If AST or ALT still  $> 3 \times$  ULN, continue monthly LFT monitoring,
  - o If AST or ALT  $> 5 \times$  ULN or if lower elevations are associated with symptoms, then discontinue Fluconazole.

### **Secondary prophylaxis of cryptococcosis**

- Secondary prophylaxis of cryptococcosis including cryptococcal meningitis, should be offered to PLHIV following completion of initial treatment.
- Fluconazole 200 mg orally once per day is recommended.
- For pregnant women in first trimester, weekly amphotericin 1 mg/kg/day should be given. If in the event that amphotericin is not available or the patients is unable to return for OI/ART site for IV amphotericin B infusion, providers should seek expert advice on the risk and benefits of using Fluconazole 200 mg daily to prevent cryptococcal meningitis versus the risk of congenital defects in the fetus based on the patient's immune status, clinical history, and duration of pregnancy.

### **Duration of prophylaxis**

- Primary and secondary prophylaxis of cryptococcosis should be continued life-long. If PLHIV are receiving ARV and immune reconstitution results in a CD4 count consistently above 100 cells/mm<sup>3</sup> for at least 6 months then prophylaxis can be ceased.
- If the CD4 count again falls below 100 cells/mm<sup>3</sup> prophylaxis with Fluconazole should be resumed until the CD4 count is again above 100 cells/mm<sup>3</sup> on 2 measurements at least 6 months apart.

### **Fluconazole is not recommended for primary prophylaxis of penicilliosis or secondary prophylaxis of candidiasis.**

- Primary prophylaxis of penicilliosis is not recommended at present as it is not known whether the low incidence in PLHIV in Cambodia to warrant this measure. Secondary prophylaxis with itraconazole 200 mg orally once per day is recommended for PLHIV who have completed treatment for penicilliosis. Duration is the same as that detailed above for cryptococcosis. In the circumstance where Itraconazole is not available, the best drug should be used for treatment prophylaxis is Amphotericin 1mg/kg/week until the CD4 increases to 100 cells/mm<sup>3</sup>.
- In most situations the potential benefits of secondary prophylaxis for the prevention of mucosal candidiasis using a systemic antifungal are outweighed by the risk of antifungal resistance. Instead topical preparations of gentian violet, nystatin, or clotrimazole should be used. In situations where these agents are not effective, particularly with recurrent or persistent esophageal candidiasis, then fluconazole 100 mg orally once per day is recommended. Duration is the same as that detailed above for cryptococcosis.

### 3. Nutrition in HIV infected Adults and Adolescents

#### Key points:

- Untreated HIV infection frequently results in nutritional deficiencies
- Malnutrition can be due to inadequate food intake, malabsorption, or changes in metabolism of foods in PLHIV
- PLHIV have increased metabolic rates because of recurrent bacterial infections, OIs, and HIV infection itself resulting in the need for additional calorie intake
- Malnutrition associated with HIV/AIDS leads to increased rates of opportunistic infection and decreased survival
- ARV therapy and nutritional counseling can break the cycle of malnutrition of HIV.

#### Definition of Malnutrition:

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

#### 3.1 Nutrition Screening

Nutrition screening should occur at OI/ART site or interaction with community based providers. It identifies clients who need further nutritional assessment. Screening is typically brief and easy-to-complete information based on collected information. All patients with >5 % unintentional loss in body weight, moderate or severe malnutrition should be referred to a nutritionist. If a nutritionist is not available, providers will need to refer to National nutritional guidelines (See Policy Statement on National Nutrition Program Strategy, 2006), seek expert advice through the National nutrition program, or refer to additional references such as the 2010 WHO Nutritional Care and Support for People Living with HIV/AIDS-A training course.

The National Nutrition Program currently does not have specific nutrition guidelines for adults with HIV. However, nutrition experts will be able to guide providers in terms of healthy diets, required iron, macronutrient, and micronutrient supplementation, and preventive deworming in PLHIV.

Many assessment tools are available to screen for malnutrition. Most focus on loss of lean body tissue. These are a few of the more commonly used methods of nutrition screening:

a) WHO clinical staging criteria uses change of body weight relative to baseline as follows:

Unintentional weight loss is measured as the percentage of weight lost from the baseline body weight (BBW), using the following formula:

$$\% \text{ of weight lost} = [(BBW - \text{current body weight})/BBW] \times 100$$

b) WHO classification of malnutrition in adults based on body mass index (BMI is calculated by dividing weight in kilograms (kg) by height in meters (m) squared):

**Table 6: WHO classification of malnutrition in adults**

BMI	Classification
< 16.0	Severe malnutrition
≥16.0 and < 17.0	Moderate malnutrition
≥17.0 and < 18.5	Mild malnutrition
≥18.5 and < 25.0	Normal

Source: WHO. 1999. Management of Severe Malnutrition: A Manual for Physicians and Other Senior Health Workers. Geneva: WHO.

c) WHO classification of malnutrition in that can be applied to adolescents:

**Table 7: WHO classification of malnutrition in children and adolescents**

BMI-for-age	Classification
< -3 SD	Severe malnutrition
≥ -3 SD and < -2 SD	Moderate malnutrition
≥ -2 SD and < -1 SD	Mild malnutrition
≥ -1 SD	Normal

Source: WHO. 2007. Growth reference data for 5-19 years. <http://www.who.int/growthref/en/> (accessed August 21, 2009).

### **3.2 Causes of malnutrition**

The nutritional status of PLHIV is primarily affected by reduced food intake, malabsorption of food, and increased energy requirements with HIV and associated opportunistic infections.

Reduced food intake is commonly due to:

- Difficulties with eating or swallowing because of painful sores in the mouth and/or throat
- Altered taste of food, nausea and vomiting
- Poor appetite as a result of tiredness, depression and other psychological factors
- Lack of awareness of the importance of nutrition, especially when recovering from illness
- Side effects of medications, including nausea, vomiting, metallic taste in the mouth, diarrhea and abdominal cramps
- Economic issues: Because HIV often infects those with poorer socio-economic status, limited food supply and loss of household income are common

Malabsorption of food is commonly due to:

- Difficulties related to digestion, including inability to produce saliva and digestive enzymes
- Increased nutrient loss resulting from due to infectious diarrhea and/or HIV enteropathy

Increased energy requirements are due to:

- Increased resting energy expenditures and metabolism to fight opportunistic infections and HIV itself
- Energy requirements are likely to increase by 10% to maintain body weight and physical activity in asymptomatic HIV-infected adults.
- Once HIV infection becomes symptomatic, and subsequently after the development of AIDS, energy requirements increase by approximately 20–30% to maintain adult body weight.
- In cases of sepsis, the metabolic rates in PLHIV can more than double. In many cases, the lack of lean muscles and body fat reserves in ill HIV patient leads to premature death.

**Table 8: Daily Energy Requirements for PLHIV**

The nutritional requirements of people living with HIV are influenced by several factors, including age, physiological changes (pregnant, breastfeeding), physical activity, clinical stages of health, metabolism and viral load count.

	<b>DAILY ENERGY REQUIREMENTS</b>	<b>TRANSLATION INTO FOOD INTAKE</b>
<b>Adults: HIV-negative/healthy</b>	1999 to 2580 kilocalories	<ul style="list-style-type: none"> <li>▪ Education about the importance of nutrition for PLHIV.</li> <li>▪ Eating a variety of foods.</li> <li>▪ Storing and preparing foods safely.</li> </ul>
<b>Adults: HIV-positive (early/asymptomatic stage)</b>	10% more energy (an additional 210 kilocalories)	<ul style="list-style-type: none"> <li>▪ 1 additional fistful of maize meal or 1 cup of porridge taken during the course of the daily.</li> </ul>
<b>Adults: HIV-positive (late/symptomatic stage)</b>	20-30% more energy (an additional 420 to 630 kilocalories)	<ul style="list-style-type: none"> <li>▪ 2 to 3 additional fistfuls of maize meal or 2 to 3 cups of porridge taken during the course of the day.</li> </ul>

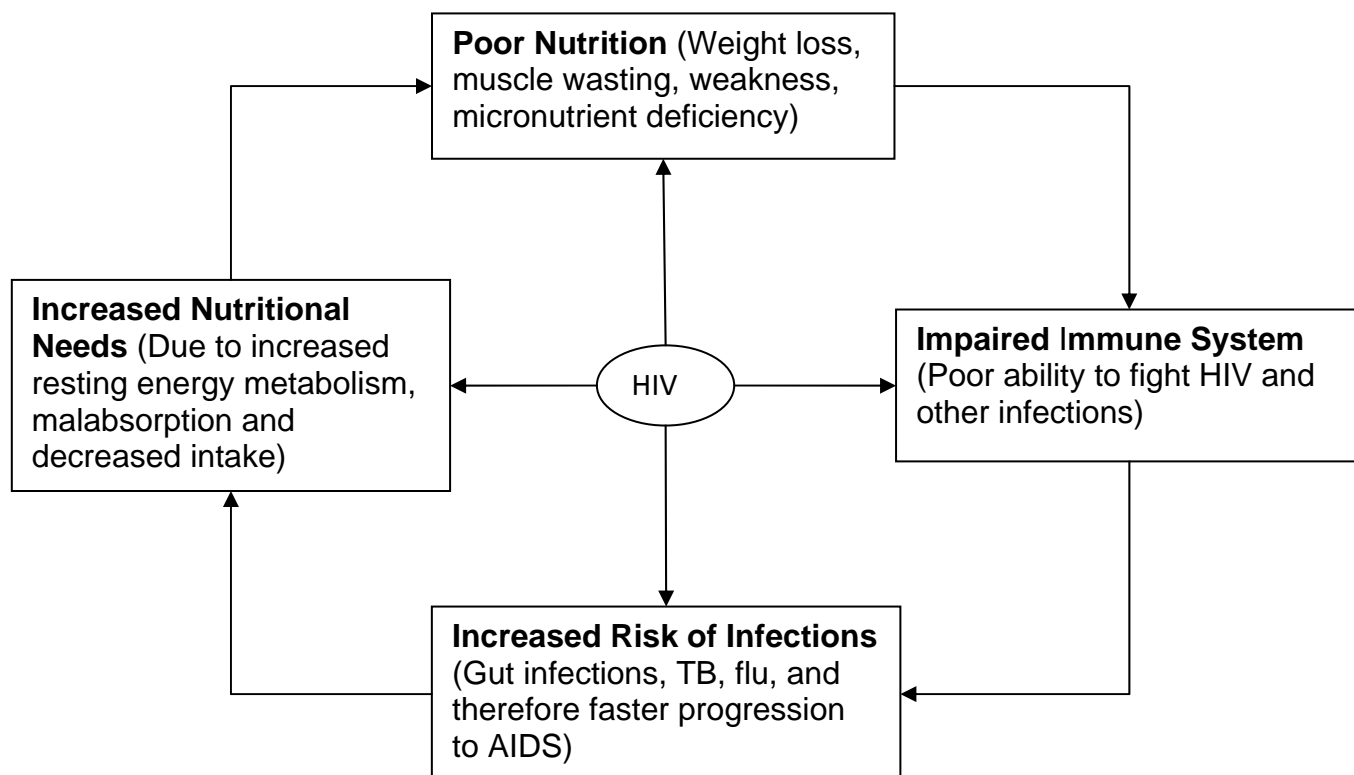
Source: Nutritional Care and Support for People Living with HIV/AIDS- A training course, WHO. 2009

### **3.3 Breaking the Cycle of malnutrition in PLHIV**

The combination of inadequate nutrition, increased resting expenditures, and opportunistic infections can keep a patient in the cycle of malnutrition in PLHIV. Outside of immune reconstitution with chronic ARV therapy, nutritional counseling is currently the only tool to reverse malnutrition in PLHIV.



**Figure 1: Cycle of malnutrition and infection in HIV**



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

### **3.4 Nutritional Assessment and Counseling**

The objective of nutrition assessment is to understand a client's nutritional status to develop a nutrition care plan, which includes nutrition goals, food and nutrition services and medical treatment. Nutrition assessment involves collecting information about a client's socioeconomic characteristics, medical history, dietary patterns, anthropometric measurements, clinical and biochemical characteristics, and current treatment including medications. Nutrition counseling refers to an interactive and open minded process between service provider and patient to interpret information generated during assessment; understand client preferences, constraints and options; and plan a feasible course of actions that supports healthy dietary practices and referral for services.

PLHIV who know dietary recommendations related to HIV and can consume a healthy diet are better able to manage symptoms, maximize the benefit of medications, enhance their quality of life, and maintain or improve their nutritional status. Patients who do not know about dietary recommendations – especially if they are pregnant or lactating or at critical points in disease progression and treatment initiation – may be at greater risk of suffering from the effects of malnutrition and HIV-related symptoms. Ideally, every PLHIV should receive individualized nutrition assessment and counseling. However, it is not always possible for facilities to provide nutrition assessment and counseling for all clients because of limited staffing.

All providers can begin with basic nutritional counseling including practical advice on healthy meal planning, food safety, taking food with ARVs, and managing symptoms.

### **Healthy meal planning**

A healthy meal includes a balance of macronutrients (fats, proteins, and carbohydrates) and micro-nutrients (vitamins and minerals). Eating healthy means eating a variety of food in the right quantity, combination and frequency to provide the body with the required macro and micro-nutrients on a daily basis. The recommended caloric intake for a PLHIV should be as close to 2500 kcal per day to accommodate for increase energy expenditures (see Table 8).

No single food contains all of the necessary macro and micro-nutrients. Healthy meal planning is a strategy to use a combination of different foods to nourish the body (see Table 9). PLHIV should begin by planning their meal around a primary starch. In Cambodian people, this is usually 2-3 servings of rice. Fats such as butter and oils (coconut, palm, or corn) should be added in moderation as an energy source and to maintain weight. Additional 2-3 portions of green vegetables, fruits, dairy products, and meats with iodized salt are then needed ensure that micro-nutrient are met. To absorb all the necessary nutrition, PLHIV should drink a liter of clean water daily during each meal.

**Table 9 : Healthy meal planning**

<b>FOOD GROUP</b>	<b>EXAMPLES</b>	<b>1 PORTION</b>	<b>PORTIONS FOR DAILY MEALS</b>
STAPLES & STARCHY FOODS	Bread	1 slice	<b>6 PORTIONS</b> - <i>Example:</i> <u>Breakfast:</u> 1 cup of porridge <u>Snack:</u> 1 slice of bread <u>Lunch:</u> 1 cup of rice during lunch <u>Snack:</u> 1 slice of bread <u>Supper:</u> 1 cup of maize meal
	Rice/ Pasta	½ cup (measured after cooked)	
	Maize-meal	1 cup (or about 1 fistful)	
	Potatoes	1 medium size potato	
MEAT, FISH, POULTRY & MILK	Chicken, beef, lamb, fish	Equivalent size to one chicken thigh	<b>3 PORTIONS + 1 PORTION OF MILK</b> <i>Example:</i> <u>Lunch:</u> 1 thigh of chicken <u>Snack:</u> 2 tablespoons of peanut butter <u>Supper:</u> 1 cup of cooked beans <u>Snack:</u> 1 glass of milk for snacks
	Eggs	1 egg	
	Milk (fresh/fermented)	1 cup	
PULSES & LEGUMES/NUTS & OIL SEEDS	Cooked beans	1 cup	
	Nuts	1 cup	
	Peanut butter	2 tablespoons	
FRUITS	Fruits	1 medium size piece of fruit	<b>3 PORTIONS</b> - <i>Example:</i> <u>Breakfast:</u> 1 glass of orange juice <u>Lunch:</u> 1 piece of fruit <u>Snack:</u> 1 piece of fruit
	Fruit juices	1 glass	
VEGETABLES	Raw chopped vegetables	1 cup	<b>5 PORTIONS</b> - <i>Example:</i> <u>Breakfast:</u> ½ cup of green beans <u>Lunch:</u> 1 cup of mixed vegetables <u>Snack:</u> 1 cup vegetable salad <u>Supper:</u> 1 cup of green leafy vegetables
	Cooked vegetables	½ cup	
FATS & OILS		1 teaspoon	<b>5 PORTIONS (INCLUDING NATURAL FATS FOUND IN MEAT)</b> <i>Example:</i> 1 teaspoon of oil for every meal
WATER		1 glass	<b>8 PORTIONS:</b> 8 glasses of safe water and fluids spread out throughout the day.

Source: Nutritional Care and Support for People Living with HIV/AIDS- A training course, 2009

### Food Safety

a. Simple steps on food handling and safety:

- Cook food thoroughly.
- Eat cooked food immediately.
- Store food carefully.
- Re-heat cooked food thoroughly.
- Avoid contact between raw and cooked food.
- Wash your hands thoroughly before and after cooking
- Keep kitchen surfaces clean
- Protect food from rodents, insects and animals
- Use clean or boiled water

b. Recommendations on which food items to avoid:

- Raw eggs
- Food that has not been thoroughly cooked, especially meat and chicken
- Unboiled water or juices made with unboiled water.

### Interactions between ARVs and Foods

Nutritional education also includes advising patient on the interaction between nutrition and ART, including food–drug interactions. It is important to realize that paying greater attention to diet and nutrition may enhance the effectiveness of ART and adherence to ART. In particular, food can affect the absorption, metabolism, distribution and excretion of medication.

- High-fat meals increase the bioavailability of TDF
- High-fat meals increase absorption of EFV
- Food reduces the absorption of some formulations of ddi.

The side-effects of medication may adversely affect the consumption and absorption of food, e.g. AZT causes nausea, anorexia and vomiting; ddi causes vomiting, diarrhea and dryness of the mouth. The combination of certain medications and alcohol can produce side-effects, e.g. taking ddi together with alcohol may result in pancreatitis. Some PIs including RTV causes changes in fat metabolism including elevated cholesterol and triglyceride levels. In these cases, patients should take AZT with low-fat meals, ddi on an empty stomach and avoid alcohol, and eat a healthy diet rich in fruits and vegetables when on a PI associated with changes in fat metabolism.

### Managing Symptoms

Unfortunately, even with management of food-ARV interactions and side effects, PLHIV may develop other symptoms related to HIV or opportunistic infections that limit calorie intake. Table 10 may help you address some of the symptoms that could result in decreased caloric intake in PLHIV.

**Table 10: Symptom targeted management in malnutrition**

Symptoms	Management
Loss of appetite	<ul style="list-style-type: none"> <li>• Eat small, frequent meals (5–6 meals/day)</li> <li>• Eat nutritious snacks</li> <li>• Drink plenty of liquids</li> <li>• Take walks before meals—the fresh air helps to stimulate appetite</li> <li>• Have family or friends assist with the preparation of food</li> <li>• Take light exercise and do light activity</li> <li>• Add flavour to drinks and food</li> </ul>
Mouth ulcer	<ul style="list-style-type: none"> <li>• Avoid citrus fruits, and acidic and spicy foods</li> <li>• Eat food at room temperature</li> <li>• Eat soft and moist food</li> <li>• Avoid caffeine and alcohol</li> </ul>
Dry mouth and Sore Throat	<ul style="list-style-type: none"> <li>• Rinse with slightly salty warm water: use clean boiled water.</li> <li>• Clean mouth frequently, at least twice a day morning and evening, preferably after every meal.</li> <li>• Use cinnamon tea as a mouthwash (1/4 teaspoon of cinnamon to one cup of boiling water; cover and allow to cool).</li> </ul>

Candidiasis	<ul style="list-style-type: none"> <li>• Eat soft, cool and bland foods</li> <li>• Add garlic (optional)</li> <li>• Avoid very hot or cold foods, sugar (glucose, cane sugar), yeast, caffeine, spicy food, carbonated drinks and alcohol</li> </ul>
Nausea and vomiting	<ul style="list-style-type: none"> <li>• Eat small, frequent meals</li> <li>• Avoid being on an empty stomach as this makes the nausea worse</li> <li>• Eat bland food</li> <li>• Avoid food with strong or unpleasant odors</li> <li>• Drink plenty of liquids</li> <li>• Rest and relax after meals</li> <li>• Avoid lying down immediately after eating</li> <li>• Avoid coffee and alcohol</li> </ul>
Diarrhea	<ul style="list-style-type: none"> <li>• Continue to eat and drink which you can tolerate when experiencing diarrhea.</li> <li>• Drink lots of fluids: more than 8 cups a day especially clean boiled water, to prevent dehydration</li> <li>• Eat ripe yellow bananas, cooked apples or mango; avoid unripe fruits.</li> <li>• Peel and cook vegetables rather than eating them raw.</li> <li>• Make rice soup by boiling one cup of rice in 5–6 cups of clean water with a bit of salt for one hour.</li> <li>• Eat both the rice and the rice water</li> <li>• Take all milk products, except yogurt, out of diet for a day, and then put it back in gradually to about two cups in the day.</li> </ul>
Constipation	<ul style="list-style-type: none"> <li>• Eat fiber-rich and sprouted food</li> <li>• Take light exercise and do light activity</li> <li>• Drink plenty of water</li> <li>• Take warm drinks</li> </ul>

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

### **Food Security**

Because HIV often infects those with poorer socio-economic status, limited food supply and loss of household income are common. All efforts should be made to connect these individuals to food support services through the CoC framework. Current home based care (HBC) programs offer some food security program in the form of monthly rice donations. HBC and community programs also provided a limited supply of vitamins. The National Nutrition Program offers nutritional support for pregnant woman.

### **3.5 Clinical Restaging of PLHIV with Malnutrition**

There may be cases when PLHIV are not on ARVs and suffer from malnutrition. Patients should always be asked about other symptoms including chronic diarrhea or fever and restaged based on WHO criteria, as they may be newly eligible for ART. Currently, under WHO guidelines a unintentional body weight loss of <10% is considered a stage II condition. The loss of body weight of more than >10% is considered a stage III condition. HIV wasting syndrome is a stage IV condition and defined as:

*The involuntary weight loss of 10% of baseline body weight plus either chronic diarrhea (two loose stools per day for more than 30 days) or chronic weakness and documented fever (for 30 days or more, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that would explain the findings.*

### 3.6 Malnutrition in 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).

According to the Institute of Medicine at the United States National Academy of Sciences (IOM), 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 (see Table 11). The National Nutrition Program offers special nutrition services for pregnant women including provision of iron and micronutrient supplements.

**Table 11: Recommended weight gain in pregnant mothers**

Pre-pregnancy category BMI	Recommended total gain	Recommended weekly weight gain, second and third trimesters	Recommended monthly weight gain, second and third trimesters
< 18.5	12.7 – 19.5 kg	0.5 kg	2.0 kg
18.5 – 24.9	11.3 – 17.1 kg	0.5 kg	2.0 kg
25.0 – 29.9	6.8 – 12.2 kg	0.3 kg	1.2 kg
≥ 30.0	5.0 – 9.8 kg	0.2 kg	0.8 kg

Source: IOM. May 2009. Resource Sheet: *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: IOM.

## 4. Initial Assessment of Opportunistic Infections

### Key points:

- WHO clinical restaging based on clinical events can meet criteria for initiation of ART
- The risk of different opportunistic infections at different level of immunosuppression varies with immunological status
- IRIS presents similarly to the underlying OI and should be considered in patients who have recently started ART

### 4.1 Clinical events and restaging

WHO clinical staging should be performed at every visit. **Stages can be increased but not decreased unless prior staging was incorrect.** Clinical events such as weight loss or new opportunistic infections can raise the clinical stage of PLHIV and mandate initiation of ART prior to the return of CD4 results and also prompt the initiation of OI prophylaxis.

All PLHIV who present with new clinical events should be restaged based on World Health Organization system of clinical staging (see Annex 1). If restaging results in higher clinical stage than previously recorded, the higher stage should be recorded as the patients Clinical Stage in terms of determining ART eligibility (See the *National Guidelines for use of Antiretroviral Therapy in Adults and Adolescents, 2011*).

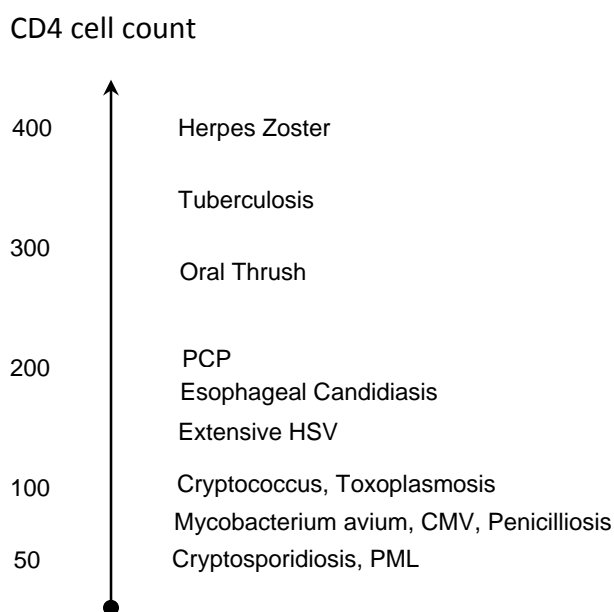
Prior to initiation of ART, restaging can only result in a higher clinical stage. The highest clinical stage recorded should be maintained until after the patient starts ART. For example, a patient not yet on ART and diagnosed with esophageal candidiasis would be assessed as clinical stage

4. Although the esophagitis may resolve after 2 weeks with antifungal treatment, the patient would continue to be assessed as clinical stage 4 until after starting ART.

#### **4.2 Risk of OIs at different levels of immunosuppression**

The risk of OIs varies at different levels of immunosuppression, with the exception of TB. Patients will present with clinical syndromes with a number of potential diagnoses. Assessing the patient's level of immunosuppression may help narrow this list of potential diagnoses.

**Figure 2: Risk of HIV-related illness by CD4 count**



#### **4.3 IRIS associated with recent ART**

IRIS commonly presents 2-8 weeks after starting ART but can occur any time in the first 6 months of ART, and in rare cases, later. The risk of IRIS is higher for those patients started on ART at lower CD4 counts and higher viral loads.

The symptoms and signs of IRIS overlap with those of the underlying opportunistic infection. When ART is given it strengthens the immune reaction to infections, leading to an appearance or increase in various clinical manifestations. This can result in:

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

These manifestations are not a result of an infection alone or the immune system alone, but are due to an interaction between the two. TB is the most common cause of immune reconstitution syndrome. 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.

IRIS also occurs in MAC, PCP, toxoplasmosis, HBV and HCV, cytomegalovirus, varicella-zoster virus, cryptococcal infection, histoplasmosis, and PML. Patients will present with worsening symptoms similar to those of the underlying OI.

The usual approach to management of IRIS is to:

- Patients should **continue** ART, except in cases of severe cryptococcal meningitis
- Aggressively investigate for new OI or active OI that is failing treatment or treat all newly discovered OIs. This usually requires checking blood cultures, new chest x-ray, and lumbar puncture if CNS symptoms are present. Any new or worsening lymph node lesions or skin lesions are important clues and should be biopsied if results of blood and CSF do not reveal the diagnosis. Patients with worsening TB symptoms should have repeat sputum cultures and sensitivity testing to evaluate for multi-drug resistant (MDR) or extensively drug resistant (XDR) TB or MAC.
- Start/continue treatment for the symptomatic opportunistic infection when discovered
- Non-steroidal anti-inflammatory agents can be used to reduce symptoms related to inflammation, e.g. lymphadenitis and fever.
- If necessary, a short course of corticosteroids are occasionally required if symptoms become severe (e.g. dyspnea, CNS symptoms, renal obstruction).

## 5. Candida Infections

**Key points:**

- Candida infections are common in HIV patients
- ART should be started in patients with recurrent oral candidiasis (stage III) or esophageal candidiasis (stage IV)
- Secondary prophylaxis is not commonly recommended.

### Candidiasis

The most common manifestations of candidiasis in HIV patients are oral candidiasis, cervicovaginal candidiasis and esophageal candidiasis. In immunosuppressed patients, candida can disseminate throughout the body (candidemia).

The majority of infection is caused by *Candida albicans*. The occurrence of oral or esophageal candidiasis is recognized as an indicator of immune suppression. Most patients present with CD4 counts less than 200 cells/mm<sup>3</sup> and respond to treatment with anti-fungal medications. Resistance to azoles, including fluconazole, is still rare in Cambodia.

Providers should **not** use fluconazole and itraconazole in the first trimester of pregnancy due to its teratogenic effects. If necessary, use amphotericin-B as a substitute or consult an medical expert.

### 5.1 Oral candidiasis

#### Clinical presentation

Multiple painless creamy-white, easily removable patches or pseudomembraneous plaques on the tongue, gums, buccal mucosa, and palate, anterior surface of tonsils, posterior wall of throat. Lesions often show bleeding when removed. In rare cases, patients may also have angular chelosis.

#### Diagnosis



Clinical Fungal microscopy and culture should only be performed if clinical manifestations are atypical or treatment is ineffective. Microscopy from mouth scraping demonstrates pseudohyphae and/or blastopores.

#### **Standard treatment**

Local application of gentian violet, 1 % aqueous solution twice daily for 7 day, or Nystatin pessary, 100 000 IU, oral use 3 times daily for 7 days, or Clotrimazole oral troches 10 mg. pastille 4-5 times a day for 10-14 days Miconazole gumpatch 1/day for 7 days.

#### **Alternative treatment**

1. Nystatin oral solution 500,000 units oral drip 5 times daily (if available);
2. Fluconazole 100mg once daily for seven days ;
3. Ketoconazole 200 mg once daily for 7 days (avoid in patients on Rifampicin. Drugs interact to lower active blood levels of each drug)
4. Amphotericin-B 0.3-0.5 mg.kg./day intravenous drip for 7-14 days (refractory cases).

### **5.2 Esophageal candidiasis**

#### **Clinical presentation**

Esophageal candidiasis can be asymptomatic but typically presents with dysphagia, and/or painful swallowing with retrosternal pain. Esophageal candidiasis can present with or without signs of oropharyngeal candidiasis.

#### **Diagnosis**

Clinical as endoscopy is not available in most settings. Endoscopy reveals whitish plaques and exudate similar to those observed with oral candidiasis with occasional superficial ulceration of esophageal mucosa.

#### **Standard treatment**

1. Fluconazole 200 mg, once daily for 14 days.
2. Ketoconazole 200mg, 2 tablets daily for 14 days after meals (avoid in patients on Rifampicin. Drugs interact to lower active blood levels of each drug).
3. Itraconazole 200 mg, once daily for 14 days.

### **5.3 Cervicovaginal candidiasis**

#### **Clinical presentation**

Patients may complain of itching or burning sensation as well as white vaginal discharge. Recurrence is common.

#### **Diagnosis**

Clinical. White adherent vaginal discharge creamy white vaginal discharge with cheese-like plaques Vulvo- vaginal area is erythematous, swollen and painful. If clinical features are atypical or treatment is ineffective perform microscopy with potassium hydroxide.

#### **Standard treatment**

1. Nystatin 100,000 units vaginal suppository for daily for 14 days
2. Clotrimazole vaginal cream 5 g/day or clotrimazole vaginal suppository tablet 100 mg once daily for 3-7 days or until no longer have symptoms, or Clotrimazole 500 mg suppository x 1
3. Miconazole cream 5 g/day or 100 mg as vaginal suppository for 7 days.

#### **Alternative treatment**

1. Fluconazole 150-200 mg take once time (higher dose and more prolonged duration of treatment in case of severe immunodeficiency), or
2. Itraconazole 200 mg orally twice times in the first day. Follow by once daily over the next 3 days ; or
3. Ketoconazole 200 mg orally once daily for 7 days.

#### **5.4 Disseminated Candida (Candidemia)**

Candidemia is very rare in patients in PLHIV in Cambodia. It is usually seen in HIV patients with associated neutropenia from non-Hodkin's Lymphoma or HIV itself. Candidemia an immediate life threatening infection. Patients should be immediately hospitalized for monitoring and treatment:

##### **Clinical presentation**

Asymptomatic, fever, or sepsis

##### **Diagnosis**

Clinical with likely source or blood culture

##### **Standard treatment**

Transfer to higher level of care for unstable patients to receive Amphotericin therapy. Otherwise, treat with Amphotericin-B 0.7 mg/kg/day intravenous drip for 14-21 days. If patient continues to be stable throughout first 7 days of antibiotic course, may consider switch to fluconazole 400 mg orally for 14 days.

##### **Alternative treatment:**

Fluconazole 400 mg daily for 21 days if asymptomatic

#### **5.5. Secondary prophylaxis**

Secondary prophylaxis is generally not recommended unless patient has repeated candida infections.

- Oral and Esophageal Candidiasis: Fluconazole 100 mg daily
- Cervicovaginal Candidiasis: Miconazole cream 5g/day

### **6. Tuberculosis**

#### **Key points:**

- PLHIV who are also infected with TB have a 30-50% lifetime risk of active TB
- TB should be considered in all PLHIV with respiratory symptoms
- PLHIV are more likely to have prolonged fever, minimal cough, AFB negative smears, and atypical CXR findings.

In Cambodia, 64% of population is infected with TB (approximately 8 million), with an estimated 65,000 active cases in 2009. TB is the leading cause of death due to an opportunistic infection in HIV infected persons. PLHIVs are more likely to have active TB, treatment failure, relapse, and high rate of mortality. A person infected with TB may have a lifetime reactivation risk of 5-10%, while that of a PLHIV is 30-50%, or 5-8% every year (see Table 12). Even with ART, PLHIV have a 5 times greater risk of mortality during TB therapy compared to non-HIV patients. In a CENAT report, HIV patients enrolling at CENAT's afternoon clinic have a 37%

mortality rate within the first two months of TB treatment. Most of these patients had low CD4 counts (<200 cells/mm<sup>3</sup>) and were not on ART.

**Table 12: Lifetime risk of active TB with and without HIV**

HIV status	Lifetime risk of developing TB
Negative	5-8%
Positive	30-50%

Therefore, all TB patients should have a screening test for HIV regardless of whether they have risk factors to HIV infection or not. Sputum microscopy is absolutely necessary and culture and sensitivity testing, when available, should be done. If extrapulmonary disease is suspected, samples of lymph nodes or fluids such as CSF should be taken for AFB staining and culture and sensitivity, when available.

In the upcoming year, CENAT will likely make GeneXpert, a rapid MTB/RIF assay to evaluate sputum for MTB at OI/ART sites. The tests sensitivity for AFB positive smear TB is 90% and for AFB negative smear is 80%. This test is a ground breaking tool that detects TB and rifampicin drug resistance within 2 hours.

## 6.1 Pulmonary Tuberculosis

### Clinical presentation

Fever and weight loss are more prominent in HIV-positive patients, whereas productive cough and haemoptysis are more common in HIV-negative patients. Pulmonary TB (PTB) should be suspected in any PLHIV presenting with any of the following symptoms over the past four weeks:

- fever, any time of any duration
- cough, any time of any duration
- two weeks of more of drenching night sweats

### Diagnosis

PLHIV who are suspected to have TB must be screened for pulmonary with sputum AFB testing and chest x-ray (CXR) as per National Guidelines on Management of TB in TB/HIV coinfection (2009) and SOP for 3Is.

The CXR presentation of PTB depends on the degree of immunosuppression. At a relatively good level of immunity (CD4 >500 cells/mm<sup>3</sup>), it usually presents as classical TB, with typical cavitory TB or upper lobe consolidation (post primary pattern).

At CD4 counts below 200 cells/mm<sup>3</sup>, atypical radiographic presentations are more likely. These include normal-appearing chest radiographs, diffuse bilateral or lower lobar infiltrates, mediastinal lymphadenopathy, pleural effusion, interstitial nodules, or other patterns resembling primary TB.

At CD4 counts between 200 and 500 cells/mm<sup>3</sup>, radiographic presentations can have both classic and atypical patterns (see Table 13).

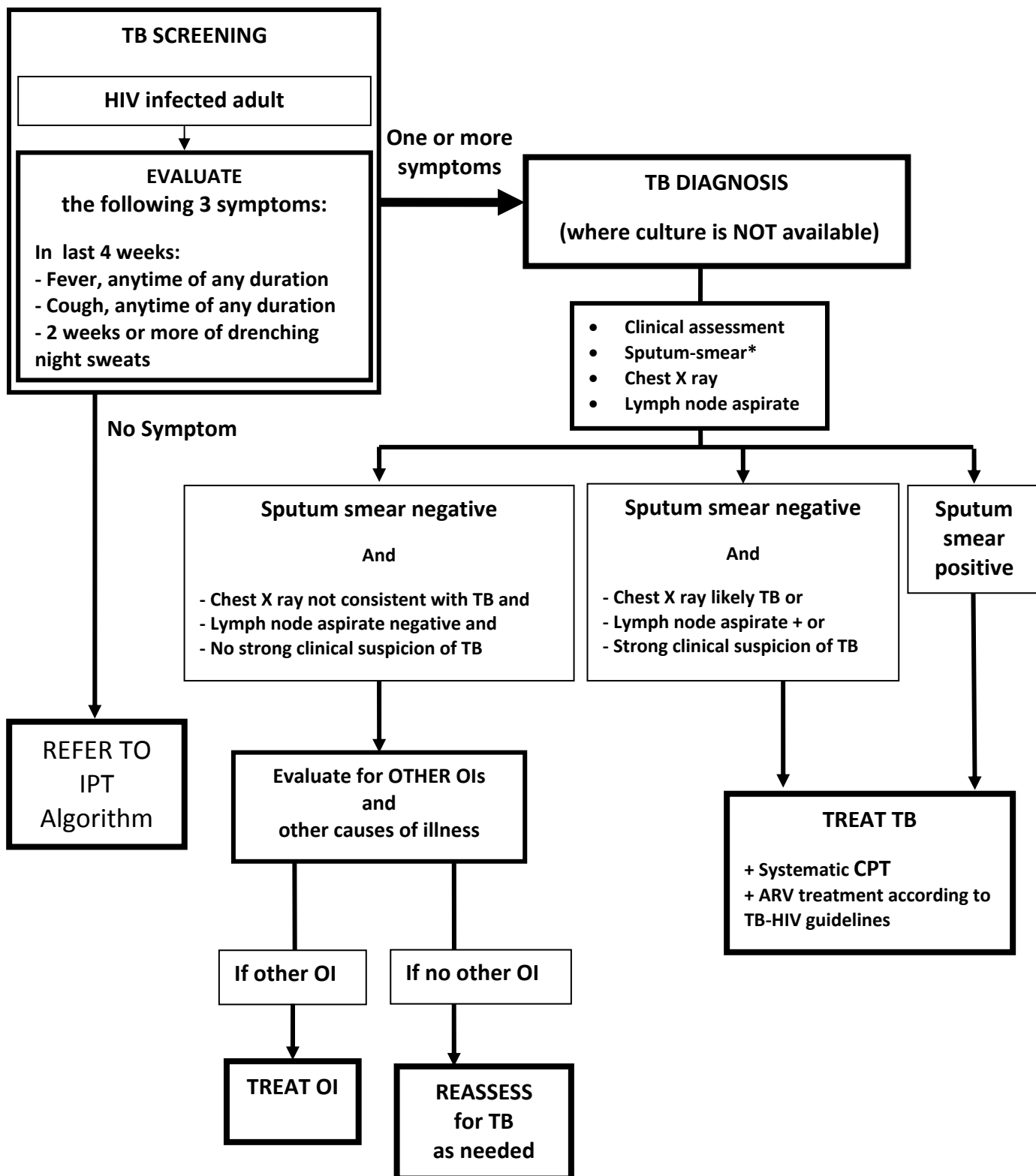
**Table 13: Characteristics of PTB in advanced vs. early HIV infection**

Clinical Characteristics	Late HIV infection CD4 < 200 cells/mm <sup>3</sup>	Early HIV infection CD4 > 200 cells/mm <sup>3</sup>
Clinical presentation	Often resembles primary TB	Often resembles post-primary TB
CXR		
1. Intrathoracic lymphadenopathy	Common	Rare
2. Lower lobe involvement	Common	Rare
3. Cavitation	Rare	Common
4. Sputum smear positive	Less common	Common
Adverse drug reaction	Common	Rare
Relapse after treatment	Common	Rare

In the event that initial two AFB smears are negative, guidelines allow for treatment of TB if clinical suspicion is high or a trial of antibiotics for another infection with repeat clinical evaluation, CXR and/or AFBs after completion of the antibiotic course (see algorithm 2). Currently, mycobacterial culture can only be done at CENAT (routinely), National Institute of Public Health (NIPH), Pasteur Institute in Phnom Penh, and laboratory in Battambang and Kampong Cham provinces. MTB culture is useful in smear negative cases (pulmonary and extrapulmonary), especially in TB meningitis, for which definitive diagnosis is often difficult. It should be done for drug susceptibility testing in suspected cases of drug resistance. Culture results usually take 6-8 weeks and should be used to initiate and guide treatment when available. Algorithm 2 is currently used for the diagnosis of pulmonary TB and HIV without TB available TB cultures.

NCHASDS and CENAT will publish additional algorithms for the use of the GeneXpertMTB/RIF assay once the test is made available in Cambodia.

**Algorithm 2: TB screening and diagnosis among adult's with any cough, fever, drenching nights sweats or weight loss in past 4 weeks**



In cases of smear negative TB, initial treatment will rely on clinical suspicion and CXR findings. Table 14 provides a differential diagnosis for pulmonary TB which may increase a provider's confidence in starting treatment.

**Table 14: Differential diagnosis for pulmonary TB**

Diagnosis	Factors supporting diagnosis
Other common infections 1. Bacterial pneumonia 2. Lung abscess  3. PCP (pneumocystis jiroveci pneumonia)	1. Usually more acute, febrile, response to antibiotic 2. Cough with large amounts of purulent sputum, fetid breaths, consolidation with cavitation with fluid level on CXR in lower lobes 3. Usually subacute, dry, non-productive cough with prominent dyspnoea.
Bronchiectasis	<ul style="list-style-type: none"> <li>Large amount of purulent sputum</li> </ul>
Bronchial carcinoma (lung cancer)	<ul style="list-style-type: none"> <li>Risk factors (smoking, older age)</li> </ul>
Congestive heart failure	<ul style="list-style-type: none"> <li>Symptoms of heart failure (left ventricular failure): dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, oedema, epigastric discomfort from hepatic congestion</li> <li>Signs of heart failure</li> </ul>
Reactive airway disease (asthma)	Chronic, intermittent symptoms; expiratory wheezes; known triggers
Chronic obstructive airways disease (COPD)	Risk factor (smoking); chronic symptoms

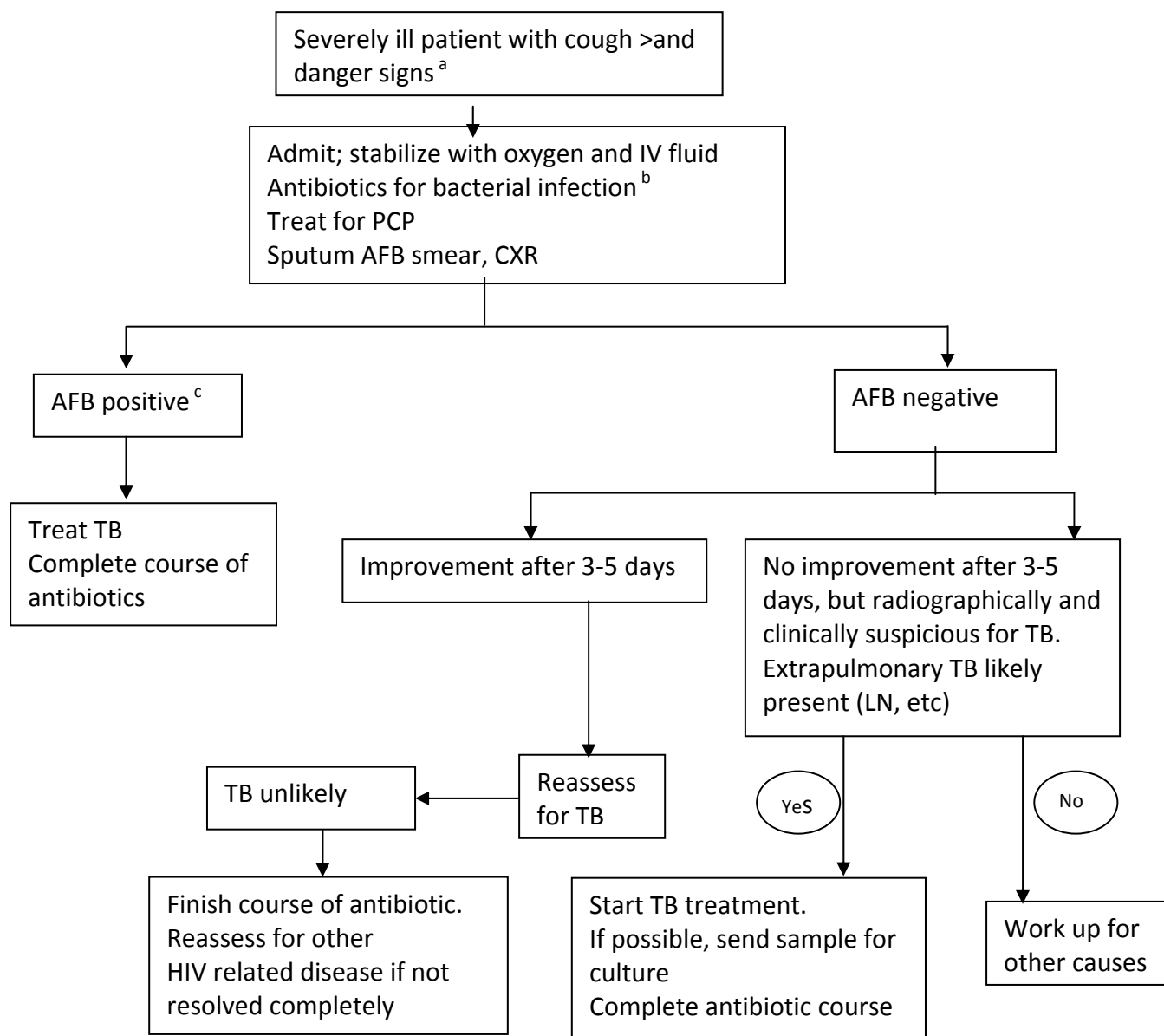
### Standard treatment

The highest priority is to treat smear-positive pulmonary tuberculosis. However, there may be cases when TB diagnosis is made on purely clinical basis and treatment is started in TB/HIV coinfecting cases. **Please refer to National Clinical Guidelines for the Management of TB/HIV Co-infection (2009), National TB Guidelines, and National SOP for Three I's strategy when initiating treatment for TB and infectious case control.** Most adults without a prior history of TB receive Category 1 treatment (2RHZE/4RH).

**All patients with Pulmonary TB not on ARVs are eligible for ART regardless of CD4 count. ARV therapy should start two weeks after initiating TB treatment. Providers should refer to National Guidelines on the Treatment of HIV/TB coinfection (2009) and National Guidelines for use of Antiretroviral Therapy in Adults (2011) to address potential TB-ARV drug interactions and management of potential IRIS.**

In cases with severely ill patients, it may be necessary to start treatment earlier. Algorithm 3 is an acceptable approach to managing severely ill PLHIV with suspected pulmonary TB.

### Algorithm 3: Diagnosis of tuberculosis in severely ill patient cough



- The danger signs include any **one** of: respiratory rate > 30/minute, fever >39 ° C, pulse rate > 120/minute and unable to walk unaided
- Amoxillin, Amoxilin + Clavulanic acid, or Cefuroxime plus Cotrimoxazole at PCP treatment dosing. Use of fluoroquinolones is discouraged to prevent TB resistance
- AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.

### 6.2 Extra Pulmonary Tuberculosis

Extrapulmonary tuberculosis (EPTB) is more common in PLHIV, regardless of CD4 counts. Roughly 50% of TB cases are extra pulmonary in PLHIV with CD4<200 cells/mm<sup>3</sup> whereas only 20% of cases in PLHIV with CD4>200 cells/mm<sup>3</sup>.

## Clinical presentation

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

- CNS abscess or meningitis
- Gibbus deformity (Pott's disease)
- Serositis (pleural, percardial, and/or peritoneal)
- Abdominal mass or ascites
- Hepatitis or enteritis
- Urinary obstruction or enlargement of kidneys
- Joint or bone swelling or deformity
- Cutaneous lesions.

## Diagnosis of extrapulmonary TB disease

Obtaining a smear or culture-proven diagnosis of extrapulmonary TB is difficult. Acid-fast stains of samples such as pleural fluid, CSF, and joint fluid are usually negative. A definitive diagnosis of EPTB disease requires AFB staining and whenever available isolation of *M. tuberculosis* in culture from lymph node fine-needle aspiration (FNA) or other site. Table 15 summarizes the presentation and initial management and treatment of EPTB, and may help provides consider other causes if EPTB is less likely.

## Standard Treatment

The treatment of most forms of EPTB, except TB meningitis is the same category 1 treatment for pulmonary TB (2RHZE/4RH). TB meningitis requires and slightly different regimen with streptomycin (2RHSE/6RH). Please refer to National Tuberculosis guidelines.

All patients with TB meningitis or pericarditis should receive high dose steroids to reduce inflammation. The recommended dose for TB meningitis is 60 mg 2 x daily (1–2 mg/kg) daily for 1–4 weeks, then decrease over 4–6 weeks. The recommended dose for TB pericarditis is 60 mg (1–2 mg/kg) daily for 1–4 weeks, 30 mg (0.5–1 mg/kg) daily for 5–8 weeks, then decrease over 4–6 weeks – (Source WHO TB/HIV Manual 2004, MSF Guidelines to Clinical HIV Guidelines, 2006).

Moreover, an essential part of treatment is to initiate ART in those patients who are newly eligible based on their EPTB diagnosis (STAGE IV), excluding isolated lymph node TB, two weeks after of initiating TB therapy. For those patients on ART, the diagnosis of EPTB warrants the investigation of ARV treatment failure.

For those patients who will receive ART while on therapy for EPTB, providers should reference to National Guidelines for use of Antiretroviral Therapy in Adults and Adolescents (2011) and National Guidelines for the TB/HIV Co-infection (2009) to address potential TB-ARV drug interactions and management of potential IRIS.



**Table 15: Clinical features and diagnosis of common extra-pulmonary tuberculosis**

Extrapulmonary manifestation of TB	Tuberculosis meningitis	Lymph Node (LN) TB	Miliary TB	Bone and joint TB Spinal TB	Tuberculosis serous effusions
Symptoms	<ul style="list-style-type: none"> <li>• Constitutional features</li> <li>• Gradual onset and progression of headache</li> <li>• Decreased consciousness</li> <li>• Neck stiffness possible</li> <li>• Cranial nerve palsy</li> </ul>	<ul style="list-style-type: none"> <li>• Constitutional features</li> <li>• Firm, discrete nodes</li> <li>• Fluctuant nodes matted together</li> <li>• Skin break down, abscesses, chronic draining fistula</li> </ul>	<ul style="list-style-type: none"> <li>• Constitutional features</li> <li>• Hepato-spleno-megaly</li> <li>• diffuse lymphadenopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Constitutional features</li> <li>• Local features such as pain, swelling, rubor, stiffness</li> <li>• Back pain, gibbus, Psoas abscess, radicular pain, spinal cord compression</li> </ul>	<ul style="list-style-type: none"> <li>• Constitutional features</li> <li>• Local features according to site                             <ul style="list-style-type: none"> <li>- Pulmonary</li> <li>- Abdominal</li> <li>- Pericardial</li> </ul> </li> </ul>
Diagnosis	<ul style="list-style-type: none"> <li>• Lumbar puncture, hazardous if patient has raised intracranial pressure</li> <li>• Rather start empiric treatment and perform lumbar puncture upon improvement.</li> </ul>	<ul style="list-style-type: none"> <li>• Needle aspirate of LN</li> <li>• Ultrasound (intra-abdominal lymph nodes)</li> </ul>	<ul style="list-style-type: none"> <li>• CXR</li> <li>• Fundoscopic examination</li> </ul>	<ul style="list-style-type: none"> <li>• Plain X-ray</li> <li>• Tissue biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Physical examination</li> <li>• CXR</li> <li>• Ultrasound</li> <li>• Aspirate of effusion</li> </ul>
Results	<ul style="list-style-type: none"> <li>• CSF opening pressure is high</li> <li>• CSF with mild elevation in white blood cell count, predominantly lymphocytes</li> </ul>	<ul style="list-style-type: none"> <li>• Caseation</li> <li>• AFB may be seen</li> </ul>	<ul style="list-style-type: none"> <li>• Diffuse, uniformly distributed, small miliary</li> </ul>	<ul style="list-style-type: none"> <li>• AFB may be seen</li> <li>• Granulomatous reaction seen on histology</li> </ul>	<ul style="list-style-type: none"> <li>• CXR- pleural effusion, or large globular heart shadow seen</li> </ul>

	<ul style="list-style-type: none"> <li>• Protein level is high</li> <li>• Glucose is low</li> <li>• AFB smear rarely positive.</li> </ul>		<p>shadows</p> <ul style="list-style-type: none"> <li>• (Choroidal tubercles on fundoscopic examination)</li> <li>• CBC may show pancytopenia</li> <li>• Liver function tests may be abnormal</li> <li>• AFB smear on sputum, CSF or bone marrow may be positive</li> </ul>		<ul style="list-style-type: none"> <li>• Ultrasound: ascites and intra-abdominal LN</li> <li>• Pleural biopsy: AFB and/or granulomas seen</li> </ul> <p>Aspirate:</p> <ul style="list-style-type: none"> <li>• Usually AFB negative</li> <li>• TB culture usually takes 4-8 weeks</li> <li>• White cell content is variable</li> <li>• Exudate: Protein content &gt; 30 g/l (Simply leave the aspirate standing: if it clots, it is an exudate).</li> </ul>
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CSF=Cerebrospinal Fluid, AFB=Acid Fast Bacilli, CBC=Complete Blood (Cell) Count, CXR=Chest X-Ray, LN=Lymph

## 7. Pneumocystis pneumonia (PCP)

### Key points:

- PCP is common in Cambodia and is a WHO Stage IV condition
- Clinical presentation is sub-acute with dyspnea on exertion
- Pneumothorax should raise suspicion of PCP
- Coinfection with other pulmonary infection occurs in 10-18% of patients.

*Pneumocystis pneumonia (PCP) is caused by Pneumocystis jiroveci.* It is ubiquitous organism classified as a fungus but that shares biologic characteristics with protozoa. Initial infection with *P.jiroveci* occurs through airborne transmission in early childhood. PCP in PLHIV is a result either of reactivation of latent infection or new exposure. Approximately 90% of cases occur in adults with CD4 counts <200 cells/mm<sup>3</sup>. Risk of PCP is increased in persons with prior episodes of PCP, oral thrush, recurrent bacterial pneumonias, unintentional weight loss, and higher viral loads. PCP occurs frequently in Cambodia an AIDS defining event (WHO stage 4 conditions). Patients should start ART if not already on treatment. Patients with PCP on ART should be evaluated for treatment failure.

### Clinical presentation

PCP is characterized by a sub-acute onset of symptoms gradually getting worse in a period of days to weeks. Patients complain of dyspnea, fever, chest discomfort, and non-productive cough that are gradually getting worse. The duration of illness until diagnosis is typically 1 to 2 weeks, although considerable variation exists. Dyspnea and tachycardia on exertion is always present. Oral thrush is a common coinfection.

Physical findings include tachypnea, tachycardia, and cyanosis. Auscultation of the chest is generally unremarkable. Some dry crackles can sometimes be found. Hypoxemia is an indication for steroids. Arterial blood gas measurements are not often available in Cambodia. However, providers can use the following indicators to initiate steroids in the setting of PCP:

- Decrease in O<sub>2</sub> saturation during physical effort, or
- Cyanosis, or
- Respiratory distress

### Diagnosis

In general the diagnosis of PCP is based on the history and physical exam, combined with a suggestive chest X-ray and hypoxia. The classic findings on chest X-ray consist of bilateral interstitial shadowing, extending from the hilar area (ground glass appearance without air-bronchogram, butterfly pattern). Sometimes there are nodules, blebs, or cysts, but the X-ray can be (at first presentation) normal (25%). Cavitations, intrathoracic adenopathy, and pleural effusion are uncommon in isolated PCP infection but pulmonary coinfection occurs in approximately 10-18% of patients.

Pneumothorax in a PLHIV should raise the suspicion of PCP. More than 80% of cases of pneumothorax in HIV-infected patients are due to PCP. Therefore all patients with pneumothorax should be given empirical PCP treatment.

If the diagnosis is in question, patients should be referred to a higher level of care. Some national hospitals can measure LDH. A normal LDH makes PCP unlikely. A strongly elevated LDH (>2 times the normal value) suggests that PCP is likely. A few hospitals in Cambodia

also have the ability to silver stain induced sputum for *P. Jiroveci* oocysts. PCP can be identified in about 60% of induced sputum sputum smears. In the future, some national hospitals will also offer bronchoalveolar lavage, which can identify PCP in more than 90% of cases.

It is difficult in differential diagnosis between PCP and PTB, and many patients may end up with treatment for both. In Table 16 may be helpful in distinguishing between these two frequent pathologies.

**Table 16: Difference between PCP and PTB**

	PCP	PTB
Symptoms	Subacute onset (1-3 weeks) Dry cough Dyspnea with exertion	Slower onset (>2-4 weeks) Minimal or productive cough with purulent sputum Pleuritic chest pain Drenching nights sweats
Signs	Normal Fine inspiratory crackles	Signs of consolidation Signs of pleural effusion
Chest X-ray	Bilateral diffuse interstitial shadowing Pneumothorax No air bronchograms Normal	Lobar consolidation Cavitation Pleural effusion Intrathoracic lymphadenopathy

*Adapted from Clinical HIV/AIDS Care Guidelines in Resource Poor Settings, MSF, 2006*

#### Standard treatment

- Cotrimoxazole 2 DS tab 3-4 x daily for 21days is the standard dose for adults >60kg.
- Table 17 offers weight adjusted dosing based on a recommended dose of Trimethoprim (TMP) of 15-20 mg/kg/day divided 3 to 4 times daily.
- Each single strength (SS) cotrimoxazole contains 400mg, and 80mg of Trimethoprim, and double strength (DS) cotrimoxazole contains 80 and 160 mg of TMP, respectively.
- All treatment courses should last 21 days.

**Table 17: Weight based cotrimoxazole dosing for treatment of PCP**

Weight	Minimum TMP daily treatment dose	Recommended dose in tablets
30-40 kg	450 – 600 mg daily	1 DS (2SS) tablets 4 x daily
40-50 kg	600 – 750 mg daily	3 SS tablets 4 x daily or 2 DS (4SS) tablets 3 x daily
50-60 kg	750 – 900 mg daily	2 DS (4 SS) tablets 3 x daily
>60 kg	900 mg daily	2 DS (4 SS) tablets 3 - 4 x daily

Source: MSF Guidelines 2006, The Sanford Guide to HIV/AIDS Therapy 2008

In cases of hypoxemia with signs of respiratory distress or cyanosis initiate a course prednisone:

- dose - 40mg twice daily for 5 days, 40 mg daily for 5 days, the 20 mg daily for 11 days
- In Cambodia, always provide treatment for Anguillulosis (*Strongyloides*) before or during treat with Corticosteroids. For PLHIV, use Albendazole 400mg/day for 5 days

to prevent cancer due to Anguillulosis. (Source: The Sanford Guide to HIV/AIDS Therapy 2008).

### **Alternative treatment**

- Trimethoprim 15 mg/kg/day + dapsone 100 mg/day orally for 21 days, or
- Clindamycin 300-600mg 4 x daily with primaquine 15 mg daily for 21 days  
(Source: MSF Guidelines 2006, The Sanford Guide to HIV/AIDS Therapy 2008)

## **8. CRYPTOCOCCAL MENINGITIS**

### **Key points**

- Cryptococcus is most common life-threatening infection in PLHIV
- Less than 50% of infected patients have signs of meningitis
- Lumbar puncture to release elevated intracranial pressure (ICP) is a life-saving and essential part of treatment
- Cryptococcal Meningitis is a WHO Stage 4 condition
- Affected patients require higher dose fluconazole prophylaxis, after treatment.

*Cryptococcus neoformans* is the most common life-threatening fungal infection in patients with AIDS. Disseminated cryptococcus is most often in HIV-positive patients with CD4 <50 cells/mm<sup>3</sup> and it is the leading cause of meningitis in patients with AIDS in Cambodia.

The management of high intracranial pressure (ICP) is considered one of the most important factors influencing early mortality in cryptococcal meningitis. High ICP is present in more than 50% of patients with cryptococcal meningitis and is associated low host immune response. ICP increases because resorption of CSF is blocked by the fungus. Mortality of cryptococcal meningitis with elevated ICP is high and upwards of 25% in Cambodia.

Cryptococcal meningitis is a STAGE 4 condition of WHO. If not on ART, patients should be initiated after induction with amphotericin B. If patients are on ART, the possibility of IRIS and ARV treatment failure should be assessed. IRIS is typically caused by improved recognition of antigens from treated yeast during a prior infection.

### **Clinical presentation**

Ninety percent of those infected with *Cryptococcus neoformans* will present with meningeal involvement. However, less than 50% have meningeal signs. The onset is insidious, fever and headache being often the only symptoms. Neck stiffness can be absent. Cognitive decline and behavioural changes and confusion are also seen. In rare cases, patients may present with disseminated cryptococcal skin lesions.

### **Diagnosis**

A lumbar puncture is essential for diagnosis of cryptococcal meningitis. Increased ICP > 200 mm is hallmark of condition but many patients present with only slight increases. CSF studies show increased WBC count with predominant lymphocytes but cell counts are normal in 25% of cases. Cysts will also stain positive on India Ink. Culture is definitive but difficult to obtain.

In the future, Cambodia may have access to inexpensive cryptococcal antigen testing that clearly identifies infection. This test has a sensitivity of 92%, and is highly specific. Active

cryptococcal infection can be present in some patients with a positive serum CRAg (sCRAg) but negative fungal cultures, which encourages clinicians to treat HIV patients with a positive sCRAg even in the absence of significant symptoms. Quantification with CRAg is not helpful in evaluating patients with previous treatment.

### Standard treatment

- **Amphotericin B** 0.7 mg/kg daily for 2 weeks followed by Fluconazole 400 mg daily for 8 weeks (Source: The Sanford Guide to HIV/AIDS Therapy 2008).
  - **An example flow sheet and protocol for the initial treatment of cryptococcal meningitis can be found in Annex 2.**
  - If patient has contraindication to fluconazole, 1<sup>st</sup> trimester of pregnancy or hepatitis, an expert should be consulted to discuss the risk of benefits of fluconazole therapy versus intermittent use Amphotericin B infusions.
- **Lumbar Puncture**
  - With any sign of increased ICP including headache, nausea, or vision loss, providers should perform an emergent lumbar puncture with an 18 gauge needle to release ICP pressure.
  - In addition, serial lumbar punctures to maintain ICP<200 mm or half of the initial measured opening pressure are life saving and needed on a daily basis. Up to 30-35 ml of CSF fluid can be removed with each tap.
  - Once ICP normalized, patients should have repeat pressures checked weekly during the first 2-3 weeks of treatment.
  - **If your facility does not perform lumbar puncture or CSF studies, the patient should be transferred to a higher level of care.**

Treatment of IRIS related cryptococcal infection is identical to the one mentioned above. In cases of high ICP it is important to do frequent LPs with evacuation of 30 cc of CSF. ART should not be stopped. If the diagnosis of IRIS is unclear, restart standard antifungal therapy.

Steroids have not proven useful in reducing ICP in patients with cryptococcal meningitis and should not be used, except in cases of severe IRIS related CNS cryptococcal with focal neurological deficits.

### Alternative treatment

- In patients with less severe disease or waiting for referral to the referral hospitals (provincial hospital or referral hospital), provide an oral fluconazole treatment alone (400 mg once daily during 10 weeks, after an initial loading dose of 800 mg during 3 days) may be sufficient.
- This should be only be used:
  - in patients with less severe headache and normal CSF studies (patients who only have a positive serum CrAg).

### Secondary prophylaxis

- After treatment for at least 8 weeks, fluconazole 200 mg daily should be continued until CD<sup>+</sup>>100 cells/mm<sup>3</sup> on 2 separate measurements at least for 6 months (Source: The Sanford Guide to HIV/AIDS Therapy 2008).
- If patient has contraindication to fluconazole, 1<sup>st</sup> trimester of pregnancy or hepatitis, use Amphotericin B 1 mg/kg IV infusion per week.

## 9. PENICILLOSIS AND HISTOPLASMOSIS

### Key points:

- Anti-fungal therapy is life saving for disseminated penicilliosis and histoplasmosis
- Incidence of these disease is not known in Cambodia due to diagnostic capabilities
- Consider in patients with clinical picture similar to TB
- Penicilliosis and histoplasmosis are Stage 4 clinical events
- Secondary prophylaxis with itraconazole is required until immune restoration.

### 9.1 Penicilliosis

Penicilliosis is an invasive fungal disease cause by the organism *Penicillium marneffe* that is endemic in Southeast Asia, including Cambodia. The majority of cases in adults below CD4 counts below 100 cells/mm<sup>3</sup>. The exact route of infection in humans is not known. The organism proliferates in macrophages and is disseminated throughout the body, especially in the reticulo-endothelial system. Unfortunately, mortality from disseminated P.marneffe infection in patients with AIDS is about 20%, despite effective anti-fungal therapy.

Penicilliosis can be the initial presentation of HIV and is should be considered a WHO's STAGE 4 diagnosis. Patients on ART should be evaluated for treatment failure. IRIS is uncommon with penicilliosis.

### Clinical Presentation

- In the majority of patients with AIDS, penicilliosis presents as a disseminated infection with signs and symptoms of abrupt fever, anemia, weight loss, skin lesions but also possible lymphadenopathy and hepatosplenomegaly. Respiratory complaints (cough, shortness of breath) are also common.
- The 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.
- Patients with hepatic penicilliosis present with fever abdominal pain, and hepatomegaly.
- Involvement of other organs such as the brain, bone marrow, lymph node, lung, liver and intestine has also been reported but are rare.

### Diagnosis

- If there are no skin lesions, the diagnosis is difficult.
- CBC will often show pancytopenia.
- High levels alkaline phosphatase are indicative of hepatic penicilliosis but available lab testing is limited.
- Fungal identification from blood culture, microscopy of skin lesions with Wright's stain, lymph node, or bone marrow aspirate is definitive.

### Standard treatment

- Initial treatment should be with amphotericin B 0.7 mg/kg daily IV for 2 weeks, followed by itraconazole 200 mg twice daily for 10 weeks (Source: The Sanford Guide to HIV/AIDS Therapy 2008).
- Fluconazole is minimally active against *Penicillium*; failure rates of 64% have been reported.

- Without access to itraconazole, providers should first try to use 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.

### **Alternative Treatment**

For less severe cases, itraconazole 200 mg three times daily for 3 days then 200 mg twice daily for 12 weeks (Source: The Sanford Guide to HIV/AIDS Therapy 2008).

### **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<sup>3</sup> on two measurements at least 6 months apart (Source: The Sanford Guide to HIV/AIDS Therapy 2008).
- Otherwise, if itraconazole is not available, providers should administer Amphotericin B 1 mg/kg IV infusion per week until CD4 count consistently above 100 cells/mm<sup>3</sup>.

## **9.2 Histoplasmosis**

*Histoplasma capsulatum* is a dimorphic fungus that likes soil enriched by dropping of certain birds and bats. 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. The fungus typically affects adults with CD4 counts in adults below 150 cells/mm<sup>3</sup> and presents as a disseminated infection in 95% of the cases.

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

Disseminated histoplasmosis is a WHO stage 4 or AIDS-defining event. Patients on ART should be evaluated for treatment failure. IRIS is uncommon with histoplasmosis.

### **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.
- Disseminated histoplasmosis is characterized by prolonged fever, weight loss, hepatosplenomegaly, lymphadenopathy, large oral ulcerations, or discrete erythematous fungating skin papules or masses (Please refer to Annex 3).

### **Diagnosis**

- If there is no convincing exposure history, the diagnosis is difficult. CBC will often show pancytopenia.
- High levels LDH (>500) are highly suggestive of disseminated histoplasmosis but available lab testing is limited.
- Chest x-ray in the acute pulmonary form shows a pneumonitis, hilar lymphadenopathy or miliary pattern. 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 formation is typical. Isolation of the fungus using culture is diagnostic but rarely available.

- 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.

#### **Treatment**

- Amphotericin B 0.7 mg/kg/day IV for 2 weeks, then itraconazole 200 mg twice daily for 12 weeks.
- If itraconazole is unavailable, use fluconazole 400 mg twice daily for the remainder of the course (Source: The Sanford Guide to HIV/AIDS Therapy 2008).

#### **Alternative Treatment**

- Non-hospitalized patients can initiate with itraconazole 200 mg 3 x daily for 3 days, then 200 mg 2 x daily for 12 weeks.
- If itraconazole is unavailable, use fluconazole 400 mg twice daily (Source: The Sanford Guide to HIV/AIDS Therapy 2008).

#### **Secondary Prophylaxis**

- Amphotericin B 1 mg/kg IV infusion per week or Itraconazole 200 mg daily life-long until the patient's CD4 is above 150 cells/mm<sup>3</sup> on two measurements at least 6 months apart (Source: The Sanford Guide to HIV/AIDS Therapy 2008).

## **10. TOXOPLASMA ENCEPHALITIS**

### **Key points**

- Consider in patients with headache and focal neurological deficits
- Clinical presentation develops over weeks and can culminate in encephalitis
- Diagnosis is typically confirmed based on response to treatment
- Toxoplasma Encephalitis is a Stage IV diagnosis.

Toxoplasma encephalitis occurs primarily in severely immunosuppressed patients with CD4 counts less than 100 cells/mm<sup>3</sup>. It is rarely diagnosed in Cambodia. The true prevalence of toxoplasmosis both in cities and in rural areas is currently not known. As a result, Toxoplasma encephalitis should be considered in evaluation of headache and neurological symptoms that are focal in nature.

Toxoplasma encephalitis is caused by the protozoan Toxoplasma gondi. Most infection stem reactivation of latent oocysts in the body. Toxoplasma oocysts are ingested, either via excretion by household pets or their presence in undercooked meat. Invasive forms enter the bloodstream to reach the brain, heart and lungs where they form cystic aggregates that remain latent, but subject to reactivation throughout the life of the host. In many communities, the majority of people will have been infected by early childhood, but otherwise healthy persons do not develop clinically evident disease. Primary infection with toxoplasma is rare. It may result in focal necrotizing encephalitis and occasionally chorioretinitis and pneumonitis as a result of the unrestrained multiplication of toxoplasmosis

As mentioned earlier, Toxoplasma encephalitis primarily affects PLHIV with CD4 <200 cells/mm<sup>3</sup> (greatest risk below 100 cells/mm<sup>3</sup>) and is a WHO's STAGE 4 diagnosis. Patients on ART should be evaluated for treatment failure. IRIS is uncommon with toxoplasmosis.

### **Clinical presentation**

Symptoms are variable.

- Some patients may initially present with headache, confusion, motor weakness, and fever. These patients may go on to develop focal neurological signs suggestive of an intracerebral space-occupying lesion including hemiplegia, hemiparesis, or partial seizures over the next several weeks in about 60% of patients.
- Retinochoroiditis, pneumonia, and multifocal organ system involvement represent disseminated infection.

### **Diagnosis**

- Toxoplasma should be considered in any patient who presents with headache and **focal** neurological signs.
- CSF findings are typically normal which can be helpful in ruling out other potential diagnoses.
- Without readily available CT imaging, most providers in Cambodia will need to treat empirically and observe the response to treatment to confirm the diagnosis.
- If patients do not respond to treatment, patients should be referred to a higher level of care for imaging to evaluate for Toxoplasma or other CNS lesions, including Tuberculosis abscess, Cryptococcoma, purulent abscess, PML, and CNS Lymphoma. Toxoplasma typically shows multiple contrast-enhancing lesions that are often associated with edema on Brain CT imaging.

### **Standard treatment**

- Cotrimoxazole 10/50mg/kg divided over 2 doses daily for 6 weeks, followed by 1 DS daily (Source: The Sanford Guide to HIV/AIDS Therapy 2008).
- For increased ICP from mass effect use prednisolone 40 mg 4 x daily or dexamethasone 4 mg 4 x daily (Source: Clinical HIV/AIDS Care Guidelines, MSF, 2006).
- In Cambodia, provide treatment for Anguillulosis (Strongyloides) before (or during) treatment by Corticosteroids. For AIDS patients, use Albendazole 400mg/day for 5 days to prevent cancer due to Anguillulosis.

### **Alternative treatment**

- Pyrimethamine 200 mg loading dose, followed by 50 mg daily + sulfadiazine 1-1.5g 4 x daily + folinic acid 20 mg daily for 6 weeks (Source: The Sanford Guide to HIV/AIDS Therapy 2008).

### **Secondary prophylaxis**

- Cotrimoxazole 1 DS (Cotrimoxazole 800mg+ TMT 160mg) daily until CD4 count greater than 200 cells/mm<sup>3</sup> on two measurements at least 6 months apart.

## 11. CYTOMEGALOVIRUS (CMV)

### Key points

- CMV retinitis is common in severely immunosuppressed patients and is often associated with IRIS.
- 5-10% of patients with CMV and  $CD4 < 50$  cells/mm<sup>3</sup> will present with CMV esophagitis or colitis.
- CMV diagnosis is difficult and limited treatment options are available in Cambodia.
- CMV is a WHO's stage 4 clinical event.

### Cytomegalovirus (CMV) Infection

CMV is a common virus which causes disseminated or local disease in advanced HIV infection. Prior to the availability of ART, an estimated 30% of adult patients with  $CD4 < 100$  cells/mm<sup>3</sup> could be expected to develop CMV retinitis during the course of their HIV.

ART dramatically reduce the risk of CMV. However, it is important to suspect CMV in newly-diagnosed patients with visual abnormalities and very low CD4 counts, and in patients developing visual abnormalities soon after starting ART, when it can present as an IRIS reaction

### Clinical presentation

- Most commonly causes retinitis but can infect any organ.
- The most common presentation is as retinitis with visual "floaters," photophobia (light sensitivity), and visual field defects. Pain and redness of the eye are absent.
- Non-ocular presentations of CMV infection typically occur at CD4 counts  $< 50$  cells/mm<sup>3</sup> and account for only about 20% of cases.
- CMV also affects other parts of the nervous system. It can cause encephalitis, dementia, cranial nerve palsies, nystagmus or ataxia, myelopathy, or ascending polyradiculomyelopathy. CSF may reveal lymphocytic pleocytosis, low glucose and increased protein (similar to TB meningitis) but is usually not helpful in confirming the diagnosis.
- In addition to the neurological system, CMV can affect multiple organ systems including the gastrointestinal tract.
- CMV esophagitis is of concern in patients who do not respond to treatment for candida or herpes esophagitis. It affects 5-10% of patients with  $CD4 < 50$  cells/mm<sup>3</sup> and is associated with fever, mid-epigastric or retrosternal pain, in addition to odynophagia.
- CMV colitis occurs in 5-10% of patients with  $CD4 < 50$  cells/mm<sup>3</sup>. These patients present with fever, weight loss, anorexia, abdominal pain, and debilitating diarrhea (with blood from mucosal ulcerations and tissue necrosis), and malaise. Uncontrolled CMV colitis can cause perforation, leading to peritonitis.

### Diagnosis

- CMV retinitis can be detected on retinal exam using a direct ophthalmoscope as large white perivascular exudates with or without associated hemorrhage. Experienced ophthalmologists can distinguish CMV retinitis lesions from cotton-wool spots, toxoplasmosis, acute retinal necrosis, and progressive outer retinal necrosis. The latter two diseases are related to herpes viruses and should be treated with acyclovir.

- Diagnosis at other organ sites requires PCR testing, tissue biopsy and histopathologic identification of characteristic inclusions and positive immunoperoxidase staining that is currently not available in Cambodia.

### **Treatment**

- PLHIV in Cambodia have limited access to treatment to CMV.
- Retinitis responds well to intravitreal ganciclovir.
- All other forms of CMV require induction therapy with IV ganciclovir or other antiviral drugs.
- Treatment with ART for those not on ART can improve CMV disease significantly.
- Start ART with CD4 < 350 cells/mm<sup>3</sup> is for the prevention of CMV.

## **12. NON-TYPHOID SALMONELLA**

### **Key points**

- Salmonella septicemia is a common cause of death among PLHIV in Cambodia.
- Cotrimoxazole prophylaxis does not offer full protection from infection.
- Treatment duration should be extended in severely immunosuppressed patients.
- Salmonella septicemia is a WHO's stage 4 clinical event.

Non-typhoid Salmonella enteritis is common in HIV infected and non-infected persons in Cambodia. Transmission is typically through uncooked meats or contaminated water. Salmonella is a common cause of chronic diarrhea and septicemia in PLHIV in Cambodia. The reason for increased risk of septicemia with salmonella with or without diarrhea in immunosuppressed patients (CD4<200 cells/mm<sup>3</sup>) is most likely due to a decrease or unregulated immune response within the gastrointestinal tract results in increase translocation of bacteria into the blood stream.

### **Clinical presentation**

- Patients present with persistent fever, nausea, abdominal pain, and profuse bloody or non-bloody diarrhea.
- If the bacteria translocates into the blood stream, patients can develop isolated deep abscess and septicemia.

### **Diagnosis**

- Is clinical without stool culture capabilities.
- Stool microscopy may indicate increased leukocytes and blood but rarely help differentiate non-typhoid salmonella from other common disease causing enteric bacteria such as Shigella or Campylobacter.

### **Standard treatment**

- Although cotrimoxazole is used to treat non-typhoid salmonella, it is not the treatment of choice in Cambodia. Most patients with HIV are on cotrimoxazole prophylaxis.
- Surveillance of antimicrobial resistance at Center for Hope Hospital in Phnom Penh found 77.5% resistance of cotrimoxazole and 10% resistance of ciprofloxacin to non-typhoid salmonella.

- Given current resistance patterns in Cambodia, the recommended initial treatment for non-typhoid salmonella is ciprofloxacin 500 mg **2 x daily for a minimum of 7 to 14 days**.
- In cases of severe immunosuppression (<200 cells/mm<sup>3</sup>) treatment can be extended to six weeks (Source: The Sanford Guide to HIV/AIDS Therapy 2008).
- All patients should be screened for TB symptoms per SOP for 3Is prior to using ciprofloxacin. If positive TB case findings, see alternative treatment.
- In patients with suspected salmonella septicemia, treatment consist of aggressive fluid replacement and broad antibiotic coverage with ceftriaxone IV 1 g 2 x daily and metronidazole 500 mg IV or orally 4 x daily for seven days. Providers may also consider gentamicin 4 mg/kg/day divided over 3 doses daily for expanded coverage of bacteroides.

#### **Alternative Treatment**

- Azithromycin 1 gram daily x 1 day, then 500 mg daily x 6 days (Source: The Sanford Guide to HIV/AIDS Therapy 2008). This is the choice for pregnant women.
- If pregnant women do not respond to azithromycin within 1-2 days of treatment, consider ceftriaxone 1 gram 2 x daily for 7-10 days (MSF Guidelines 2006).

#### **Secondary prophylaxis**

- Salmonella is prone to relapse.
- If patients have recurrent salmonella infections begin suppressive therapy with cotrimoxazole (cotrimoxazole 800mg+TMT 160mg) 1 DS tablet daily, which is also part of standard cotrimoxazole prophylaxis for Stage IV patients.

### **13. SKIN LESIONS**

#### **Key points**

- Skin lesions are often the first manifestation of HIV noted by patients and health professionals and occur frequently in PLHIV
- Characteristic lesions can often provide evidence of underlying, systemic infection
- Prompt diagnosis and treatment of cutaneous manifestations can prevent complication and improve quality of life for HIV-infected persons.

Skin disorders are common with HIV. More than 80% of PLHIV develop skin conditions stemming from a primary dermatologic disorder, mild superficial infection, disordered inflammatory response to common antigens, or severe disseminated opportunistic infection. Table 18 lists common dermatologic manifestations in HIV-infected children.

**Table 18: Causes of skin disease in HIV infection**

Category	Causes
Infections	<ul style="list-style-type: none"> <li>• Varicella zoster</li> <li>• Herpes simplex virus</li> <li>• Molluscum contagiosum</li> <li>• Condyloma lata (syphilis)</li> <li>• Condyloma accuminata (human papilloma virus)</li> <li>• Superficial fungal infection (eg Candida, Tinea)</li> <li>• Disseminated fungal infection <ul style="list-style-type: none"> <li>○ Cryptococcosis</li> <li>○ Penicilliosis</li> <li>○ Histoplasmosis</li> </ul> </li> <li>• Impetigo</li> <li>• Mycobacterial infection</li> <li>• Secondary syphilis</li> <li>• Furunculosis and Folliculitis</li> <li>• Pyomyositis</li> <li>• Verucca planus</li> <li>• Scabies</li> </ul>
Neoplasia	<ul style="list-style-type: none"> <li>• Kaposi's sarcoma (rare in Cambodia)</li> <li>• Lymphoma</li> <li>• Squamous and basal cell carcinoma</li> <li>• Sarcoma</li> </ul>
Others	<ul style="list-style-type: none"> <li>• Pruritic papular eruption</li> <li>• Seborrheic dermatitis</li> <li>• Drug eruptions</li> <li>• Vasculitis</li> <li>• Eczema</li> <li>• Psoriasis</li> <li>• Granuloma annulare</li> <li>• Thrombocytopenic purpura</li> <li>• Telangiectasia</li> <li>• Hyperpigmentation</li> </ul>

The remainder of this section provides a summary of common cutaneous manifestations of HIV. Providers should refer to Annex 3 on dermatology atlases or [www.aidsimages.ch](http://www.aidsimages.ch) for illustrative examples of these as well as less common skin manifestations in PLHIV.

### ***Herpes simplex virus***

- Anorectal-genital is most common location and risk factor for HIV transmission.
- Oro-labial lesions are also common.
- Lesions are small, painful clusters of vesicles.
- Can become chronic (>3 weeks) with associated ulceration.
- Diagnosis is made by clinical appearance but may be verified by Tzank test.
- Treatment of mucocutaneous HSV is with oral aciclovir 400 mg 5 x per day for 7 days
- Application of genitain violet can reduce superinfection.

- If superinfection with staphylococcal or streptococcal species is suspected, give cloxacillin 500 mg 4 x daily for 7 days.
- Recurrent (more than 6 episodes per year) can be suppressed by 200 to 400 mg acyclovir 2 x daily.
- See Section 16 for information on pain management.

### ***Herpes zoster***

- Herpes Zoster in a young person suggest HIV infection.
- Affects about 25% of PLHIV.
- May have multidermal involvement in PLHIV but does not cross midline.
- Complications include deep skin lesions, corneal scarring, chronic neuropathic pain.
- Diagnosis is clinical. May confirm with Tzank test if available.
- Treat with acyclovir 800 mg 5 x daily or 7 to 14 days, acyclovir eye drops for keratitis when available (refer all patients with vision complaints to higher level of care immediately).
- Application of gentian violet can reduce superinfection.
- If superinfection with staphylococcal or streptococcal species is suspected, give cloxacillin 500 mg 4 x daily for 7 days.
- Recurrent (more than 3 episodes per year) can be suppressed by 200 to 400 mg acyclovir 2 x daily.
- See Section 16 for information on pain management.

### ***Molluscum Contagiosum***

- Commonly found in persons with advanced HIV infection and is due to a virus.
- Molluscum contagiosum lesions are pearly or flesh-colored, round papules 3-5 mm in size with a central dimple and appear on face, neck, and ano-genital areas.
- Can look like cutaneous *cryptococcus*, *penicillium*, or *histoplasma* but is usually not associated with fever, pulmonary, or meningeal involvement (see Sections 8 and 9)
- Giant molluscum lesions often occur on the face when immunosuppression is severe, and can be disfiguring.
- Treatment includes opening lesion with needle dipped in 80% phenol or iodine and expressing contents, curettage, or liquid nitrogen cryotherapy.
- When severe or disfiguring, strongly consider initiation of ART which is the only therapy likely to prevent recurrence.

### ***Syphilis (Treponema pallidum)***

Dermatological manifestations primarily occur at the secondary stage of syphilis. The primary stage is characterized by a painless, indurated genital ulcer (chancre) at the site of inoculation, usually accompanied by inguinal lymphadenopathy. Weeks to months later, about 25% of untreated patients will develop a systemic illness with fever, rash, condyloma lata, lymphadenopathy and oral lesions (mucous patch). The rash typically involves the palms and the soles, and is maculo-papular. Treat with:

- once weekly benzathine benzyl penicillin 2.4 MIU IM weekly for 3 weeks
- doxycycline 100 mg 2 x daily for 14 days
- erythromycin 500 mg 4 x daily for 4 weeks.

## Genital Warts

- Caused by HPV virus.
- HPV strains 16 and 18 are associated with cervical cancer.
- Extensive and cauliflower-like lesions in genital and peri-anal area.
- Treat with non-mucosal affected surfaces with podophyllotoxin 0.5% solution lesions twice daily for 3 consecutive days per week for up to 4 weeks (maximum). Protect unaffected skin from inadvertent ulceration with vaseline or zinc ointment, then wash with water and soap after 1-4 hours. DO NOT ADMINISTER DURING PREGNANCY.
- Cryotherapy is alternative treatment, if available.

## Bacterial Skin Infections

- Typically caused by staphylococci and streptococcus
- May represent local invasion of organisms into the dermis or be manifestations of systemic infection
- Cellulitis is extension of infection into subcutaneous tissue
- Extension from skin can result in Pyomyositis
  - Initial phase starts with vague complaints of muscle ache, pain and low grade fever
  - Later phase develop worsening pain, swelling, fever and abscess formation in muscle
  - Can lead to septicemia.
  - More common in patients with CD4<150 cells/mm<sup>3</sup>
- **Bacillary angiomatosis** is caused by gram negative bacilli
  - Lesions resemble those of Kaposi Sarcoma (violaceous hard nodules)
  - Small red papules->larger papular, nodular, or pedunculated lesions.
  - Treat all suspected cases.

**Table 19: Causes of bacterial skin infection and initial suggested treatment**

Bacterial skin infection	Causative organism	Description	Treatment
Folliculitis	<i>Staphylococcus aureus</i>	Inflammation, infection of the hair follicles	<ul style="list-style-type: none"> <li>• Warm compress</li> <li>• Cleansing</li> <li>• Topical gentian violet</li> <li>• Cloxacillin in severe cases*</li> </ul>
Cellulitis	<i>Streptococcus, Staphylococcus aureus, Haemophilus influenzae</i>	Inflammation of skin and subcutaneous tissues, characterized by edema, erythema, and pain	<ul style="list-style-type: none"> <li>• Cloxacillin 500 mg 4 x daily for 10 days. Severe cases require IV antibiotic (cloxacillin or ceftriaxone)</li> </ul>



Skin abscess	<i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i>	Localized collection of pus in a cavity formed by disintegration of tissue; may complicate untreated cellulitis	<ul style="list-style-type: none"> <li>• Surgical drainage</li> <li>• Systemic antibiotics if surrounding cellulitis</li> </ul>
Impetigo	<i>Staphylococcus aureus</i> , <i>Streptococcus</i>	Vesicles or bullae with characteristic honey-colored crusting	<ul style="list-style-type: none"> <li>• Topical antibiotic or antibiotic/salicylic acid preparation</li> <li>• Cloxacillin for disseminated lesions</li> </ul>
Furunculosis (boil)	<i>Staphylococcus aureus</i> , <i>Streptococcus</i>	Infection of the skin and subcutaneous tissues surrounding a hair follicle; larger than folliculitis	<ul style="list-style-type: none"> <li>• Warm compress</li> <li>• Cleansing</li> <li>• Occasionally need drainage</li> <li>• Rarely requires systemic antibiotics</li> </ul>
Paronychia	<i>Staphylococcus aureus</i>	Infection involving the folds of tissue surrounding the fingernail or toenail	<ul style="list-style-type: none"> <li>• Surgical drainage</li> <li>• Cloxacillin for 5-7 days</li> </ul>
Pyomyositis	<i>Staphylococcus aureus</i>	Abscess formation within muscle	<ul style="list-style-type: none"> <li>• Surgical drainage</li> <li>• Ceftriaxone 2 grams IV per day or Cloxacillin 1-2 grams IV 4 x daily for 10 days</li> </ul>
Bacillary angiomatosis	<i>Bartonella henslae</i>	Disseminated vascular lesions that may mimic Kaposi's sarcoma	<ul style="list-style-type: none"> <li>• Erythromycin 500 mg 4 x daily or doxycycline 100 mg 2 x daily for two months</li> <li>• Consult expert</li> </ul>
Staphylococcal Scalded Skin Syndrome	<i>Staphylococcus aureus</i>	Diffuse bullous lesions starting on face, most common in infants; may mimic Stevens Johnson Syndrome but without precipitating exposure and NO mucosal involvement	<ul style="list-style-type: none"> <li>• Cloxacillin 200 mg/kg/day IV divided in every 6 hours</li> <li>• Surgical consultation</li> <li>• Aggressive wound care and attention to hydration status</li> </ul>

\*If patients do not respond to treatment, seek expert advice. In rare cases, patients may present with eosinophil folliculitis and respond to alternative treatments. Eosinophilic folliculitis presents with urticarial follicular papules above the nipple line and may be responsive to treatment with metronidazole or steroids.

## ***Fungal skin infections***

Fungal skin infections among people with HIV/AIDS are varied, and include both local skin infections or lesions caused by severe disseminated infection. Most common are candidiasis and dermatophytosis.

### **Cutaneous candidiasis:**

- Found most commonly in skin fold or under breasts. It appears as a vivid, erythematous rash with well-demarcated borders and satellite lesions.
- Also presents as balanitis, urethritis, or paronychia in severely immunocompromised patients.
- Treatment:
  - Topical 1% aqueous solution of gentian violet, nystatin ointment, or miconazole cream applied to lesions three times per day until 48 hours after the rash resolves.
  - If there is no response to topical treatment, systemic therapy with fluconazole 100 mg x 7 days may be rarely needed.

### **Dermatophytosis:**

- Usually occurs as tinea corporis (ringworm), tinea capitis, or onychomycosis. It is characterized by flat, scaling lesions with raised borders. The lesions may be very extensive and refractory to treatment in HIV-infected persons.
- Treatment:
  - Apply Whitfield's ointment (benzoic acid with salicylic acid) 2 times daily for 2 to 5 weeks on body lesions; if not successful switch to 2% miconazole cream for two to four weeks.
  - Extensive disease and tinea capitis should be treated with systemic fluconazole 100 mg daily for four weeks.
  - Treat onychomycosis only if severe. Initial therapy with fluconazole 200 mg weekly for six weeks. If fails, itraconazole 200 2 x daily for first seven days of 4 consecutive months. When using azoles monitor for interaction with current ARV medications (see National Guidelines on the use of Antiretrovirals in Adults and Adolescents, 2011).

## ***Scabies***

- Highly contagious mite infection of the skin characterized by pruritic papular lesions found most commonly in the webs of the fingers and toes, folds of the wrist, antecubital area, and axilla.
- Generalized scabies occurring in patients with advanced HIV is called Norwegian scabies and is highly contagious.
- Clinical diagnosis but can confirm diagnosis with microscopy of skin scrapings with KOH staining.
- Treatment
  - Benzyl Benzoate 25% lotion: apply over the body except head/face, leave in place 12 hours, then wash off for 2-3 consecutive days.
  - Permethrin 5% cream applied head to toe for 12 hours followed by bath is preferred where available. Toxicity is minimal, treatment effective, and it may be used in infants.

- Alternative is 1% gammabenzene hexachloride (lindane) applied from neck to toe may be used.
- Norwegian scabies is best treated systemically with ivermectin, 200 mg/kg in a single dose (The Sanford Guide to HIV/AIDS Therapy, 2008), where available. A repeat dose may be given on day 14 if lesions persist. Otherwise, attempt treatment with measures above.
- Pruritis can persist for 1-2 weeks due to persistent antigen in the skin even when treatment has been effective.
- Oral antihistamines and topical steroids may be given to relieve itching.
- All household members should be treated along with the child, regardless of symptoms.
- All contaminated clothes and bedsheets should be washed and hung to dry in the sun.

### **Drug Eruptions**

- Medications commonly causing drug eruptions include cotrimoxazole, penicillins, cephalosporins, dapsone, and nevirapine.
- Drug eruptions usually appear as pink to erythematous papules that run together and create a blotchy appearance.
- Other manifestations include pruritic papules (hives), mucous-membrane ulceration, scaling, and light sensitivity with abnormal pigmentation of skin or nails.
- Often an offending agent is obvious; however, in severe cases it may be necessary to discontinue ALL medications and restart one-by-one when the drug responsible is not known.
- Treatment:
  - Discontinue causative medication; if reaction is severe, DO NOT rechallenge
  - Oral antihistamine such as diphenhydramine 1 mg/kg every six hours as needed for pruritus.
  - Systemic corticosteroids are very rarely indicated; an exception includes DRESS syndrome (Drug rash, eosinophilia, and systemic symptoms including liver enzyme elevation).
- Systemic corticosteroids have not clearly shown to be beneficial with Stevens Johnson syndrome and their use should be avoided whenever possible due to the risk of additive immunosuppression and increased risk of infection. Seek expert advice if you are considering using steroids in the treatment of Stevens Johnson syndrome.

### **Seborrheic Dermatitis**

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.

Treatment:

- Selenium sulfide or ketoconazole shampoo for scalp lesions
- 1% hydrocortisone cream can be applied to the affected area three times per day but should be used sparingly on the face or diaper area as skin atrophy can occur.

### ***Pruritic Papular Eruption***

- Stage II event and most common in patients with CD4<100 cells/mm<sup>3</sup>
- Chronic eruption of papular lesions on the skin
- May be related to disordered inflammatory response to common antigens such as those due to repeated mosquito bites.
- Very pruritic.
- Usually evenly distributed on the trunk and extremities
- May become superinfected with *Staphylococcus* or *Streptococcus* organisms
- Generally refractory to treatments other than ART; when severe, strongly consider early initiation of ART.

### ***Psoriasis***

- Extensive Psoriasis can be observed in severely immunosuppressed patients
- Presents with thick plaques with silver or gray scale
- Plaques thicken with increased rubbing
- Treatment includes exposure to sunlight, coal tar 5-10% ointment in salicylate ointment 2 x daily with coal tar shampoo (if scalp is involved), and potent topical steroids (betametasone 0.1%) cream applied to lesions 1-2 x daily for 14 days

## 14. HIV ASSOCIATED MALIGNANCIES

### Key points:

- HIV-infected patients are at increased risk of malignancy, particularly lymphoma
- HIV-associated malignancy should be considered when fever and cytopenias are present
- Primary CNS or B cell non-Hodkin's lymphoma, invasive cervical carcinoma, and Kaposi sarcoma are clinical stage 4 conditions
- ART reduces the risk of HIV associated malignancy through immune restoration
- Treatment with ART is recommended in all HIV-infected patients with malignancy
- Radiation and chemotherapy is rarely available in many resource-limited settings

Immune suppression puts PLHIV at increased risk for malignancies. A number of studies have shown that immunologic suppression and interruption of ART increase risk for both HIV associated and non-associated malignancies. HIV associated malignancies occur significantly more often in PLHIV who are immunosuppressed. Specifically, primary CNS and B cell variant Non-Hodkins Lymphomas, Invasive Cervical Carcinoma, and Kaposi Sarcoma are common in immunosuppressed patients with HIV and are considered AIDS defining cancers (clinical Stage 4).

The relationship between immunosuppression and increased risk of malignancy is complex. During the course of HIV, the virus enters and destroys CD4 cells, which are integral to the body's defense against other viruses. Some of these other viruses have been known to cause cancer. EBV has been linked to both Burkitt lymphoma (>30%) and other types of large B-cell lymphomas (75%), particularly patients with primary CNS lymphoma; Human papilloma virus (HPV) is linked to cervical cancer; and human herpes virus 8 (HHV-8) is linked to Kaposi Sarcoma.

Although ART reduces the risk of malignancies, even at low levels, the HIV virus continues to interfere with the body's cell replication process and response to cancer cells. Over time, defects in the body's cell replication process accumulate, leading to cell dysplasia and cancer. These cancerous cells are less likely to be destroyed by immune system in persons with HIV and gain access into tissues. Upwards of 25% of adults on long-term ART will develop cancer despite ART.

Kaposi sarcoma is a vascular tumor caused by infection with Human Herpes Virus-8 and is extremely rare in Cambodia and not furthered discussed in this section. It most commonly presents with asymptomatic explosive growth of violaceous, red, pink, or brown plaque-like skin or oral lesions. It can infiltrate other organ systems including the lungs, gastrointestinal tract, liver, and brain. Diagnosis is made on clinical basis as well through tissue biopsy and cytology. Immune restoration with ART and chemotherapy is the most effective therapy. The remainder of this section highlights two forms of cancer that providers will no so infrequently encounter in Cambodia – non-Hodgkin's lymphoma and invasive cervical cancer.

## 14.1 Non-Hodgkin's lymphoma (NHL)

Non-Hodgkin's lymphomas are seen in about 10% of PLHIV. Three types of non-Hodgkin's lymphoma are common:

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

Except for Burkitt lymphomas, Non-Hodgkin lymphomas (NHLs) including Primary CNS lymphoma are primarily encountered in patients with more advanced HIV infection with CD4 counts less than 50 cells/ml<sup>3</sup>. ART reduces the risk for NHL by more than 50% (80% in Primary CNS lymphoma) when given early during the course of HIV.

### Clinical presentation

Symptoms of lymphoma can be highly variable, depending on what organ system is most involved. Most patients will present with fever and lymphadenopathy, but fatigue, weight loss, and night sweats are also common. Lymphoma is frequently misdiagnosed as TB but fails to improve with TB medications. Lymphoma should be in the differential in any patient with fever and lymphadenopathy who does not have an alternative explanation for their symptoms, especially if splenomegaly or any cytopenias are present.

**Table 20: Site-dependent symptoms of NHL**

Mediastinal or Pharyngeal tumor	Abdominal tumor
<ul style="list-style-type: none"> <li>• Dyspnea</li> <li>• Tachypnea</li> <li>• Stridor</li> <li>• Localized decrease in breath sounds</li> <li>• Dry cough</li> </ul>	<ul style="list-style-type: none"> <li>• Abdominal distension</li> <li>• Ascites</li> <li>• Palpable abdominal mass</li> <li>• Jaundice</li> <li>• Pain</li> </ul>
Central nervous system disease	Maxillofacial tumor
<ul style="list-style-type: none"> <li>• Headache</li> <li>• Vomiting</li> <li>• Visual disturbances</li> <li>• Gait instability</li> <li>• Cranial nerve palsies</li> <li>• Hemiparesies</li> <li>• Seizures</li> </ul>	<ul style="list-style-type: none"> <li>• Jaw mass</li> <li>• Numbness of the chin (peripheral facial nerve compression)</li> <li>• Asymmetric facial expression</li> </ul>

## **Diagnosis**

The differential diagnosis of for lymphoma is complicated by the high incidence of constitutional symptoms and lymphadenopathy seen in HIV associated opportunistic infections, particularly TB, penicilliosis, and histoplasmosis. Cytology is limited at the referral hospital setting. Patients with symptoms consistent with lymphoma without a diagnosis of TB, should be referred to a national hospital to investigate for fungal infection and make definitive diagnosis of cancer with CSF cytology or biopsy of affected tissue including bone marrow.

## **Treatment**

Treatment of NHL requires specialty care in a national hospital with access to oncology specialists and chemotherapy which may not be available. NHL is a clinical stage 4 disease and requires early initiation of ART for optimal outcome.

## **14.2 Invasive Cervical Cancer**

Infection of the cervical mucosa with HPV, in particular HPV strains 16 and 18, has been linked to cervical dysplasia and cancer. HIV at any level of immunosuppression increases the risk of acquiring HPV and lowers the ability of the body to clear HPV infection. In addition to HIV, smoking, high risk sexual activity, and sexually transmitted diseases increase the risk of acquiring HPV and clearing HPV infection.

Cervical dysplasia is a precursor form to cervical cancer and is five time more likely in women with HIV. It can also occur at younger age than in non-HIV infected adults and adolescents. For this reason, any sexually active adolescent or young adult and with vaginal bleeding should be tested for HIV in addition to gynecological screening, and **all adult and adolescent women with HIV should receive routine gynecological screening every 6 months to screen for cervical dysplasia and cancer.**

## **Clinical presentation**

Cervical dysplasia and cancer can be asymptomatic or present with intermittent vaginal bleeding, bleeding after sexual activity, or non-infectious mucoid watery vaginal discharge. Invasive carcinoma can also 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.

## **Treatment**

Immune restoration through ART can reduce levels of dysplasia before they become cancerous. Gynecological treatment for cervical dysplasia consists of topical treatments, loop electrical excision or cauterization, or cone excision procedures. Treatment for cervical cancer includes the above with additional surgery, radiation, and chemotherapy that are limited in Cambodia.

## 15. APPROACH TO COMMON CLINICAL SYNDROMES

### 15.1 Respiratory Symptoms

**Definition(s):** Cough, dyspnea or respiratory distress; often associated with fever. Dyspnea is defined as subjective shortness of breath at rest or on minimal exertion. Respiratory distress is defined as objective evidence of respiratory dysfunction including hypoxemia, cyanosis, tachycardia and signs of increased ventilatory effort (intercostal retractions or use of accessory muscles).

#### Causes

Common infectious causes include mycobacterium tuberculosis, PCP, Cryptococcus neoformans, S.pneumoniae, H. Influenza and Nocardia asteroides. Other less common causes include penicilliosis, cryptococcosis, histoplasmosis, cytomegalovirus disease, and helminthic disease including strongyloides stercoralis and paragonimus westermanii (lung fluke). Non-infectious causes associated with HIV include lymphoma. Other causes of respiratory symptoms commonly seen in non-HIV infected persons such as smoking, bronchitis, and congestive heart failure can also be seen in PLHIV.

#### History taking

Chronicity is very important in identifying the etiology of respiratory symptoms. Onset can be acute (<1 week), sub-acute (1-3 weeks), or chronic (>3 weeks). Patients should be asked about their functional status and level of dyspnea with effort and at rest. Characteristics of the sputum (blood versus non-bloody) can be helpful as well as identifying associated symptoms include fever, foul smelling breath, chest pain.

All providers should also review the patient's ART and prophylaxis history to assess prior clinical stage and immune states as well as risk factor for PCP and TB.

#### Clinical examination

Focused exam to evaluate for signs of wasting, lymphadenopathy, respiratory failure, dyspnea, cyanosis, pneumonia, or severe immunodeficiency (oral thrush). In addition providers should exam skin for lesions, lymph nodes, and abdomen for hepatomegaly. Skin lesions are present in disseminated cryptococcosis, penicilliosis, and histoplasmosis (less common). Pyomyositis and cellulitis may point toward staphylococcal infection. Hepatomegaly and lymphadenopathy is often associated with tuberculosis, penicilliosis, histoplasmosis, and disseminated cryptococcosis, as well as lymphoma.

#### Diagnosis

Diagnosis of pulmonary disease in HIV-positive patients often requires a multi-step approach, starting with a thorough history and physical examination and leading up to chest X-ray and sputum examination. To use resources rationally, it is important to identify those patients who will benefit from additional tests. In a smear-positive pulmonary TB patient, the diagnosis of PTB is confirmed by the positive smear and treatment effect can be evaluated by examining the smears or repeat cultures at certain intervals.

The evaluation of new respiratory symptoms begins with clinical history and sputum microscopy. If TB is not identified, patients should have CXR and sputum and blood culture.



Direct sputum microscopy may reveal gram-positive bacteria in pairs/chains (*S. Pneumoniae*), gram-positive bacteria in clusters (*Staphylococcus*), cysts of PCP, or *Strongyloides stercoralis* larvae or eggs of *Paragonimus* species. *Nocardia* will stain weakly AFB+. Consider pleural tapping and lymph node aspiration in case of pleural effusion and lymphadenopathy and perform AFB stain, GS stain, culture and additional pleural fluid studies such as protein and cell count. An AFB Positive lymph node is more than 80% sensitive for pulmonary TB in patients presenting with respiratory conditions and sputum negative AFB smears.

### Treatment

In many cases, providers will have to treat patients empirically. If a trial with antibiotics to treat pneumococcal pneumonia is justified use amoxicillin or amoxicillin-clavulanic acid. Cotrimoxazole can be used but most PLHIV are on cotrimoxazole prophylaxis making the drug less effective for acquired pneumonia. Table 21 summarizes common treatment regimens for different respiratory conditions

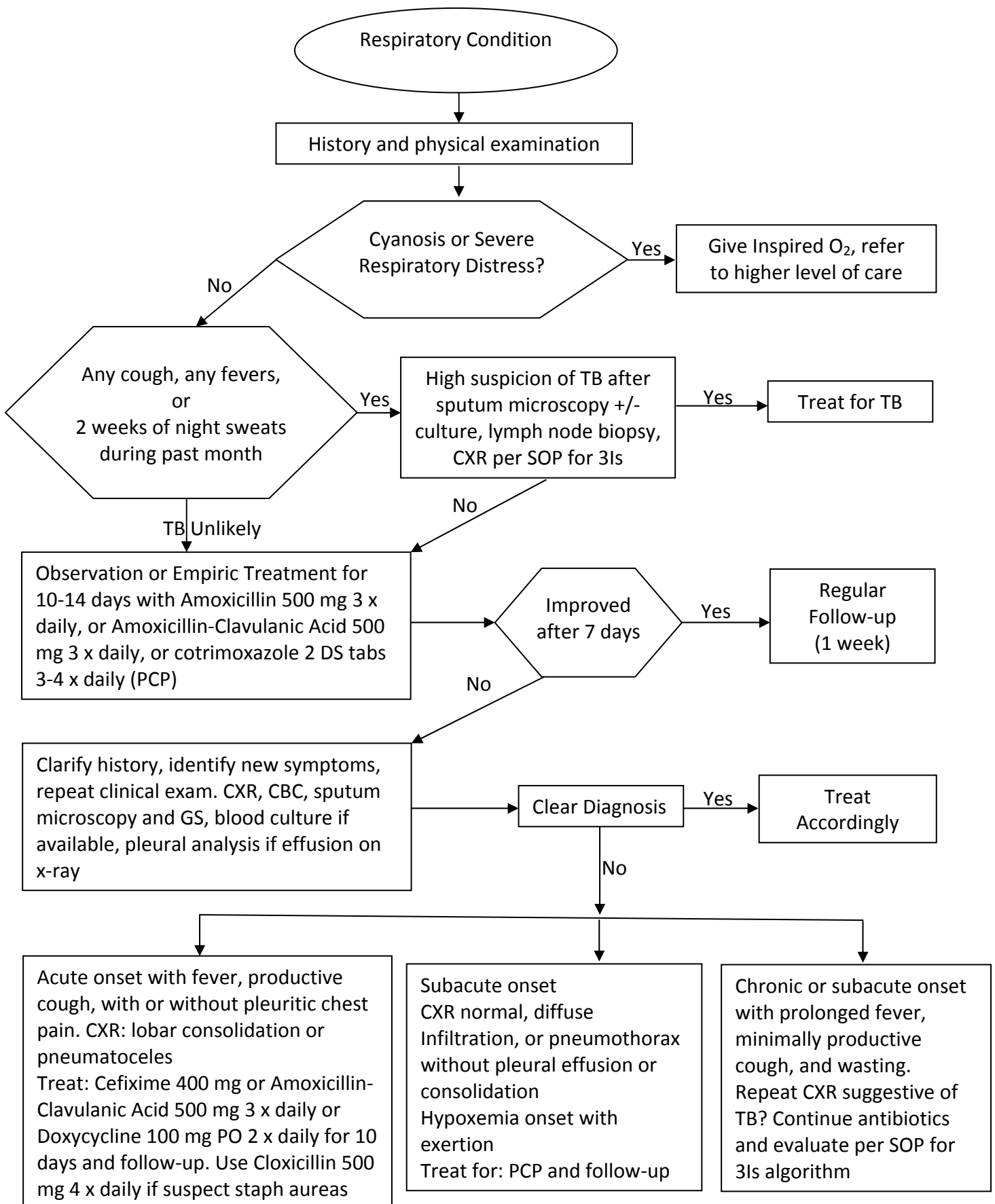
**Table 21: Treatment of common respiratory conditions**

Condition	Treatment
Pulmonary Tuberculosis (AFB+)	See TB guideliness. Category I treatment is 2RHZE/4RH.
Pulmonary Tuberculosis (AFB-)	See TB guideliness
Bacterial Pneumonia	Amoxicillin 500 mg PO 3 x daily or Amoxicillin-Clavulanic Acid 500 mg PO 3 x daily (preferred choice if abscess). Or Cotrimoxazole DS tab 2 x daily (if not on prophylaxis) for 10 days. Ceftriaxone 2 gram IV if severe. Consider Cloxacillin 500 mg PO 4 x daily if suspect Staph Aureus
Nocardia	Cotrimoxazole 2 DS tab 2 x daily (if not on prophylaxis) for 6 weeks (localized disease)
PCP	Cotrimoxazole 2 DS tab 3-4 x daily for 21 days (see section 7 for weight based dosing). Prednisone at initiation of respiratory distress or cyanosis; dose is 40mg twice daily for 5 days, 40 mg daily 5 days, then 20mg daily for 11 days.
Penicilliosis	Amphotericin B 0.7 mg/kg/day IV for 2 weeks, then itraconazole 200 mg twice daily for 10 weeks, then itraconazole 200 mg daily until CD4>100
Histoplasmosis	Amphotericin B 0.7 mg/kg/day IV for 2 weeks, then itraconazole 200 mg twice daily for 12 weeks, then itraconazole 200 mg daily until CD4>100. Non-hospitalized patients can initiate with itraconazole 200 mg 3 x daily for 3 days, then 200 mg 2 x daily for 12 weeks. After treatment itraconazole 200 mg 2 x daily until CDR>150
Strongyloides Stercoralis	Ivermectin 12 mg daily x 3 days, or albendazole 400 mg 2 x daily for 7 days. May suppress after treatment with albendazole 400 mg monthly
Lymphoma	Chemotherapy
Pulmonary Kaposi Sarcoma	ART, chemotherapy

Source Clinical HIV/AIDS Care Guidelines for Resource Poor Settings, MSF, 2006. The Sanford guide to HIV/AIDS Therapy. 2008; The Sanford Guide to Antimicrobial Therapy, 2008;

It is also not rare to find more than one pathogen involved. Therefore, in a patient who does not respond to therapy as expected, do not hesitate to review the history and the physical examination, to repeat the respiratory algorithm and to add a second or even a third treatment if necessary.

### Algorithm 4: Respiratory Condition



## 15.2 Odynophagia

**Definition:** Odynophagia is painful feeling in the throat and retrosternal space on swallowing food, with or without problems swallowing.

### Causes

The cause of odyophagia is typically esophagitis in patients with HIV. The most common cause of odynophagitis is candida esophagitis. Other causes of odynophagia include reflux-esophagitis, cytomegalovirus esophagitis, herpes simplex virus esophagitis, aphthous ulcers, neurological deficits due to PML, HIV encephalopathy, Kaposi sarcoma or lymphoma.

### History taking

History taking should focus on symptoms and nutritional intake. Patients should have symptoms with both solids and liquids. It is also important to ask about weight loss, fever, chills, night sweats, abdominal pain, and neurological changes to identify more systemic causes of odynophagia such as lymphoma or cytomegalovirus.

### Clinical examination

Focused Exam to evaluate for face and oropharynx for signs of candida or herpes simplex virus.

### Diagnoses

Diagnosis is clinical as esophagoscopy is not readily available at most facilities. Oral thrush suggest candida esophagitis in 90% of cases. However, sometimes patients have candida esophagitis occurs without oral candida. Consider CMV if patients have more systemic symptoms including fever, nausea, vomiting, abdominal pain, hepatomegaly, or bloody stools. 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.

### Treatment

Treatment is usually empiric. If patients do not respond, they should be referred to a higher level of care for further studies. Esophagitis is also a STAGE IV condition and severely limit nutrition in immunocompromised patients. Those patients not on ART should be initiated on cotrimoxazole and scheduled for follow-up to initiate ART. Table 22 summarizes treatment for candida and herpes esophagitis.

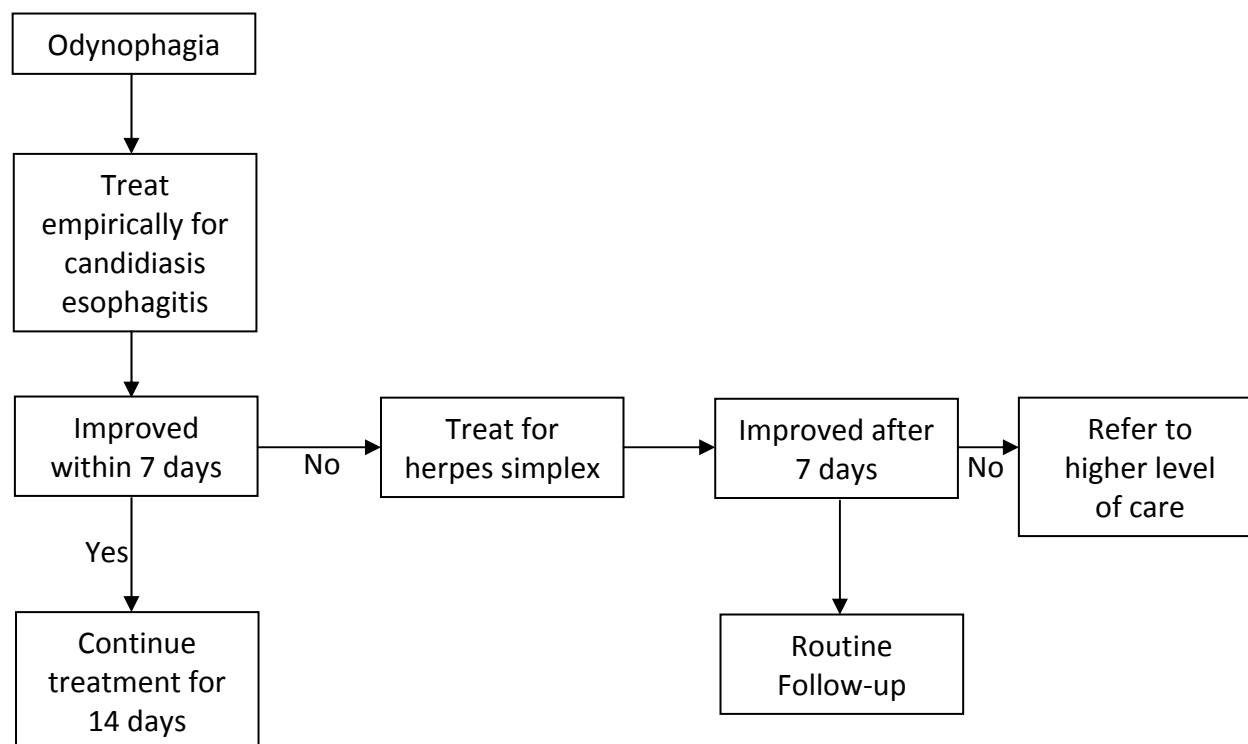
**Table 22: Treatment for Odynophagia**

Respiratory Condition	Treatment
Candida Esophagitis	Flucanazole 200 mg daily for 14 days (see section ? for additional treatment options)
Herpes Simplex Virus Esophagitis	Acyclovir 800 mg 3 x daily for 7 days

Source Clinical HIV/AIDS Care Guideliness for Resource Poor Settings, MSF,2006. The Sanford guide to HIV/AIDS Therapy, 2008; The Sanford Guide to Antimicrobial Therapy,

If patients do not respond to treatment they should be referred to a higher level of care as CMV and other causes of esophagitis require endoscopy for diagnosis.

### Algorithm 5: Odynophagia



## 15.3 Lymphadenopathy

### Definition

Lymphadenopathy is defined as a lymph node greater than 1.5 cm in diameter

### Causes

TB is a common cause of lymphadenopathy in PLHIV in Cambodia. In addition to TB, the differential diagnosis of lymphadenopathy includes:

- HIV-related
  - Persistent generalized lymphadenopathy (PGL)
- Opportunistic infections
  - Tuberculosis lymphadenitis
  - CMV
  - Toxoplasmosis
  - Syphilis
  - Fungal infections: histoplasmosis, penicilliosis, cryptococcosis
  - Infections with Nocardia species
- ART-related
  - Immune reconstitution inflammatory syndrome (IRIS)

- Malignancies
  - Lymphoma, Kaposi's sarcoma
- Reactive lymphadenopathy
  - Pyomyositis
  - Pyogenic skin infections
  - Ear, nose and throat (ENT) infections

### **History taking**

History should focus on the duration of lymphadenopathy and associated symptoms including fever, weight loss, night sweats, cough, skin eruptions, and pain or swelling around the node(s).

### **Clinical examination**

Providers should conduct a full clinical exam with a targeted focus on cervical, supraclavicular, axillary, abdominal, and inguinal lymph nodes. The abdomen should be assessed for hepatosplenomegaly. When available an abdominal ultrasound can be helpful in quantifying abdominal lymphadenopathy and hepatosplenomegaly.

### **Diagnosis**

The cause of lymphadenopathy is identified by clinical history, exam, and results of lymph node aspiration and culture (when available).

Syphilis can be identified by clinical presentation and a positive VDRL in serum.

History or AFB staining of lymph node aspirates can identify TB. Fluctuant cervical nodes that develop over weeks to months without significant inflammation or tenderness suggest infection with *M.tuberculosis* or atypical mycobacterium.

In severe immunocompromised patients, tuberculosis associated lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis. In HIV patients there is a high rate of positive smears for acid-fast bacilli on wide-needle aspirates of the involved lymph nodes. A CXR may also be helpful in identifying TB, which is often associated with cervical lymphadenopathy.

There are several features of lymph nodes that warrant further investigation if an immediate cause is not identified:

- large (>4 cm diameter) or rapidly growing lymph nodes
- asymmetrical lymphadenopathy
- tender/painful lymph nodes not associated with a local infection
- matted/fluctuant lymph nodes
- obvious constitutional symptoms (fever, night sweats, weight loss)
- hilar or mediastinal lymphadenopathy on chest X-ray
- suspicion of pulmonary TB
- evidence of abscesses (cutaneous, pulmonary, etc).

In any of these situations, patients should undergo lymph node biopsy. If not available at your health facility, patients should be transferred to a higher level of care for lymph node aspiration, biopsy, culture and additional studies.

In patients who have recently started ART within the past year, lymphadenopathy can be

due to treatment associated IRIS. IRIS typically presents as lymphadenitis in patients with untreated or previously treated Mycobacterium avium complex (MAC) and Mycobacterium tuberculosis but can also be seen with penicilliosis, cryptococcosis and malignancies.

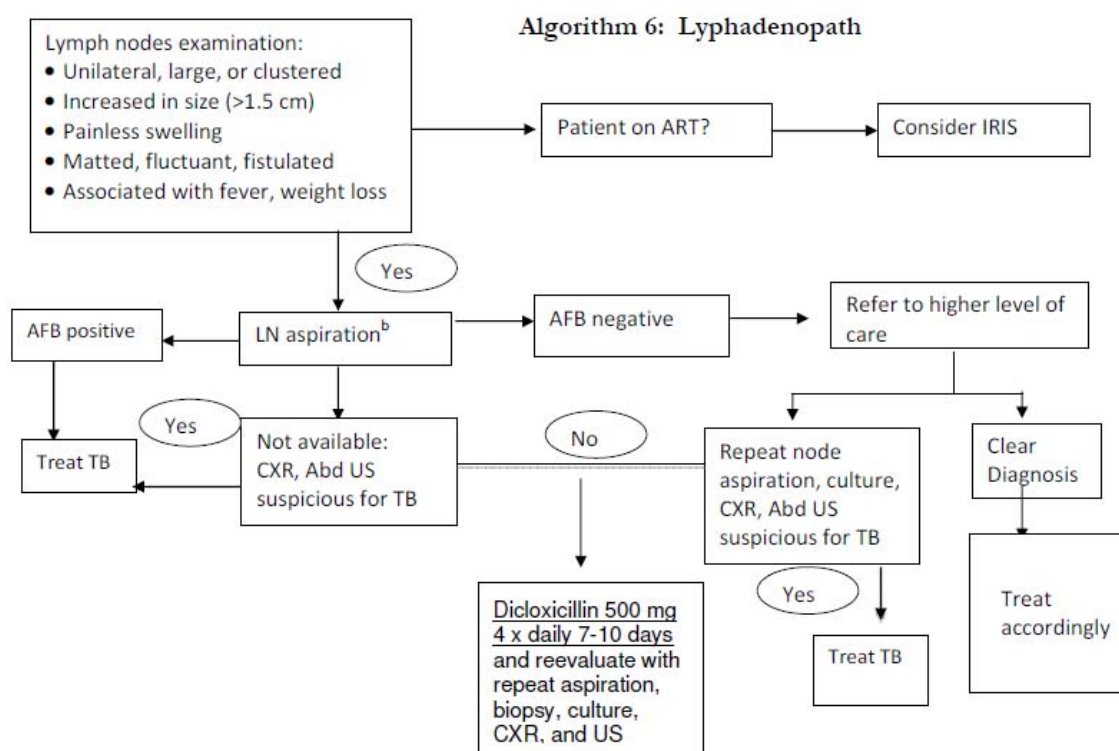
IRIS associated lymphadenitis is typically focal and differs from the generalized form seen with untreated HIV. It is often painful and associated with fever. Worsening radiographic appearances or inflammatory masses (e.g. skin) can be present as well. Peripheral lymphadenopathy may also be associated with lymphadenitis in other locations (e.g. intrathoracic, abdominal). The histological examination of the lymph nodes reveals granulomatous inflammation, sometimes containing acid-fast organisms. MAC or TB can be cultured from the lymph nodes and blood, but a negative culture certainly does not exclude MAC or TB associated IRIS.

### Treatment

Treatment of lymphadenopathy is based on the most likely underlying cause (see appropriate disease specific section for management). In cases of IRIS, patients should be treated for the underlying OI if not currently under treatment and ART should be initiated or continued. Symptoms can be managed with anti-inflammatory medications (e.g. ibuprofen, diclofenac) and may require steroids (prednisone at 1 mg/kg/day) at full dose for 1-2 weeks, then taper over 1-2 weeks) in severe cases.

Source Clinical HIV/AIDS Care Guidelines for Resource Poor Settings, MSF, 2006. The Sanford guide to HIV/AIDS Therapy, 2008; The Sanford Guide to Antimicrobial Therapy, 2008

### Algorithm 6: Lymphadenopathy



## 15.4 Chronic Diarrhea

### Definition

Liquid stool 3 or more times a day, continuously or episodically or more than one month, in a patient with symptomatic HIV infection.

### Causes

The increased incidence of chronic diarrhea stems from underlying immunodeficiency in PLHIV. Individuals with CD4 counts less than 200 are disproportionately affected. Diarrhea can be associated to infection, malignancies, drugs (antiretrovirals or antibiotics), or HIV infection itself.

An infectious agent can be identified in about 50% of patients with AIDS-associated diarrhea. In Cambodia, HIV patients are heavily exposed to bacterial and protozoal infection and infection is more frequent.

#### 1. Frequent

- Cryptosporidiosis - Campylobacter spp
- Isospora belli - Entamoeba histolytica
- Giardia lamblia - Strongyloides stercoralis
- Salmonella spp - Shigella flexneri
- Microsporidium

#### 2. Uncommon

- Cytomegalovirus
- Mycobacterium avium complex
- Lymphoma

**Clinical exam:** The priority of a clinical exam for wasting and to assess the severity of dehydration and begin rehydration

**Table 23: Assessment of dehydration**

Table 23: Assessment of dehydration

Clinical Signs and Symptoms	Dehydration	
	Moderate	Severe
- General appearance/condition	- Restless, irritable	- Usually conscious; apprehensive; cold, sweaty, cyanotic extremities
- Pulse	- Rapid	- Rapid, feeble, sometime impalpable
- Respiration	- Deep, may be rapid	- Deep and rapid
- Skin elasticity	- Pinch retracts slowly	- Pinch does not retract
- Eyes	- Sunken	- Deeply sunken
- Mucous membranes	- Dry	- Very dry
- Urine flow	- Reduced amount and dark	- None passed for 6 or more hours; empty bladder.



In case of moderate dehydration, correct with oral rehydration salts (ORS), prescribe perfusion in case of severe dehydration. Supplemental feeding should not be done too quickly, but by multiple and divided feeding, using various nutrients, and completed with correct hydration (minimum 1.5 liter of water a day).

Providers should also thoroughly examine the abdomen for hepatomegaly or lymphadenopathy (MAC) and skin for serpiginous lesions (strongyloides). In addition, a small number of patients may have a hyperinfection syndrome that presents with fever, abdominal pain, cough (pulmonary infiltration), and bleeding.

### **Diagnosis**

Stool microscopy is readily available in most district health centers and referral hospitals. Stool should be examined for white blood cells, blood, parasites, and bacteria. Microscopy becomes increasingly sensitive for identifying parasitic infection if repeated three times on consecutive stools.

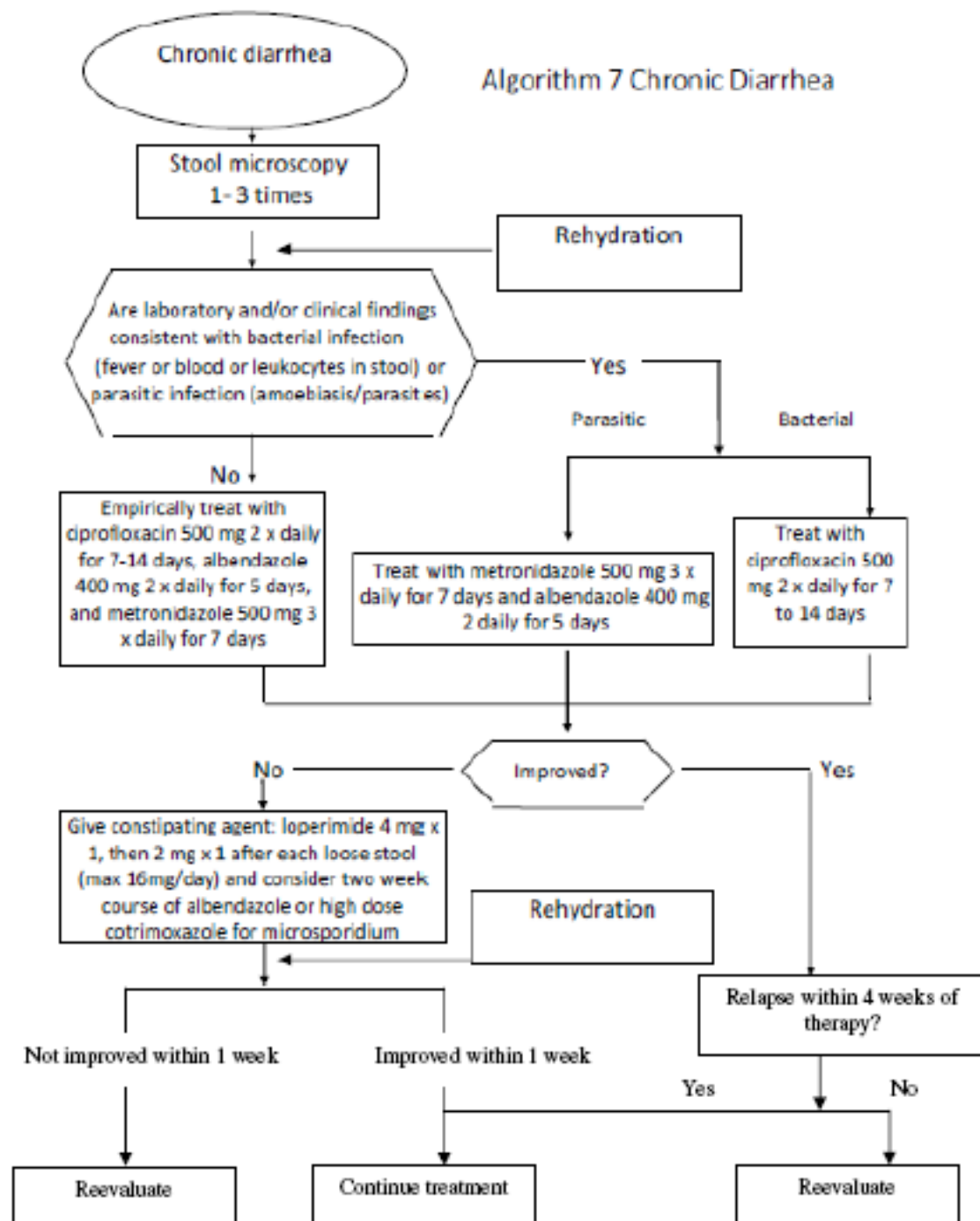
In cases where MAC is suspected, an abdominal ultrasound may be helpful in evaluating enlarged intrabdominal lymph nodes and hepatosplenomegaly. Diarrhea can result from TB or MAC associated IRIS if ART was started recently. Some ARVs can cause diarrhea as well, in particular LPV/r.

### **Treatment**

- Treatment is primarily based on clinical suspicion or results of stool microscopy.
- When results are inconclusive or not available, empiric treatment is warranted, in particular, treatment to cover for non-typhoid salmonella (see section 12).
- In many cases such as patients with chronic diarrhea caused by cryptosporidium or microsporidiosis or without an identifiable cause, effective ART offers the only available therapy.

All patients should be screened for TB per SOP for 3Is before administration of ciprofloxacin.

## Algorithm 7: Chronic Diarrhea



## 15.5 Headache

### Definition

Headache is defined broadly as a possible symptom suggestive of an underlying neurological symptoms including meningismus, altered consciousness, increased intracranial pressure, and/or focal neurological deficits.

### Causes

There are numerous types of headaches in PLHIV that may occur in non-HIV infected persons. PLHIV with headache should initially be evaluated for typical migraine, tension headaches, and sinusitis as well as signs and symptoms of uncontrolled HTN or stroke. These cases can be managed similarly to those of non-HIV infected adults.

There are however other HIV associated causes of headache in PLHIV need to be considered:

- Malaria, dengue fever, rickettsial disease
- Opportunistic infections: Toxoplasma encephalitis, cryptococcus, TB, bacterial (purulent) meningitis, neurosyphilis, histoplasmosis, penicilliosis, cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV)
- Lymphoma, HIV-related encephalopathy, progressive multifocal leukoencephalopathy (PML)
- Medications: d4T, AZT

### History Taking

Ask about duration and characteristics of symptoms including 1/10 pain scale for headache, fever, focal vs. non-focal neurological symptoms, nausea, vomiting, loss of vision, photophobia, neck stiffness, and weakness or paralysis of any sort. Inquire about symptoms of TB or pneumonia; often these are the source of meningitis. Inquire about the patient immune status and fluconazole prophylaxis history, which can significantly decrease the likelihood of cryptococcal meningitis. Likewise, ask about skin eruptions suggestive of cryptococcus or penicilliosis.

### Clinical examination

Neurological findings are often subtle. Often a patient only complains of headache. It is important to note that fever may be absent or low-grade with headache despite an infectious source, particularly in cases of cryptococcal meningitis or toxoplasmosis. Check for decreased cognition, papilloedema, retinal hemorrhages or necrosis (CMV), cranial nerve palsies (CMV, TB, Cryptococcus – loss of cranial nerve III or VI suggest increased ICP, ataxia, or focal weakness or loss of sensation, or paralysis). Begin by looking for neurological abnormalities including:

1. Evidence of meningeal irritation or raised intracranial pressure (neck stiffness, vomiting, high blood pressure and bradycardia in the presence of fever).
2. Seizures.
3. Focal neurological deficits: paresis, cranial nerve palsies, movement disorders, ataxia, aphasia.
4. Changes in mental state; including loss of concentration, personality change (mild to psychotic), confusion, cognitive impairment, dementia

Also look for lymphadenopathy, hepatomegaly, or skin eruptions. Skin findings may also

help in making a diagnosis of disseminated cryptococcus, tuberculosis, or HSV/VZV encephalitis. If a patient has a septic picture, they will need immediate fluid resuscitation, initiation of broad spectrum antibiotics such as ceftriaxone 2 gram IV 2 x daily, Gentamicin 4 mg/kg daily for extended bacteroides coverage, metronidazole 500 mg 4 x daily, and/or treatment for cryptococcal meningitis and transfer to higher level of care as soon as possible.

### **Diagnosis**

Initial lab evaluation is based on clinical history and physical exam. Blood gram stain or culture can be helpful in identifying a source. The threshold to perform an LP should be very low. Many patients with cryptococcal meningitis will not have neck stiffness. CSF studies including opening pressure, gram stain, protein, cell count, microscopy, VDRL, and culture are essential in diagnosing meningitis (see Table 24). Even if CSF studies are not available a lumbar puncture should be conducted to check intracranial pressure. An ICP>250 mm is highly suggestive of cryptococcal meningitis and serial lumbar punctures to maintain ICP<200 mm are needed on a daily basis (ICP is present in 50% of patients with cryptococcal meningitis). **If your facility does not perform lumbar puncture or CSF studies, the patient should be transferred to a higher level of care.**

If CSF VDRL is not available, providers may use a serum VDRL for aiding in the diagnosis of neurosyphilis. Serum VDRL is associated with more false positive tests, so the diagnosis will have to be made in the setting of the patient's clinical presentation. A CXR may also be of value if the patient has respiratory symptoms and may lead to a source of infection as well. Likewise, a lymph node biopsy that is AFB+ suggests TB meningitis. Symptoms of IRIS from TB, Cryptococcus, or PML can mimic those of meningitis. In any patient with worsening symptoms after the start of ART, IRIS should be suspected.

If the diagnosis is unclear, providers should have a low threshold to transfer in order to complete full CSF studies. Providers may consider treating empirically for bacterial meningitis in febrile unstable patients prior to transport. In a few cases, infectious etiologies will be ruled out and a non-infectious cause such as lymphoma will be identified on advanced imaging.

**Table 24: Suggestive Differential Diagnosis based on cerebrospinal fluid (CSF)**

**Table 24: Suggestive differential diagnosis based on cerebrospinal fluid (CSF) changes:**

CSF	Opening Pressure	Protein content	Cell count	Microscopy	Culture
Cryptococcal meningitis	Very high	Slightly elevated or normal	Slightly elevated or normal	+ India Ink stain	+ Cr Ag +
TB meningitis	High or normal	Slightly elevated to very high	Elevated (lymphocytes predominate)	+/- --	+/-
Bacterial meningitis	High	Very high	Granulocytes predominate	+/-	+
Herpes Encephalitis	Normal	Slightly elevated or normal	Lymphocytosis with RBCs (non-traumatic)	NA	NA

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**Treatment:** In many cases, providers will have to treat patients empirically for Toxoplasmosis, IRIS, or meningitis. Table 25 summarizes common treatment regimens in Cambodia.

**Table 25: Treatment for common CNS infections**

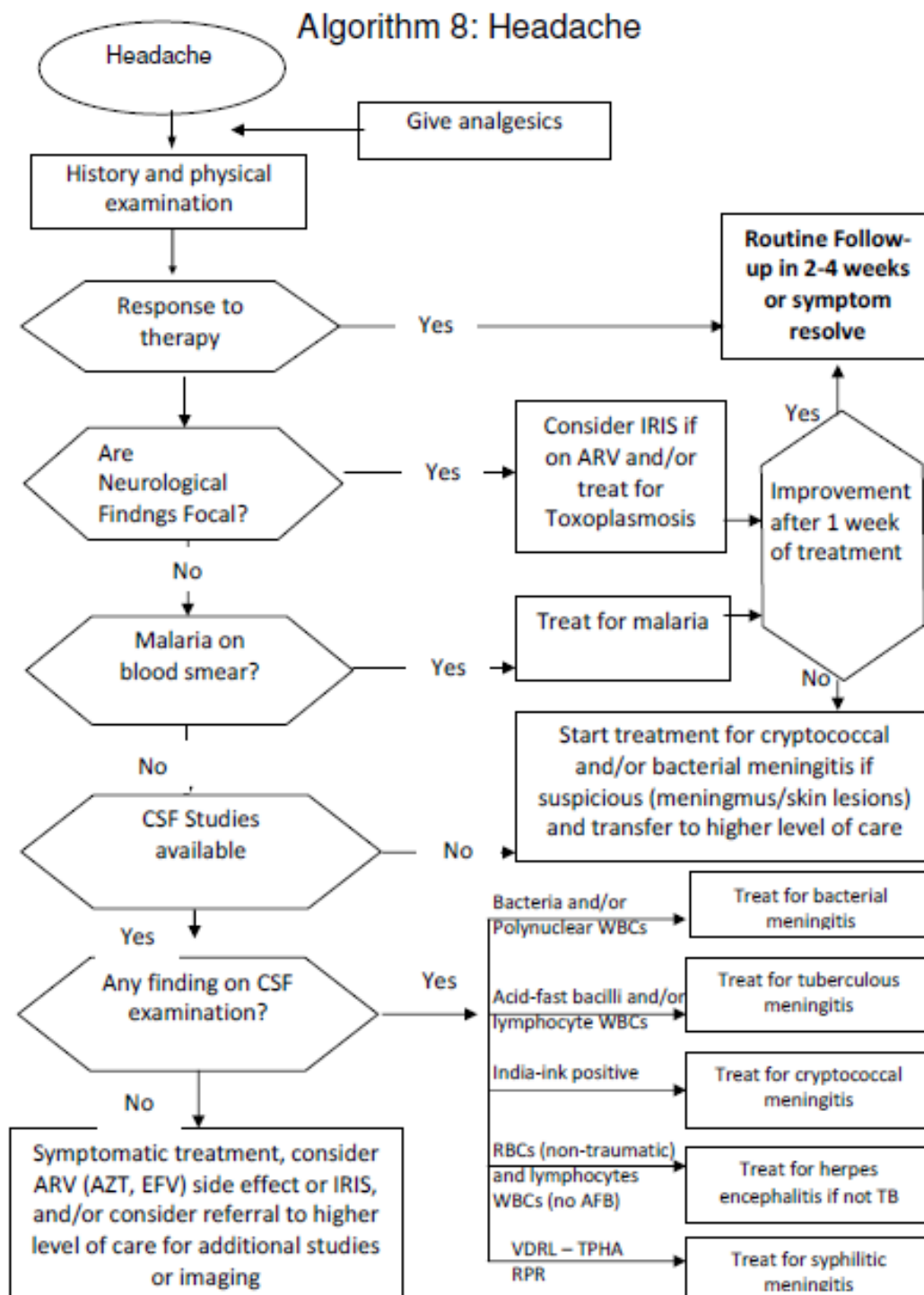
Condition	Treatment
Toxoplasmosis	Cotrimoxazole 10/50 mg/kg daily divided over two doses for four weeks, followed by 1 DS daily lifelong. For ICP from mass effect use prednisolone 40 mg 4 x daily or dexamethasone 4 mg 4 x daily until symptoms improve
IRIS (Cerebral)	Prednisone 40mg/day x 2 weeks, then 20mg/day for 1 week, then 10 mg/day for 1 week
Bacterial Meningitis	Ceftriaxone 2 grams IV twice daily or Benzylpenicillin 12-24 million IU daily by IV injections divided into 4 doses for 10-14 days if low resistance to S. Pneumonia in area
TB Meningitis	Category TB Treatment (2RHSE/4RH). May consider steroids prednisolone 60 mg 2 x daily (2 mg/kg) or dexamethasone 4 mg 4 x daily with taper extending up to six weeks (see section 6)
Cryptococcal Meningitis	Amphotericin B 0.7 mg/kg/day for 2 weeks followed by Fluconazole 400 mg twice daily for 8 weeks, then fluconazole 200 mg daily until CD>100 for 6 months
Neuro-syphilis	Benzylpenicillin 18-24 million IU daily by IV injections divided into 6 doses for 14 days, then 2.4 million weekly for 3 weeks.

Source Clinical HIV/AIDS Care Guidelines for Resource Poor Settings, MSF, 2006. The Sanford guide to HIV/AIDS Therapy, 2008; The Sanford Guide to Antimicrobial Therapy, 2008. TB/HIV Manual, WHO, 2004.

**Follow-up**

Patients with headache need close follow-up with treatment. Providers should see these patients weekly during treatment. Moreover, providers should clinically restage patients and repeat CD4 count and viral load when available to check the eligibility for ART or to assess for possible of treatment failure.

Algorithm 8: Headache



## 16. Evaluation and Management of Pain in PLHIV

*This section is based on existing National Pain Management Guidelines, 2007 issued by the MoH in collaboration with Douleurs Sans Frontieres (DSF) and WHO guidelines (Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers issued by WHO, 2004). Recommended doses from both sources are presented to give providers alternative treatment options.*

### Definition and General Introduction

The International Association for the Study of Pain (IASP 1976) defines pain as **“an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage”**.

### Different types of pain

- **Acute pain** is the most frequent. Pain is a symptom that alerts the patient and the physician (eg. pain due to acute appendicitis, meningitis...). Acute pain should be treated with analgesics immediately after diagnosis.
- **Chronic pain** (eg. back pain, phantom pain, ...) should be considered not only as a symptom but as an illness caused by multiple factors.

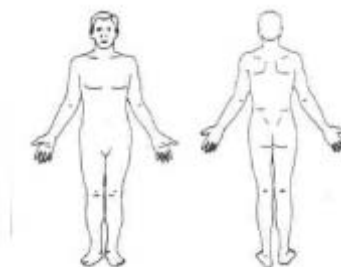
### Two main pathophysiologic mechanisms of pain

- **Nociceptive pain** is caused by the stimulation of intact ‘nociceptors’ or pain receptors in the afferent nerves.
- **Neuropathic pain** (involves stimulation of damaged or compromised nerve tissue) results from a failure of the regulatory systems (inhibition, exacerbation) which control transmission and which modify the perception of pain

## 16.1 Assessment of Pain

### Location of pain

Use a corporal sketch (both front and back views) to help the patient to locate pain. Ask the patient to locate his/her painful areas.



### Intensity of pain

You may use three types of scales:

- Visual Analogue Scale (VAS), e.g. a 100mm horizontal line





Ask the patient to check on the scale (length of 100mm) in order to indicate the intensity of pain that s/he is experiencing. The intensity of pain is expressed in mm. Example: "I am experiencing pain at the level of 80/100" This indicates severe pain and should be taken care of immediately.

- **Numeric Rating Scale (NRS)**

From 0 (no pain) to 10 (unbearable pain), if the patient is able to understand, ask the patient to measure his pain from 0 to 10.

- **Simple Verbal Scale (SVS)**

Ask the patient to choose between the following pain indicators:

- 0 = no pain
- 1 = little pain
- 2 = moderate pain
- 3 = severe pain
- 4 = very severe pain

**Develop a detailed history of his/her pain by spending time with the patient**

Help the patient to describe his/her pain:

- ✓ Date when pain started (chronology)
- ✓ How the pain developed (suddenly, progressively)
- ✓ The pattern of the pain over time
- ✓ Location of pain and spread if any
- ✓ Variations during the day
- ✓ What aggravates or relieves pain
- ✓ How does the pain interfere with activity? (Effects on sleep, appetite, physical activities, personal relationship)
- ✓ Efficacy of previous treatment
- ✓ Comprehensive medication history

**Observe the patient's behavior**

Look for positions or attitudes (including the overall behavior) of the patient to cope with pain (posture, guarding, splinting, signs of sympathetic dysfunction).

**Perform a systematic and complete clinical examination**

followed by a

**Precise examination of the painful areas**

And a

**Detailed neurological examination** will help to look for motor disturbances and/or sensitive (neurogenic) and/or signs of disturbances in the sympathetic system:

- ✓ Pain felt in areas away from the supposed lesion
- ✓ Previous nervous lesions
- ✓ Specific description of pain (burning, sharp shooting pain, electrical discharges, abnormal sensations, pins and needles, itchiness...)
- ✓ Problems with stimulation sensitivity:
  - Hypoesthesia or anesthesia

- Hyperesthesia
- hyperpathia (abnormally prolonged duration of pain)
- allodynia (pain due to a stimulus which normally does not provoke pain: light touch, caress...)
- ✓ Problems with deep sensitivity
  - Bad recognition of the position of part of the body in space
  - Abnormal gestures
  - Poor movement coordination
- ✓ Motor problems
  - Decreased muscular strength (paresthesia, paralysis)
  - Muscle deficit in a given innervated area
  - Disturbed reflexes
- ✓ Vasomotor problems
  - Redness
  - Congestion
  - Heat
  - Sweating
  - Vasoconstriction
- ✓ Cutaneous anomalies
  - Dry and brittle nails
  - Thin and fragile skin
  - Abnormal colour
  - Hair loss

## 16.2 Standard Pain Treatment

### Treatment of nociceptive pain

The initial treatment of pain is symptomatic and should be started right away without waiting for results of the treatment of the cause (etiological).

The World Health Organization suggests a stepwise analgesic ladder for treating nociceptive pain.

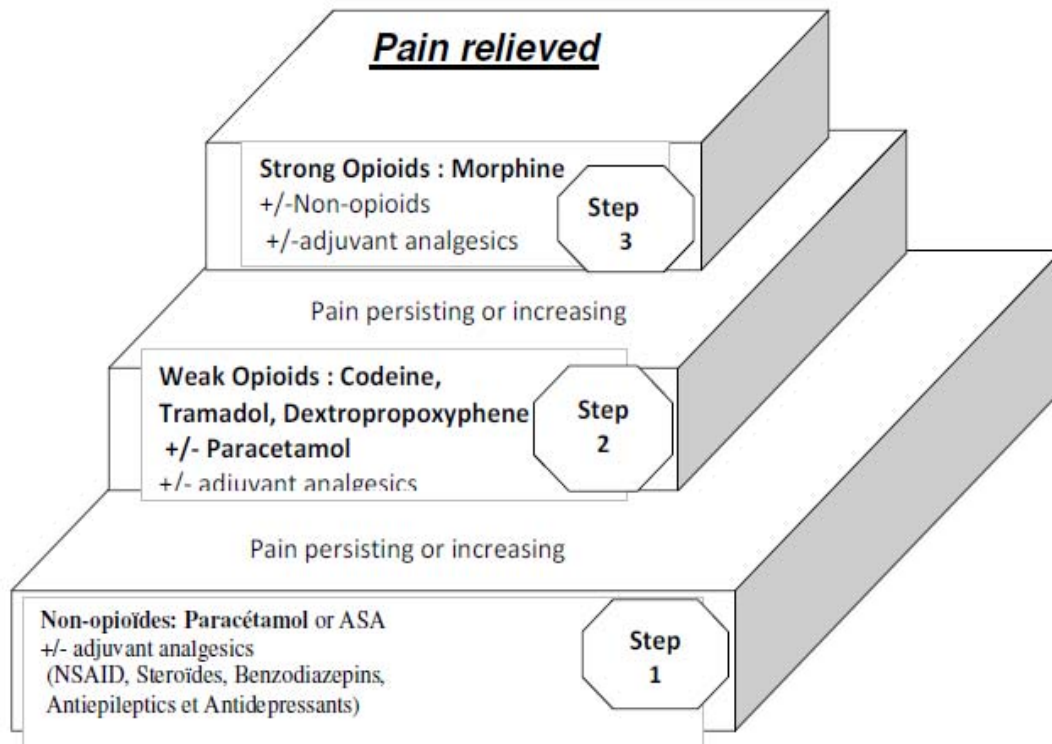
- **Individualized, simple** and the most **convenient** treatment for the patient
- Relieving pain **progressively**, firstly at night, then during rest and, finally during activity.
- Regular timely intake of medicines, **orally** if possible, **without waiting for the reappearance** of pain.
- Prescription of analgesics based on the **three levels of efficacy** (WHO)

**Based on the intensity of pain** (mild, moderate & severe)

And not based on the level of pain

And not based on the prognosis of the illness

And in association with adjuvant analgesics if necessary



**Table 26: WHO 2004 Pain Management Steps and Medications**

	<b>Analgesics</b>	<b>Starting dose in adults</b>	<b>Range</b>	<b>Side effects/ cautions</b>
	↓	↓	↓	↓
	<b>Non-opioid</b>			
<b>STEP 1</b>	<b>paracetamol</b> (also lowers fever).	500 mg 2 tablets every 4 to 6 hours (skip dose at night or give another analgesic to keep total to 8 tablets).	Only 1 tablet may be required in elderly or very ill or when combined with opioid. Mild pain might be controlled with every 6 hour dosing.	Do not exceed eight 500 mg tablets in 24 hours (more can cause serious liver toxicity).
	<b>aspirin</b> (acetylsalicylic acid) (also anti-inflammatory and lowers fever).	600 mg (2 tablets of 300 mg) every 4 hours.		Avoid use if gastric problems. Stop if epigastric pain, indigestion, black stools, petechiae or bleeding. Do not give to children under 12 years. Avoid if presence of any bleeding.
	<b>ibuprofen</b> (also anti-inflammatory, lowers fever, for bone pain).	400 mg every 6 hours.		Max. 8 tablets per day.
	<b>Opioid for mild to moderate pain</b> (give in addition to aspirin or paracetamol)			
<b>STEP 2</b>	<b>codeine</b> (if not available, consider alternating aspirin and paracetamol*).	30 mg every 4 hours.	30-60 mg every 4 to 8 hrs. Maximum daily dose for pain 180-240 mg due to constipation—switch to morphine.	Give laxative to avoid constipation unless diarrhoea. <b>Cost</b>
	<b>Opioid for moderate to severe pain</b>			
<b>STEP 3</b>	<b>oral morphine</b> 5 mg/5 ml or 50 mg/5 ml. Drop into mouth. Can also be given rectally (by syringe).	2.5-5 mg every 4 hours (dose can be increased by 1.5 or doubled after 24 hours if pain persists).	According to need of patient and breathing. <b>There is NO ceiling dose.</b>	Give laxative to avoid constipation unless diarrhoea.

Source: WHO guidelines (Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers issued by WHO, 2004)

The decision to change the treatment of a level should be undertaken if the lower step medication failed to provide relief. In some case, reevaluation of pain and doses of medications within each step can be increased to achieve better pain control, specifically:

- Pain evaluation should be carried out regularly: in case of treatment failure, you should proceed to the next higher level.
- As long as the patient tolerates morphine, dosage of morphine should be increased by 30-50%, until relief is obtained (see Table 26 for WHO recommendations and Table 27 for DSF recommendations for medication dosing options)
- Anticipate and treat adverse effects

**Table 27: DSF recommended pain medication for pain management steps**

<b>Analgesics</b>	<b>Dosage</b>	<b>Monitoring, and side effects</b>
<b>Step I - Mild pain</b>		
<b>Paracetamol</b> Tablets 100 or 500 mg Syrup Suppository 300 mg	<u>Adults:</u> 500 mg to 1000 mg every 4-6 hours Maximum dose: 4 g / 24 h	Hepatotoxicity
<b>Acetyl salicylic acid</b> Tablets 300 or 500 mg	<u>Adults:</u> 500 mg to 1000 mg every 4-6 hours Maximum dose: 3 g / 24 h	Gastro-duodenal Ulcers Coagulation difficulties (platelet aggregation)
<b>Step II – Moderate pain</b>		
<b>Codeine 30mg</b> (+Paracetamol 500 mg)	<u>Adults:</u> 30-60 mg every 4-6 hours Maximum dose: 240mg/24h	Constipation Drowsiness Nausea
<b>Tramadol 50 mg (IR)</b> Immediate release <b>Tramadol 100 mg (SR)</b> Sustained release	<u>Adults:</u> 50 to 100 mg every 4-6 hours <u>Adults:</u> 100-200 mg every 12 hours Maximum dose: 400 mg/24h	Vertigo Drowsiness Nausea Vomiting Constipation
<b>Level III – Severe pain</b>		
<b>Morphine</b> Tablets I.R. 5 mg, 10 mg, 20 mg, 30 mg Tablets S.R. 30 mg Vial 10 mg/mL	Usual dosage to start the treatment <b>Oral intake:</b> 0.5-1 mg/kg/day <b>immediate release:</b> 1 tab. every 4hours <b>sustained release:</b> 1 tab. every 12hours <b>Sub-cutaneous :</b> 0,25-0,5mg/kg/day divided into 6 doses per day (every 4 hours) In case of severe malnutrition, or renal or respiratory insufficiency start with minimum dosage <b>Oral intake:</b> 0,25-0,5 mg/kg/day <b>Sub cutaneous:</b> 0,125-0,25 mg/kg/day divided into 6 doses/day No maximum dose	Monitor the respiratory function regularly, particularly at the start of the treatment or if the patient had never taken morphine before.  If these guideliness were complied with there is no risk of respiratory depression. Good liquid intake (hydration) and appropriate diet to prevent constipation (laxatives) Nausea could be controlled with metoclopramide, (taken orally or by injections) or haloperidol.
<b>Oxycodone</b> Sustained release tablets 10 mg and 20 mg	10-20 mg every 12 hours	Better availability than morphine
<b>Fentanyl</b> Transdermic patch 12 ug/hour; 25 ug/hour; 50 ug/hour; 75 ug/hour; 100 ug/hour	1 patch every 72 hours	Patch to be stuck on the skin Effect starts 12 hours after applying

Source: National Pain Management Guideliness, 2007 issued by the MoH

In some cases, additional medications may be given to patients when doses are maximized on analgesics in Step 2 and 3. Table provides some medications that can be given in addition to opioids including codeine, tramadol, and morphine (adjuvant pain medications).

**Table 28: Adjuvant pain medications**

Adjuvant pain medication	Dosage	Indications, Monitoring and side effects
<b>Diclofenac</b> 50 mg	<u>Adults:</u> 50-100 mg/day in 2 intakes	Idem
<b>Ibuprofen</b> 200 mg	Adults: 600-800 mg/day in 3 intakes	Idem
<b>Steroids Prednisolone</b> 5 mg Tablet	<u>Adults:</u> 0,5 - 1 mg/kg/day preferably to be taken as a single dose in the morning	<b>Contraindications</b> Uncontrolled Arterial Hypertension Unstable diabetes Uncontrolled Infections and mycosis Evolutive gastro-duodenal ulcers Severe mental illnesses <b>Useful</b> for their anti inflammatory and anti oedema action. Also a psychostimulant Improves appetite. It is advisable to prescribe effective minimal doses and preferably for short periods (less than 7 days without decreasing progressively)
<b>Dexamethasone</b> vial 4mg/ml	<u>Adults</u> 0.05 to 0.2 mg/kg/day oral intake or intra muscular injection only once a day	
<b>Butylhyoscine</b> Antispasmodic 20 mg vial	<u>Adults:</u> 60 to 120 mg/day divided into 4 - 6 injections	Indicated whenever there is a spasmodic aspect (hepatic, renal or intestinal colics). For example in association with morphine.
<b>Diazepam</b> Myorelaxant Anxiolytic Tab. 5 mg Vial 10 mg	0,1–0,2 mg/kg/day at bedtime or divided into 3 doses per day (oral or anal for children)	<b>Small doses don't cause</b> side effects if taken orally.

National Pain Management Guideliness, 2007 issued by the MoH

### Treatment of neuropathic (neurogenic) pain

Neuropathic pain is expressed as:

- deep pain with nagging burning sensation in a particular part of the body
- sharp and shooting pain often provoked by touch or by movement
- abnormality of the neurological examination : allodynia (pain induced by non-noxious stimuli, e.g. light touch), hyperalgesia (increased response to a noxious stimuli), or hyperpathia (exaggerated responses to painful stimuli, with continuing sensation of pain after the stimulation has ceased).

The usual analgesics are generally little or not effective at all. The usual treatment is based on **tricyclic antidepressants and antiepileptics**

	<b>Dosage</b>	<b>Indications, side effects</b>
<b>Amitryptilin Clomipramine Imipramin Nortryptilin</b>	Adult:15-100 mg /24hours	Antidepressant. Dry mouth, fatigue, vertigo. Analgesic effect after one week of treatment
<b>Carbamezapin</b>	200-800 mg /24 hours	Antiepileptic. Interacts with other medication. Fatigue, vertigo, allergies, hepatic problems. Analgesic effect quicker
<b>Gabapentine</b>	300-2400 mg/24 hours	Antiepileptic. Does not interact with other medication or does not cause hepatic problems. Fatigue, vertigo, peripheral oedema, nausea and vomiting.

National Pain Management Guidelines, 2007 issued by the MoH

Examples:

- Start with, amitryptilin, (clomipramin, imipramin) 10 drop at bedtime as a single dose (1 drop= 1mg)
- To be taken at bedtime due to their sedative effect (amitryptilin).
- Increase dosage progressively in order to avoid side effects (drowsiness, constipation, hypotension-orthostatic, acute urine retention, glaucoma...)

This treatment is effective for pain caused by nerve compression or nerve invasion. If it is insufficient to treat eventual paroxysmic access, you can add antiepileptic (to be taken in the evening):

- diazepam 0,1 to 0,2 mg/kg/day

or

- clonazepam 3 to 5 drops on evening (0,1mg=1drop) and progressively increase the dosage without exceeding 10 to 20 drops/day)

or

- carbamazepin 200 to 600 mg/day

or

- valproic acid 4-10 mg/kg/day,

**16.3 Common Pain Syndromes in PLHIV and Specific Management Recommendations**

**Table 29: Common pain syndromes in PLHIV**

<b>Headaches</b>	<b>Abdominal pain</b>
<ul style="list-style-type: none"> <li>• Infectious Causes</li> </ul>	ALWAYS CHECK IT IS NOT A SURGICAL

<ul style="list-style-type: none"> <li>- Cryptococcal Meningitis</li> <li>- Meningitis (Tuberculosis)</li> <li>- Viral Meningitis (HIV, CMV, Herpes virus)</li> <li>- Toxoplasmosis</li> <li>- Neurosyphilis</li> <li>• Tumor of Lymphoma type</li> <li>• Drug side effect causes <ul style="list-style-type: none"> <li>- ARV: AZT</li> <li>- Anti TB treatment</li> <li>- Treatment for candidosis</li> </ul> </li> <li>• Post-PL headaches</li> <li>• Dehydration</li> <li>• Fever</li> <li>• Stress headaches, migraines</li> </ul>	<p><b>EMERGENCY</b></p> <p><b>Gastro-intestinal</b></p> <ul style="list-style-type: none"> <li>• Infectious: <ul style="list-style-type: none"> <li>- Tuberculosis, Mycobacterium avium complex</li> <li>- CMV</li> <li>- Cryptosporidies</li> <li>- Salmonellosis</li> <li>- Shigellosis</li> </ul> </li> <li>• Tumors: <ul style="list-style-type: none"> <li>- Lymphoma</li> <li>- Kaposi syndrome</li> </ul> </li> <li>• Stress ulcers</li> </ul> <p><b>Hepato-biliary</b></p> <ul style="list-style-type: none"> <li>• Infectious Hepatitis: CMV, mycobacterium avium, tuberculosis</li> <li>• Amoebic abscess</li> <li>• Viral Hepatitis: VHB, VHC</li> <li>• Neoplasia ( Kaposi, LMNH, CHC)</li> <li>• Cholecystitis (CMV, cryptosporidis)</li> </ul> <p><b>Pancreatic</b></p> <ul style="list-style-type: none"> <li>• Infectious (CMV, HIV)</li> <li>• Iatrogenic (ddl, d4T)</li> </ul>
<p><b><u>Peripheral Neuropathies</u></b></p> <ul style="list-style-type: none"> <li>• Viral (HIV,CMV, herpes...)</li> <li>• Medication (d4T,ddl,INH, metronidazole)</li> <li>• Lymphomatous Infiltration</li> <li>• Meningomyeloradiculopathies (CMV,VZV)</li> <li>• Degenerative illness</li> </ul>	<p><b><u>Thoracic Pain</u></b></p> <ul style="list-style-type: none"> <li>• Pneumopathy (bacterial, tuberculosis, pneumocystis, mycosis)</li> <li>• Mediastinal Lesions</li> <li>• Kaposi Syndrome</li> <li>• Lymphoma</li> </ul>
<p><b><u>Oropharyngeal pain</u></b></p> <ul style="list-style-type: none"> <li>• Fungal: candidosis</li> <li>• Viral: herpes, CMV</li> <li>• Bacterial: stomatitis, dental abscess, gingivitis</li> <li>• Neoplasia: Kaposi syndrome</li> <li>• Idiopathic mouth ulcers</li> <li>• Tonsillitis and pharyngitis</li> </ul>	<p><b><u>Cutaneous pain</u></b></p> <ul style="list-style-type: none"> <li>• Herpes Infection</li> <li>• Herpes zoster</li> <li>• Bacterial infection</li> <li>• Lyell syndrome</li> <li>• Bed/pressure sores</li> </ul>
<p><b><u>Oesophageal pain</u></b></p> <ul style="list-style-type: none"> <li>• Oesophageal Candidosis</li> <li>• Viral: Herpes, CMV, HIV</li> <li>• Iatrogenic</li> <li>• Oesophagitis</li> <li>• Idiopathic oesophageal ulcerations</li> </ul>	<p><b><u>Rheumatic Pain</u></b></p> <ul style="list-style-type: none"> <li>• Muscular pain <ul style="list-style-type: none"> <li>- Viral: HIV</li> <li>- Iatrogenic: AZT</li> <li>- Infectious</li> <li>- Malnutrition, Atrophy</li> </ul> </li> <li>• Joint pain <ul style="list-style-type: none"> <li>- Reiter syndrome</li> <li>- Septic arthritis</li> </ul> </li> </ul>
<p><b><u>Rectal</u></b></p> <ul style="list-style-type: none"> <li>• Infectious ulcers (CMV, herpes)</li> <li>• Tumoral Ulcerations (Kaposi or Lymphoma)</li> <li>• Ulcerations linked to HIV</li> <li>• Haemorrhagic rectal inflammation</li> </ul>	
<p><b><u>Iatrogenic pain</u></b></p> <ul style="list-style-type: none"> <li>• Injection</li> <li>• Invasive interventions</li> </ul>	



<ul style="list-style-type: none"> <li>• Medical care</li> </ul>	<ul style="list-style-type: none"> <li>- HIV</li> <li>- Iatrogenic : pyrazinamide</li> </ul>
<b><u>Mental pain</u></b> <ul style="list-style-type: none"> <li>• Nervousness</li> <li>• Anxiety</li> <li>• Psycho-social problems</li> </ul>	<b><u>General Pain</u></b> <ul style="list-style-type: none"> <li>• Fever</li> <li>• Bed ridden</li> <li>• Non-specific etiologies</li> </ul>

### Specific Pain Management of HIV Conditions

All patients with HIV should receive analgesic level I, II, or III depending on the pain intensity evaluated by the patient. In addition, there are additional measures based on the Etiology of pain that can reduce pain as well (see Table 30)

**Table 30: Pain Treatment for Specific HIV Related Conditions**

Condition	Etiological Treatment
Cryptococcal Meningitis/Encephalitis	Regular depletive lumbar punctures to reduce ICP,
Tuberculosis Meningitis	prednisolone 60 mg 2 x daily or dexamethasone 4mg 4 x daily with taper extending up to six weeks*
Syphilitic Meningitis	Prednisolone 0.5 mg/kg/24 hours
Bacterial Meningitis	Tramadol 50-100 mg every 6 hours (maximum 400mg/24hr)
Cerebral Toxoplasmosis	Prednisolone 40 mg 4 x daily or dexamethasone 4 mg 4x daily until symptoms improve*
Iatrogenic Polyneuropathies	Vitamin B1 50-100 mg/day, Vitamin B6 100 mg /day, Tricyclic antidepressant 15-100 mg/day
Painful Polyneuropathies	Tricyclic antidepressant 15-100 mg/day
Post-zoster mononeuritis	Tricyclic antidepressant 15-100 mg/day
Iatrogenic Myopathy	Terazepam 50 mg, start with ½ tablet in evening and increase dose ½ tablet each time to effect. Alternative is diazepam 10 mg 3 x daily
Abdominal Pain (Colic or Spasmodic)	Buthyoscine 1 tablet 3 x daily
Gastric Ulcer	Aluminum hydroxide 1 tablet 3 x daily, Cimetidine 200 mg/24 hr or proton pump inhibitor
Joint Pain	Non-steroidal anti-inflammatories
Idiopathic ulcerations (e.g. herpes)	Prednisolone 0.5-1 mg/kg/24 hr
Iatrogenic Ulcerations	Xylocaine gel 2-3 times/24 hr
Herpes stomatitis	Xylocaine gel 2-3 times/24hr
Herpes esophagitis	Cimetidine 200 mg/24hr or proton pump inhibitor
Anorectal Herpes	Xylocaine gel 2-3 times/ 24hr

*Primary Source: National Pain Management Guidelines, 2007 issued by the MoH*

*\* Additional sources, see Guidelines to the Clinical Care of HIV/AIDS in Resource Poor Settings, MSF, 2006. HIV/TB Clinical Manual, WHO, 2004.*

## **17. Palliative Care**

### **17.1 Understanding Palliative Care**

Palliative care is total care of patients whose disease is not responsive to treatment. It is an approach that improves the quality of life of patients facing the end-of-life due to an incurable condition by assessing and treating pain, managing symptoms, and providing psychosocial and spiritual support. Specifically, palliative care in HIV infection:

- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process;
- intends neither to hasten nor to postpone death
- aims to “add life to days left” and not “days to life” by optimizing the quality of life through active participation of providers and family

The main components of palliative care include the following:

- pain management
- symptom management
- nutritional support
- psychosocial support
- spiritual support
- end-of-life care
- bereavement counseling.

These components of palliative care extend beyond family and physicians. They rely on collaboration between all participants of the CoC framework including home-based community services for those patients who die at home

### **17.2 Managing symptoms in the dying patient**

*The remainder of this section focuses on symptom management by providers and is based on Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers issued by WHO, 2004 (WHO guidelines, 2004) and Clinical care for HIV/AIDS in Resource Poor Settings, MSF, 2006 (MSF guidelines, 2006). Recommended doses from both sources are highlighted with each recommendation to alleviate symptoms at the end-of-life.*

To begin, all providers should know the disclosure status of the patient when interacting with family members. In many cases, family members do not know the dying patients HIV status. All providers and family members should also follow basic precautions (cover existing wounds, wear gloves, and wash hands) when caring for patients dying with HIV.

Patients in pain should receive analgesic in stepwise fashion as highlighted in section 16. The specific management of HIV related conditions can also be applied in caring for patients during the palliative care stage. If possible, administer all medicines by mouth or rectally.

Injections are not preferred as most dying patients have limited subcutaneous tissues and injections can be painful.

### **Cough**

Healthcare and home-based community workers and family members have to be aware of the possibility of TB or another infection whenever a patient is coughing and should transfer the patient to a designated TB ward. Always ask the patient to cover his/her mouth while coughing. Be sure that expectorations can be collected in a small container or in a tissue, to avoid the airborne transmission of certain pathogens. For patients with diagnosed active TB, they should also continue on their previous TB treatment to limit spread of TB to family and providers during the palliative care stages. Moreover, all caregivers should wear appropriate airborne protect masks when caring for dying patients with TB. See National SOP 3 I's Guideliness.

Simple measures should be attempted first including:

- Keep coughing patient in a semi-sitting position as much as possible
- Open window to allow in fresh air
- Ask a family member to fan with a newspaper or clean cloth
- Give frequent sips of water
- Apply soothing remedies such as honey, lemon, eucalyptus oil, or tiger balm

If simple measures fail, administer codeine 15-60 mg orally 4 x daily to suppress the cough (MSF guidelines, 2006) or give 2.5 mg of morphine 4 x daily (WHO guidelines, 2004). If the patient is already on morphine, increase the morphine dose by another 25% (WHO guidelines, 2004).

### **Secretions**

Secretions cause discomfort to patients as well as place and additional burden on caregivers. The following steps can limit discomfort with secretions:

- Maintain adequate hydration
- Keep mucous membranes moist
- Increase humidity in the room
- Place the patient on his or her side
- Apply soothing remedies such as honey, lemon, eucalyptus oil, or tiger balm
- Massage or gently clap on back to move sputum

If conservative measures do not help, administer hyoscine 10 mg 3 x daily (WHO guidelines, 2004) or if no alternative, give atropine: 0.4-0.6 mg SC, IM, IV 6-8 x daily (MSF guidelines)

### **Hiccups**

The following steps can temporarily reduce hiccups:

- teaspoons of sugar
- drink cold water
- Rub a cloth on inside of top of mouth where it is soft
- Hold breath or breath into a paper bag

If above fail, administer metoclopramide 10 mg tablets 3 x daily (WHO guidelines, 2004)

### **Dyspnea or respiratory distress**

Dyspnea or respiratory distress can create a significant amount of anxiety in patients. Conservative measures to improve comfort include, reduce environmental irritants such as smoke, elevating the head of bed, and using fans to keep air moving.

The use of oxygen is not essential to reduce the sense of being short of breath unless patients appear cyanotic. In many cases, oxygen masks increase anxiety in patients. Morphine 2.5-15 mg orally every hour is very effective at reducing air hunger (MSF guidelines). For associated anxiety use diazepam 5-10 mg orally 3-4 x daily (MSF guidelines). In patients with lung disease from chronic smoking, a short course of prednisone 40 mg daily may reduce airway obstruction (MSF guidelines).

### **Obstruction (stridor)**

Often caused by compression of the trachea or the main bronchi by lymph nodes or mass. Treat with stridor with prednisone 10-60 mg daily orally or dexamethasone 1-8 mg IV or orally 4 x daily (MSF guidelines, 2006)

### **Pleural effusion or Pneumothorax**

For large pleural effusions or pneumothorax perform therapeutic thoracentesis to improve ventilation. If fluid or air reaccumulates, consider repeat thoracentesis or chest tube placement.

### **Pulmonary edema**

Pulmonary edema is usually caused by heart failure. Management is conservative with elevation of the head of the bed, minimal salt intake, restriction of fluids as much as possible. Morphine given 2.5 - 5 mg orally or subcutaneously will reduce pulmonary edema. If symptoms do not improve, patients may respond to diuretics such as furosemide 20-40 mg orally as needed (WHO guidelines, 2004).

### **Mouth discomfort**

- Use baking soda mouth wash every hour: 1 teaspoon baking soda, 1 teaspoon salt, 250 cc lukewarm water.
- Mix 2 tablets of aspirin in water and rinse mouth 4 x daily
- Apply mouthwash with sponge swabs
- Avoid commercial mouthwashes
- Chew on sugarless gum or candies
- Take frequent sips of diluted fruit juices
- Xylocaine gel 2-3 times a day applied to sores or ulcers will alleviate pain
- For aphthous ulcers crush one 5 mg prednisone tablet and apply a few grains
- Treat oral herpes or candida infections

### **Abdominal pain**

Abdominal pain in dying patients is usually colicky or crampy in nature. Patients should not highly spiced foods, sweet or carbonated drinks. Patients may respond to antispasmodics or antimotility medications such as hyoscine butylbromide 10-20 mg 3x daily and Loperimide 2-4 mg as needed (maximum 16 mg per day). If no relief, administer codeine 30 mg every four hours (WHO guidelines, 2004). Some patients may have pain from organomegaly or abdominal masses patients may benefit from steroids - prednisone 10-80 mg daily or oral dexamethasone 1-8 mg 4 x daily (MSF guidelines, 2006).

## **Diarrhea**

Diarrhea is distressing for patients and family. All caregivers should maintain infectious precautions when changing bed lines and clothes. Patients should:

- have ready access to a bedside commode, bucket, or toilet and receive assistance in cleaning
- maintain adequate hydration is the most important aspect of care with uncontrolled diarrhea
- continue eating in small amounts

There are a few drugs (MSF guidelines, 2006 and WHO guidelines, 2004), which can be found at the district or referral hospital that can reduce symptoms:

- Aluminium hydroxide tablets 4 x daily.
- Loperamide 4 mg PO first dose followed by 2 mg-4 mg after each unformed stool (max 16 mg daily).
- Codeine 10-60 mg 3-6 x daily. Maximum dose = 200-300 mg in a day.
- Morphine 2.5-5 mg orally every 4 hours

## **Bed Sores**

Prevent bedsores by frequently rotation the patient at least 3-4 times throughout the day. For small sores, clean the wound gently with normal saline and keep it as dry as possible. Avoid moist or wet bed sheets. For larger sores, apply zinc oxide ointment around the wound and iodine in the wound and cover. Treat associated pain using pain management steps. In case of secondary infection, use antibiotics. In case of malodorous wounds, sprinkle crushed metronidazole tablets can be put on the lesions (WHO guidelines, 2004).

## **Last few hours of life**

Providers should focus on treating the sense of shortness of breath, clearing or reducing secretions, and decreasing anxiety and with appropriate doses of morphine. Oxygen is of minimal benefit and may prolong suffering. There are few other interventions at this time. Providers and family should remain at the bedside to support the patient.

## Annexes

### Annex 1: WHO Tables

#### WHO staging system adults and adolescents

<b>Clinical stage 1</b>
Asymptomatic Persistent generalized lymphadenopathy
<b>Clinical stage 2</b>
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
<b>Clinical stage 3</b>
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 hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 10 <sup>9</sup> /l) and/or chronic thrombocytopenia (below 50 x 10 <sup>9</sup> /l)
<b>Clinical stage 4</b>
HIV wasting syndrome Pneumocystis jirovecii pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or ano-rectal 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 nontuberculous mycobacteria infection Progressive multifocal leukoencephalopathy Chronic cryptococcosis Chronic isosporiasis Disseminated mycosis (histoplasmosis, coccidiomycosis)

Recurrent septicaemia (including nontyphoidal Salmonella)  
 Lymphoma (cerebral or B cell non-Hodgkin)  
 Invasive cervical carcinoma  
 Atypical disseminated leishmaniasis  
 Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

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

### WHO Diagnostic Criteria for HIV-related Clinical Events

Clinical event	Clinical diagnosis	Definitive diagnosis
<b>Clinical stage 1</b>		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm, in two or more noncontiguous sites (excluding inguinal), in absence of known cause and persisting for 3 months or longer	Histology
<b>Clinical stage 2</b>		
Moderate unexplained weight loss (under 10% of body weight)	Reported unexplained weight loss. In pregnancy, failure to gain weight	Documented weight loss (under 10% of body weight)
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last 6 months)	Symptoms complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillopharyngitis without features of viral infection (e.g. cough)	Laboratory studies if available, e.g. culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply does not cross midline	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment	Clinical diagnosis
Recurrent oral ulcerations (two or more episodes in last 6 months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis

<b>Clinical event</b>	<b>Clinical diagnosis</b>	<b>Definitive diagnosis</b>
Papular pruritic eruption	Papular pruritic lesions, often with marked postinflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axilla, upper trunk and groin)	Clinical diagnosis
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of nail from nail bed) of the fingernails (white discolouration, especially involving proximal part of nail plate, with thickening and separation of nail from nail bed)	Fungal culture of nail / nail plate material
<b>Clinical stage 3</b>		
Severe unexplained weight loss (more than 10% of body weight)	Reported unexplained weight loss (over 10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index below 18.5. In pregnancy, weight loss may be masked.	Documented loss of more than 10% of body weight
Unexplained chronic diarrhoea for longer than 1 month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than 1 month)	Reports of fever or night sweats for more than 1 month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever exceeding 37.6 oC with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection
Oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off	Clinical diagnosis



	pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis
Pulmonary TB	Chronic symptoms (lasting at least 2 to 3 weeks): cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, plus EITHER positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease.	Isolation of <i>M. tuberculosis</i> on sputum culture or histology of lung biopsy (together with compatible symptoms)
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	Clinical diagnosis
Unexplained anaemia (below 8g/dl), neutropenia (below $0.5 \times 10^9/l$ ) and/or chronic (more than 1 month) thrombocytopenia (under $50 \times 10^9/l$ )	No presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or other relevant guidelines.
<b>Clinical stage 4</b>		
HIV wasting syndrome	Reported unexplained	Documented weight loss

	<p>weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5, plus EITHER unexplained chronic diarrhea (loose or watery stools three or more times daily) reported for longer than 1 month OR reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarious areas.</p>	<p>(over 10% of body weight) plus two or more unformed stools negative for pathogens OR documented temperature exceeding 37.6 oC with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR</p>
Pneumocystis pneumonia	<p>Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; AND CXR evidence of diffuse bilateral interstitial infiltrates, AND no evidence of bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry.</p>	<p>Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue</p>
Recurrent bacterial pneumonia (this episode plus one or more episodes in last 6 months)	<p>Current episode plus one or more episodes in last 6 months. Acute onset (under 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.</p>	<p>Positive culture or antigen test of a compatible organism</p>
Chronic herpes simplex virus (HSV ) infection (orolabial, genital or anorectal) of more than 1 month, or visceral at any site or any duration	<p>Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis.</p>	<p>Positive culture or DNA (by PCR) of HSV or compatible cytology/histology</p>
Oesophageal candidiasis	<p>Recent onset of retrosternal pain or difficulty in</p>	<p>Macroscopic appearance at endoscopy or bronchoscopy,</p>

	swallowing (food and fluids) together with oral Candidiasis	or by microscopy/histology
Extrapulmonary TB	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis. Miliary TB: diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cervical lymph node M. tuberculosis infection is usually considered a less severe form of extrapulmonary tuberculosis.	M. tuberculosis isolation or compatible histology from appropriate site, together with compatible symptoms/ signs (if culture/histology is from respiratory specimen there must be other evidence of extrapulmonary disease)
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology
Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single/multiple intracranial mass lesion on neuroimaging (CT or MRI)

HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition, other than HIV infection, which might explain the findings	Diagnosis of exclusion, and, if available, neuroimaging (CT or MRI)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of <i>Cryptococcus neoformans</i> from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood

## Grading of Clinical and Laboratory Toxicity

Estimating severity grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially lifethreatening Grade 4
Clinical adverse event NOT identified elsewhere in the table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, persistent disability or death
Haemoglobin	8.0–9.4 g/dl OR 80–94 g/l OR 4.93–5.83 mmol/l	7.0–7.9 g/dl OR 70–79 g/l OR 4.31–4.92 mmol/l	6.5–6.9 g/dl OR 65–69 g/l OR 4.03–4.30 mmol/l	<6.5 g/dl OR <65 g/l OR <4.03 mmol/l
Absolute neutrophil count	1000–1500/mm <sup>3</sup> OR 1.0–1.5/G/l*	750–999/mm <sup>3</sup> OR 0.75–0.99/G/l*	500–749/mm <sup>3</sup> OR 0.5– 0.749/G/l*	<500/mm <sup>3</sup> OR <0.5/G/l*
Platelets	75000 -99000/mm <sup>3</sup> OR 75–99/G/l*	50000–74999/mm <sup>3</sup> OR 50–74.9/G/l*	20000–49999/ mm <sup>3</sup> OR 20–49.9/G/l*	<20000/mm <sup>3</sup> OR <20/G/l*

<b>Chemistries</b>	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>		<b>Severe Grade 3</b>	<b>Potentially lifethreatening Grade 4</b>
Hyperbilirubinaemia	>1.0–1.5 x ULN	>1.5–2.5 x ULN		>2.5–5 x ULN	>5 x ULN
Glucose (fasting)	110–125 mg/dl	126–250 mg/dl		251–500mg/dl	>500 mg/dl
Hypoglycaemia	55–64 mg/dl OR 3.01–3.55 mmol/l	40–54 mg/dl OR 2.19–3.00 mmol/l		30–39 mg/dl OR 1.67–2.18 mmol/l	<30 mg/dl OR <1.67 mmol/l
Hyperglycaemia (nonfasting and no prior diabetes)	116–160 mg/dl OR 6.44–8.90 mmol/l	161–250 mg/dl OR 8.91–13.88 mmol/l		251–500 mg/dl OR 13.89–27.76 mmol/l	>500 mg/dl OR >27.76 mmol/l
Triglycerides	–	400–750 mg/dl OR 4.52–8.47 mmol/l		751–1200 mg/dl OR 8.48–13.55 mmol/l	>1200 mg/dl OR >13.55 mmol/l
Creatinine	>1.0–1.5 x ULN	>1.5–3.0 x ULN		>3.0–6.0 x ULN	>6.0 x ULN
AST (SGOT)	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN		>10.0 x ULN
ALT (AST)	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN		>10.0 x ULN
GGT	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN		>10.0 x ULN
Alkaline phos.	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN		>10.0 x ULN
Bilirubin	1.1–1.5 X ULN	1.6–2.5 x ULN	2.6–5.0 x ULN		>5 x ULN
Amylase	>1.0–1.5 x ULN	>1.5–2.0 x ULN	>2.0–5.0 x ULN		>5.0 x ULN
Pancreatic amylase	>1.0–1.5 x ULN	>1.5–2.0 x ULN	>2.0–5.0 x ULN		>5.0 x ULN
Lipase	>1.0–1.5 x ULN	>1.5–2.0 x ULN	>2.0–5.0 x ULN		>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences		Increased lactate with pH <7.3 with life-threatening consequences
<b>Gastrointestinal</b>	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>	<b>Severe Grade 3</b>	<b>Potentially lifethreatening Grade 4</b>	
Nausea	Mild OR transient; reasonable intake maintained	Moderate discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalization required	

Vomiting	Mild OR transient; 2–3 episodes per day OR mild vomiting lasting <1 week	Moderate OR persistent; 4–5 episodes per day OR vomiting lasting ≥1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR intravenous Rx required	Hypotensive shock OR hospitalization for intravenous Rx required
Diarrhoea	Mild OR transient; 3–4 loose stools per day OR mild diarrhoea lasting <1 week	Moderate OR persistent; 5–7 loose stools per day OR diarrhoea lasting ≥1 week	Bloody diarrhoea OR orthostatic hypotension OR >7 loose stools/day OR intravenous Rx required	Hypotensive shock OR hospitalization required

<b>Respiratory</b>	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>	<b>Severe Grade 3</b>	<b>Potentially lifethreatening Grade 4</b>
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O <sub>2</sub> therapy
<b>Urinalysis</b>	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>	<b>Severe Grade 3</b>	<b>Potentially lifethreatening Grade 4</b>
Proteinuria				
Spot urine	1+	2+ or 3+	4+	Nephrotic syndrome
24-hour urine	200 mg to 1 g loss/day OR <0.3% OR <3 g/l	1 g to 2 g loss/day OR 0.3% to 1.0% OR 3 g to 10g/l	2 g to 3.5 g loss/day OR >1.0% OR >10 g/l	Nephrotic syndrome OR >3.5 g loss/day
Gross haematuria	Microscopic only	Gross, no clots	Gross, no clots	Obstructive
<b>Miscellaneous</b>	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>	<b>Severe Grade 3</b>	<b>Potentially lifethreatening Grade 4</b>
Fever (oral, >12 hours)	37.7–38.5 °C OR 100.0–101.5 °F	38.6–39.5 °C OR 101.6–102.9 °F	39.6–40.5 °C OR 103–105 °F	>40.5 °C OR >105 °F for L12
Headache	Mild; no Rx required	Moderate OR non-narcotic analgesia Rx	Severe OR responds to initial narcotic Rx	Intractable
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria, angioedema	Anaphylaxis
Rash hypersensitivity	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE OF: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25–50%	Normal activity reduced by >50% cannot work	Unable to care for self

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, version 1.0 December 20 04, clarification August 20 09.

NOTE: This clarification includes the addition of Grade 5 toxicity, which is death.

**For abnormalities not found elsewhere in the toxicity table, use the information on Estimating severity grade in the first column**



**Annex 2: Example Flow sheet and Protocol for Initial Treatment of Cryptococcal Meningitis**

**AMPHOTERICIN B PROTOCOL AND RELAY WITH FLUCONAZOLE**

Source: Service Maladies Infectieuses, Hôpital P.B.N Sihanouk, 21/02/2006

**Name :** \_\_\_\_\_ **Surname :** \_\_\_\_\_ **Age :** \_\_\_\_\_ **Bed :** \_\_\_\_\_ **Weight :** \_\_\_\_\_

**INITIAL TREATMENT :** dose = 0,7 mg/kg for 14 days

*(Preparation of Amphotericin B : 50mg vial, add 10ml of sterile water, then 1ml = 5mg, take the prescribed dose and dilute it in 500 ml G5%, to be injected protected from the light (dark paper) in 4 hours ie 40 drop/mn*

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17
Dose																	
Date																	
Biological tests*	<input type="checkbox"/>													<input type="checkbox"/>			
explorative LP* (EX)	<input type="checkbox"/>													<input type="checkbox"/>			
Emergent LP* (Number, vol CSF evacuated)																	

∓ CBC, potassium, Creatinin

\* Explorative LP (EX) done on the 1st and 14th day for diagnostic and monitoring with cytology, bacteriology, Indian Ink and if available cryptococcal Ag and culture.

Emergent LP (EM) will be done regularly according to the patient clinical status and could be done several time during the day (until 3-4 /d) when patients still present severe signs of Intra- Cranial Hypertension (ICHT) (severe headache).

**CONTINUOUS TREATMENT : Fluconazole 400mg/d (2tb de 200mg) during 8 weeks.**

**Date of start :** ..../..../.... **Date of end :** ..../..../....

**SECONDARY PROPHYLAXIS: Fluconazole 200mg /d until CD4 > 100 mm<sup>3</sup> for 6 months.**

**Date of start :** ..../..../.... **Date of end :** ..../..../.... **CD4 :** ...../m

## TREATMENT OF CRYPTOCOCCAL NEURO-MENINGITIS

Source: Service Maladies Infectieuses, Hôpital P.B.N Sihanouk, 21/02/2006

### A. INITIAL TREATMENT :

AMPHOTERICIN B: 0.7 mg/kg/day in a 4h-perfusion in glucose 5 % during at least 2 weeks

#### I. Side effects :

- a. During the perfusion : shiver, fever, Headache, diffuse pain, nausea, vomiting, anaphylactic shock, thrombophlebitis at the point of injection, dizziness, paresthesia, convulsions
- b. Long term : monitor renal function, potassium, CBC (anemia, thrombopenia), venous toxicity.

#### II. Associated treatment :

- a. Paracetamol 1 g 1 hour before the perfusion
- b. Hydrocortisone Hemisuccinate 50 mg IVD (1/2 ampoule) at the beginning of every perfusion.
- c. +/- Promethazine 25mg PO or IVD
- d. Slow-K (prevention of decreased potassium) : 600 mg x 2 /d
- e. Good hydration : saline serum, SRO
- f. In case of convulsion : Valium 10 mg IV slow, to be repeated one time if the crisis did not resolve after 5 mn
- g. DO NOT GIVE MORPHINE FOR THE PAIN (headache) SINCE LUMBAR PUNCTURE IS THE MOST EFFECTIVE TREATMENT +++

#### III. Nursing and monitoring:

- a. pulse, Blood pressure, tp every 30 minutes during the first 2 hours, then every hour.
- b. In case of high fever and shivers, inject 50 mg hydrocortisone hemisuccinate IVD.
- c. If BP < 7 , stop the perfusion and call the doctor.
- d. Indicate on the monitoring form the dose injected, time of initiation and end, hydrocortisone hemisuccinate injection, pulse, BP, temperature...

#### IV. Follow-up :

- a. Biological tests at D8 : CBC, Potassium, Sodium, glucose, creatinine then every week.
- b. Control PL at D14 (Indian Ink + culture) then every week culture still positive
- c. At the end of treatment : CBC, Potassium, Sodium, creatinine.

**V. Dose adaptation :** In case of LP still positive at D14 : Increase AMPHO B at 1 mg/kg/day

#### REPEATED EMERGENT LUMBAR PUNCTURE +++

- A 18G spinal gauge needle can be used
- Notice the opening pressure (OP) at each LP
- If OP > 25 cm of water : evacuate 30-35 ml of CSF fluid
- Repeat it every day until the OP < 20 cm or is <50% of the initial OP
- Repeat it during the day if headaches increase again (Multi-daily LP)

### Annex 3: Examples of HIV Associated Skin Conditions

EXAMPLES OF ITCHY RASHES WITH HIV	
Seborrheic Dermatitis ( <a href="http://www.aidsimages.ch">www.aidsimages.ch</a> )	
Papular Pruritic Eruption (PPE) ( <a href="http://bestpractic.BMJ.com">bestpractic.BMJ.com</a> )	
HIV Associated Eosinophilic (Sterile) Folliculitis with evidence of lichenification from chronic itching ( <a href="http://www.aidsimages.ch">www.aidsimages.ch</a> )	

HIV Associated  
Eosinophilic (Sterile)  
Folliculitis with Pustules and  
Excoriations



Nodular Prurigo from  
chronic Eosinophilic  
Folliculitis



Scabies ([www.scabiesanswers.com](http://www.scabiesanswers.com))



**EXAMPLES OF MACULOPAPULAR RASHES WITH HIV**

Macculopapular Rash of Soles of Feet with Secondary Syphilis ([www.sdcptc.edu](http://www.sdcptc.edu))



Maculopapular Rash with Primary HIV Syndrome Rash ([www.skinside.com](http://www.skinside.com))



Maculopapular  
Rash with Efavarinenz  
([www.aidsimages.ch](http://www.aidsimages.ch))



**EXAMPLES HERPES SIMPLEX 1 AND 2 RASHES**

Chronic Peri-oral Herpes  
([www.adisimages.ch](http://www.adisimages.ch))






Genital Herpes Sores  
([thetosupplment.com](http://thetosupplment.com))



Chronic Herpes  
Simplex Ulcerations  
([www.aids-images.ch](http://www.aids-images.ch))



<p>Disseminated Herpes Simplex (www.aidsimages.ch)</p>		
<p><b>EXAMPLE HERPES ZOSTER (REACTIVATION OF VARICELLA)</b></p>		
<p>Herpes Zoster (www.aidsimages.ch)</p>		
<p>Herpes Zoster -multiple dermatomes (www.aidsimages.ch)</p>		
<p><b>EXAMPLES OF UMBILICATED LESIONS ASSOCIATED WITH HIV</b></p>		
<p>Molluscum and HIV (www.bestpractice.BMJ.com)</p>		

Cryptococcus Skin Lesions of Various Sizes



Umbilicated Papules from *Penicillium Marneffeii* ([www.doctorfungus.org](http://www.doctorfungus.org))





Umbilicated Papules from  
Penicillium Marneffeii  
(www.aidsimages.com)



Histoplasmosis, Molluscum  
Contagiosum,  
Cryptococcosis, and  
Penicillium Marneffeii  
(www.aidsimages.ch)



Credits: left: P. Lohy, right: top: L. Trellu, bottom: V. Srisanthana www.aids-images.ch

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