IV CONSTITUTIONAL GOVERNMENT
MINISTERIO DA SAUDE

Opportunistic Infections and Antiretroviral Therapy Guidelines for HIV- Infected Adults, Adolescents, Children and Infants in Timor-Leste

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Acknowledgement

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References

The content of this guideline is in line with the latest recommendations of WHO, 2010.

This guideline incorporates the national recommendations of Timor-Leste for TB-HIV co-infection medical management, Malaria and HIV co-infection medical management.

The author based the edition of this guideline on the Toolkit of Médecins Sans Frontières about the recommendations for the integration of HIV Care and Treatment for adults and children. The guideline has been developed in the best feasibility of HIV care and treatment implementation in the current context of health services in Timor-Leste.

Acronyms

ABC	Abacavir
ACT	Artemisinin-based combination therapy
AFB	Acid fast bacilla (TB smear)
AIDS	Aquired Immuno-Deficiency Syndrome
ART	Anti-retroviral treatment
ARV	Anti-retroviral drug
AZT	Zidovudine
BID	twice daily
BMI	Body Mass Index
CDC	Communicable Diseases Control
CHC	Community Health Center
CTX	Co-trimoxazole
3TC	Lamivudine
D4T	Stavudine
DDI	Didanosine
DST	Drug sensitivity test
EFV	Efavirenz
FDC	Fixed dose combination
Hb	Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HNGV	Hospital National Guido Valadarès
IM	Intra-muscular
INH	Isoniazide
IPT	Isoniazide Preventive Therapy
IRIS	Immune reconstitution inflammatory syndrome
IV	Intra-veinous
LDH	Lactate Deshydrogenase
LFT	Liver Function Tests
LLIN	Long-lasting insecticidal net
LPV/r	Lopinavir/ritonavir
MCH	Mother and Child Health
MoH	Ministry of Health
MUAC	Mid-Upper Arm Circumference
NGO	Non-governmental organization
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OD	once daily

OI	Opportunistic infections
PCP	Pneumocyctis Carinii (Jirovici) Pneumonia
PHA	People living with HIV and AIDS
PI	Protease Inhibitor
PLWHA	People living with HIV and AIDS
PMTCT	Prevention Mother to Child transmission
RDT	Rapid diagnostic test
STI	Sexually Transmitted Infections
TB	Tuberculosis
TDF	Tenofovir
TL	Timor-Leste
VCT	Voluntary Counseling and Testing
VCCT	Voluntary Consent Counseling and Testing
VL	Viral Load
WBC	White Blood Cells
WHO	World Health Organization
WFP	World Food Program
ZDV	Zidovudine

Chapter 1: INTRODUCTION

1.1 International HIV/AIDS situation

By the end of 2009, there were an estimated 33.3 million people living with HIV worldwide and 5.25 million people had access to antiretroviral therapy in low- and middle-income countries, with 1.2 million people receiving ART in 2009 alone. It is estimated that approximately 3 million lives have been saved due to ART. However, only one third of people in need are receiving treatment. Efforts are taking place on using new approaches, such as Treatment 2.0, an approach launched by UNAIDS in 2010 to simplify provision and scale up of ART. Increasing access to treatment globally has resulted in a decrease in AIDS deaths by 19%. In order for a further decline in death among those who are HIV positive, new approaches that bring down treatment costs, simplify regimens, reduce the burden on already burdened health systems and improve quality of life for those infected and affected by HIV, are essential.

Sexual transmission accounts for approximately 80% of HIV transmission. New research has found that using treatment as prevention can reduce the number of new HIV infections significantly. Starting ART early with proper adherence has shown to decrease transmission in discordant couples by 96%. However, this must be used in combination with other HIV prevention options such as consistent condom use, male circumcision and few partners.

Improvement in the quality of life for those who are HIV positive includes universal access to ART and OI treatment. This is possible with an early government response, a sustainable resource flow, planning and coordination in procurement and among health workers, a strong and effective participation of civil society, strengthening prevention and treatment services and advocacy of human rights. Increased access to treatment can make a significant impact on HIV-related mortality and enable people to lead healthy lives.

1.2 History of HIV/AIDS in Timor-Leste

In 2010, Timor-Leste is still considered a low HIV prevalence country. During the last HIV sentinel surveillance, the prevalence was estimated at 0,68% among pregnant women, 2.76% among the commercial sex workers and 1.33% among the MSM group. The Ministry of Health of Timor-Leste is actively participating at maintaining the country at a low HIV prevalence rate by reinforcing its CDC department with the financial and technical support of the Global Fund for Tuberculosis, HIV and Malaria. The HIV/AIDS Program received a five - year

grant from Global Fund round 9, started in May 2007, which helps to reinforce the access to ART 1st line in the country. The HIV/AIDS program has been accepted for the global fund round 10, starting from January 2012 and will help strengthening the program for its 2nd line and HIV monitoring.

Antiretroviral treatment (ART) was initiated in Timor-Leste through the private sector (Bairo Pite Clinic) in 2002, using donated antiretroviral (ARV) drugs. The public sector followed through the National Hospital. In 2005 Timor-Leste Government is being supported by the Government of Brazil, for first line ARV drugs produced in Brazil, technical assistance and training of health workers. Since 2007, the country received its antiretroviral through the Global Fund support.

HIV treatment and services, including ARV and OI treatment, will be provided free of charge for all Timorese citizens through the government run health facilities. In the Constitution of the Democratic Republic of Timor-Leste, approved on the 22nd of March 2002, it is stated that the citizens of Timor-Leste have the following as a fundamental right, duty, freedom and guarantee in regards to health:

> 1. Everyone has the right to health and medical care, and the duty to protect and promote them.
> 2. The State shall promote the establishment of a national health service that is universal and general. The national health service shall be free of charge in accordance with the possibilities of the State and in conformity with the law.
> 3. The national health service shall have, as much as possible, a decentralised participatory management.

1.3 Objectives of the guideline

This guideline aims to provide guidance and support to health care workers of Timor-Leste involved in the HIV/AIDS clinical management, including ART and opportunistic infections (OI).

It has been developed in consideration of the present epidemiological situation of HIV infection in Timor-Leste and demand and sustainability for ART in the country.

The current revision is taking into account the latest recommendations of WHO, issued in December 2010 for adults and adolescents and for children antiretroviral therapy[1],[2].

[1] Antiretroviral therapy for HIV infection in adults and adolescents, Recommendations for a public health approach, 2010 revision, World Health Organization
[2] Antiretroviral therapy for HIV infection in infants and children: towards universal access, Recommendations for a public health approach, 2010 revision, World Health Organization

The objectives of this guideline are:

1. To enhance quality of comprehensive HIV/AIDS care in Timor Leste
2. To provide a standard approach for the use of ART
3. To be a source of reference for healthcare providers who are involved in HIV/AIDS medical management
4. To be a source of references for partners of the national HIV/AIDS control program
5. To be a source of references for the National AIDS Commission and people living with HIV/AIDS (PLHA) that will help in training and advocacy at the local level

1.4 Objectives of antiretroviral therapy

The goals of ART– in priority order – are at an individual level:

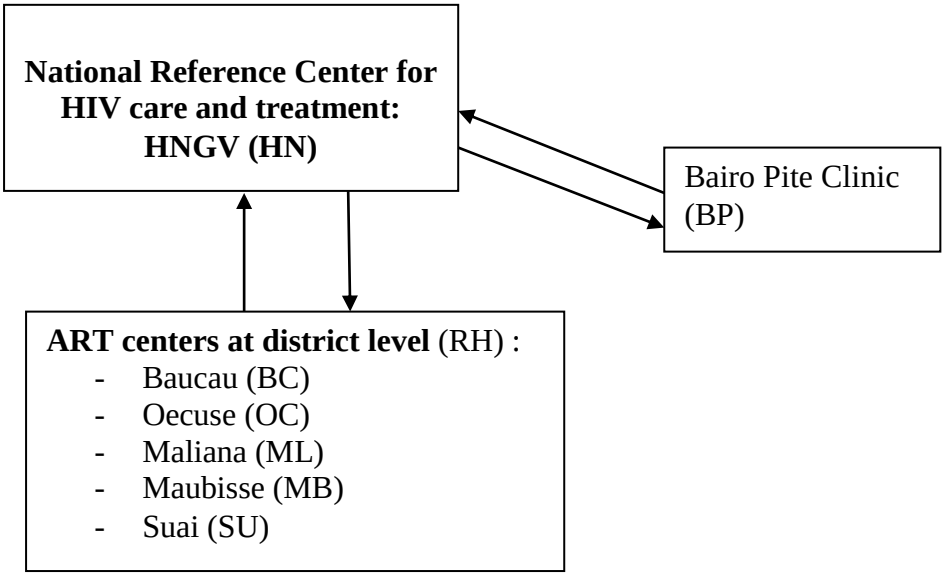
1. Reduction of HIV related morbidity and mortality
2. Improvement of quality of life
3. Restoration and/or preservation of immunological function
4. Maximal and durable suppression of viral replication

The goals of ART at public health level:

1. Improve the quality of health of the country
2. Reduce social and financial burden on the society/government
3. Control HIV epidemics

Chapter 2: NATIONAL REFERRAL SYSTEM

2.1 Referral flow and confidentiality



Transfer of medical information

When the patient is referred from an ART centre to another one, the patient will receive a copy or summary of his/her update status and a referral letter to provide to his/her doctor at the other end of the referral. All the relevant information should be shared in order to provide the best quality medical care.

National coding system

Documents provided will NOT mention names, but only **"national standard individual ID code"**. The code is used only once and can NEVER be attributed to another patient. The record of the ID codes will be kept at the ART centres in a locked cabinet and it is the only place, together with the patient individual medical record where the ID code and the name will be associated. The names and codes will NOT be shared in any case with anyone outside the scope of medical services or peer support. The code is attributed where the patient is attending the HIV services for the 1st time. The patient will keep the same ID code for the rest of his life. It will be part of the counselling to educate the patient in remembering his/her ID code. A card will be provide to the patient with his/her ID code in writing

The definition of the national ID code is following the described rule below:

1- For HNGV: HN-001, HN-002, HN-003…

2- For Bairo Pite Clinic: BP-001, BP-002, BP-003…

3- For Regional Hospital (RH) Baucau: BC-001, BC-002, BC-003…

4- For RH Oecusse: OC-001, OC-002, OC-003…

5- For RH Maliana: ML-001, ML-002, ML-003…

6- For RH Maubisse: MB-001, MB-002, MB-003…

7- For RH Suai: SU-001, SU-002, SU-003…

The national coding system will be respected by all the ART centers.

Example 1

A patient has been diagnosed HIV positive at the VCT of Maliana. After post-test counseling, the patient accepts to see the doctor and to enter in the HIV medical cohort of Maliana ART center. Only when the patient comes for his first medical consultation, the ID code will be attributed to this particular patient. Therefore if the patient presents himself at Maliana ART center, he will receive the code "ML-001" if he is the first to come in Maliana ART center. Next time he will come for a medical visit, the patient will present his ID code and the counselor will easily find his medical record as per his ID code ML-001.

Example 2

If the patient is the 50th of the HIV medical cohort of Maliana, his ID code will be "ML-050".

Example 3

If the patient is tested HIV positive in Dili and after post-test counseling, the patient decides to go to Maliana for her/his first medical HIV check-up. The patient will be registered in the HIV cohort of Maliana ART centre. In Maliana ART centre, there may be already 55 patients registered in the HIV positive medical cohort. Therefore the ID code of this new patient will be "ML-056".

Logistics

The patients referred to Dili, should be supported for their transport, accommodation and food expenses. The peer network will be aware about the possibilities available of such support through the MoH or partners' NGO.

The peer group will support the referred patients and make sure they receive proper accommodation and transport to the medical services. They will refer/recommend the patients to the appropriate NGO/service in charge of such support.

2.2 Infrastructures and Services

Hospital National in Dili (HNGV)

= National referral centre for HIV/AIDS medical management.

The HNGV is considered as the centre of excellence for HIV/AIDS medical management. It has the technical and laboratory facilities to provide accurate diagnosis for the majority of opportunistic infections.

The HNGV is responsible to provide the following services:

- OI management
- Routine 3 monthly medical monitoring of patient not on ART
- Pre-ART assessment
- 1st line ART initiation
- 1st line ART monitoring
- 1st line failure diagnosis
- Switch to 2nd line ART
- Monitoring of 2nd line ART

Services that should be available for HIV/AIDS management at the HNGV:

i. VCT/PITC
ii. Internal Medicine: infectious diseases
iii. TB management
iv. Counselling support: individual, adherence to treatment
v. Peer support network
vi. Nutritional support
vii. CD4 (2011)
viii. VL (out country)
ix. Laboratory routine tests: Hb, ALAT, creatinine
x. Laboratory specific tests: india ink, ziehl-nielsen, LDH, glucose, CSF analysis, urine tests, feces parasites, …
xi. Chest X-ray
xii. Cerebral CT-scan
xiii. Ultrasound: cardiac, abdominal

Biarro Pite Clinic

Located in Dili, it is the 1st decentralized ART services outside the Hospital National.

It can provide the same outpatient services as HNGV. However the clinic does not have intensive care unit and full diagnostic facilities (i.e.: CT scan, Lab specific tests: CSF, …) for which the referral to the national hospital will be required.

ART centers:

a. Hospital Baucau
b. Hospital Maliana
c. Hospital Oecusse
d. Hospital Suai
e. Hospital Maubisse

The referral hospitals are responsible to provide the following services:

- Referral to HNGV of all newly HIV positive diagnosed patients
- Continuation of prescription (Refilling ARV drugs) to patients initiated in Dili
- Monthly medical follow-up and OI assessment
- Reference to HNGV on 6 monthly basis of all patients for 6 monthly medical assessment and CD4 count

Reference to HNGV of all suspected cases of new infectious events among HIV positive patients (Opportunistic infections or other) or suspected cases of treatment failure.Any case of referral entering to the above criteria will benefit of financial or logistic support for transport, accommodation and basic food expenses in Dili.

The referral hospitals are NOT[3] responsible for:

- Treating complicated opportunistic infections
- Initiating 1st line ART
- Assessing treatment failure
- Switching to 2nd line ART

Services that should be available for HIV/AIDS management at district hospitals level:

i. VCT/PITC
ii. Internal Medicine: basic infectious diseases management
iii. TB management
iv. Nutritional support (?)
v. CD4 (2011)
vi. Laboratory routine tests: Hb, ALAT
vii. Chest X-ray

[3] The referral hospitals will be empowered step by step to extend their services according to the patients burden by district and the medical technical capacity during the development of the HIV national activities.

2.3 Organization of HIV/AIDS Services

HIV/AIDS activities should be integrated in the running services of the hospitals and use the existing human and infrastructure resources.

Outpatient department	Inpatient department
HIV & ART consultations: - Open twice** a week on fixed days - On appointment for patient follow-up during these 2 fixed days - Anytime in case of unexpected medical event	No specific ward, patients should be dispatched according to their condition*: - TB department - Internal medicine - Surgery - Gynaecology/ Obstetric - …

*Infection control should be prioritized and the patient living with HIV should be protected against contamination of other infectious diseases from the ward where he/she is hospitalized.
**The frequency of weekly consultation will be revised according to the patients load during the development of HIV medical services in each ART center.

The following medical staff should be officially appointed as HIV focal persons by the clinical directors to the HIV/AIDS medical services:

	Medical Doctors	Nurses
HNGV	3	2
Biarro Pite	1	2
Referral Hospitals	1	1

Nurses could be counsellors as well, but where counsellors are not nurses, a certified nurse should also be appointed for HIV medical services.

The medical doctors of HNGV and BP will be able to provide quality of HIV medical services to HIV positive patients including 1st and 2nd line ART

The nurses of HNGV and BP will be able to provide adequately the medications prescribed for opportunistic infections management and will be able to provide adequate therapeutic education to the HIV positive patients.

The medical doctors and nurses of the RH will be able to recognize:
- ARV drugs side-effects
- first sign of opportunistic infections
- first sign of treatment failure

All the staff within the health facility should be at least able to recognize signs and symptoms of HIV infection and refer to the specific medical doctor or nurse for further investigation and PITC.

Patient circuits:

1- OPD

a. Patient will go directly to **counsellor room**
   i. Registration
   ii. Prepare patient file and medical follow-up form
   iii. Adherence counselling: problems will be recorded in the patient file
   iv. Nutritional assessment: to be recorded in the file
   v. Vital signs to be registered on the new follow-up form
   vi. Current complains: in case of emergency, alert the doctor and prioritize the patient
b. Patient will go to see the doctor in the **doctor room** (1 patient at a time)
   i. Medical history to be recorded on the follow-up form
   ii. Clinical examination to be recorded on the follow-up form
   iii. Prescription to be recorded on the follow-up form
   iv. Appointment to be recorded on the follow-up form
c. Patient will go back to the **counsellor room**
   i. Counsellor will take the prescription
   ii. Counsellor will ask the OPD pharmacy for non ARV items
   iii. Counsellor will prepare ARVs prescribed
   iv. Counsellor will supply drugs with therapeutic education to the patient
   v. Counsellor will write the next appointment in the appointment agenda and on the patient appointment card

2- IPD and PITC

a. In case of HIV suspicion, the doctor should prescribe HIV test after information to the patient about his/her suspicion of HIV infection.
b. The doctor should call the HIV counsellor for counselling and testing. The choice is left to the patient to decide if he/she agrees for the test to be performed.
c. Once patient is confirmed HIV positive, the doctor trained for HIV care and treatment will start to be in charge of HIV related problems, but other problems (surgery, gynaecology etc.) remain under the specialist responsibility.
d. At discharge, the patient will be referred to the counsellor room for administrative records, drugs supply and next appointment record.

3- IPD for known HIV + cases

a. Either patient is hospitalized through emergency and if the patient has disclosed his/her status, the family should be

encouraged to inform the counsellor or HIV doctor as soon as possible

b. Either patient is hospitalized after OPD consultation
c. Patient will be hospitalized in the ward corresponding to his condition and the HIV doctor will follow the patient at the ward where he/she is hospitalized for HIV related condition and should coordinate with specialist doctors for non-HIV related conditions. It is important that confidentiality about the HIV status of the patient is respected among the strictly needed medical staff in charge of the medical management of the patient.
d. At discharge, the patient will be referred to the counsellor room for administrative records, drugs supply and next appointment record.

Medical file and confidentiality.

- An individual code is given at each new HIV positive registration; this same code will be used in place of names whenever names should not been disclosed (i.e.: blood tests, drugs prescription, …)
- The normal codes of medical confidentiality need to be maintained, but this should not be extended to a 'secrecy' that leads to practices that are potentially dangerous.
- The medical files need to be kept securely. Patients should be encouraged to disclose their status if they are seen outside their regular HIV/AIDS consultations (e.g. in emergency in OPD). Attempts should be made to ensure confidentiality and only clinicians involved in their HIV/AIDS care should know the HIV status of the patients.

The **pharmacy** may or may not be separated from the general one. A locked cabinet/cupboard is needed to securely store ARV drugs and OI medicines if any. The key of the cabinet needs to be available any time (day and night and week-end).

Free care: HIV/AIDS care is provided free of charge by the Ministry of Health.

2.4 PITC Service for OPD and IPD

A PITC session includes three steps : pre-test information, individual testing & individual post-test counseling

Pre-test information

Pre-test information may be provided in group, where resources do not permit individual sessions.

Pre-test information should include at the minimum :
- The reasons why HIV testing and counselling is being recommended
- The benefits of testing, as well as the potential adverse outcomes (violence, stigma, abandonment,…)
- The fact that the result will remain confidential
- The fact that the patient has the right to decline the test and that testing will be performed unless the patient exercises that right
- The fact that declining the test will not affect the patient's access to services that do not depend upon knowledge of HIV status
- The follow-up services that are available in the case of either an HIV-negative or an HIV-positive test result
-The HIV testing process (drawing of blood or finger-prick, testing procedure, timing of results)
- An opportunity to ask the health-care provider questions.

Additional pre-test information for women who are or may become pregnant should include the risks of HIV transmission to infants, measures that can be taken to reduce mother-to-child transmission, including antiretroviral prophylaxis, infant feeding counselling and the benefits to infants of early diagnosis of HIV.

Verbal communication is adequate for the purpose of obtaining informed consent to diagnostic HIV testing.

Pre-test information does not include individual risk assessment.

The patient has the option to accept or refuse the test to be performed.

The HIV test (see National HIV testing Policy, MoH, March 2011)

The post-test counselling

Post-test counselling is provided for all people whether they test HIV positive or negative. The test result should provide in a written format to all patients negative and positive.

The aims of post-test counselling are:
- To give the test result to the client,
- To provide emotional support to help the person to cope with the result,
- To discuss the physical, emotional and social implications of a positive result,
- To discuss prevention for HIV-positive and HIV-negative individuals,
- To refer the client for any care or treatment indicated.

Giving NEGATIVE results	- Give the result simply and clearly - Explain the meaning of the result and the window period if there has been 'at risk' behaviour in the preceding 3 months. - Discuss any other immediate concerns the person might raise - Discuss the importance of staying negative; provision of condoms and demonstration using a penis model - Assess whether the patient needs referral to more extensive post-test counselling session or additional prevention support, for example, through community-based services
Giving POSITIVE results	- Give the result simply and clearly, and give the client time to consider the result - Check with open-ended questions that the person understands the meaning of the result - allow the patient to ask questions - Let the person talk about his/her feelings about the results - Acknowledge the shock of the diagnosis; offer support - Determine how the client will get through the next few hours or days - Discuss any immediate concerns, including personal safety (suicide, depression, anger, violence) - Check to see who might be available to offer immediate support - Provide information about the Peer Group network and its roles - Discuss disclosure of the result and when it happens and with whom. Suggest telling only closest contacts (spouse, significant other) in the short term - Discuss how to protect partner(s) from infection and explain the use of condoms - If the client is healthy, explain how to maintain good health - Describe follow-up support available in the health facility i.e. treatment of OI, TB, OI prophylaxis and ART - Arrange a specific date and time for follow-up counselling visits (including family planning) and medical care, ideally the same day as the HIV diagnosis and ensure referrals for other services as appropriate.

It is very important to adapt the post counselling to the needs of each client and avoid "one conversation fits all". The discussion should be based on the concerns of the client.

Some clients receiving a positive HIV result may be unable to understand and absorb a lot of information, due to emotional state. Therefore, the counsellor should first assist them psychologically and offer further session(s) to explain general facts.

Chapter 3: PATIENT and COHORT INFORMATION RECORD

3.1 Patient admission form

The "Patient admission form" or "Patient administrative form" is filled in once at the admission and remains in the individual medical record for regular update until discharge of the patient from the cohort. At the discharge of the cohort, the reason (transfer out, lost-to-follow-up, died) and the date of discharge will be filled in.

See annex 1

3.2 Patient monitoring form

The "Patient Visit Record" or "Patient monitoring form" has to be used in every visit of the HIV positive patient to the clinic. Through the implementation of this form the main information related to each patient will be recorded, such as, clinical and laboratorial findings, ART regimen adopted, adverse side effects of ARV drugs, adherence to ART, treatment failure, OIs prophylaxis and treatment and frequency of consultations. The evaluation of this information will permit immediate, medium and long term monitoring of the HIV management and ART, by the clinical local team and by the HIV/AIDS Unit at central level.

See annex 2

3.3 Monthly data report

The "monthly data report" will be filled in on the official HIV data reporting form. The original form will be signed by the director of the hospital / clinic then it will be sent with one copy to the CDC department, HIV officer, before the 10^{th} of each month. The 2nd copy will be kept in the data reporting book at the ART center for record and monitoring purpose.

See annex 3

3.4 Appointment agenda

An agenda should be used in each ART centre for appointment record. An appointment for the next visit to the ART centre will be given to each patient and record in the agenda.

Reasons foreseen for appointment record:

- **Work management**:
    - The workload of HIV activities can be better planned by the doctor and counsellor when they keep record of when and how many patients are expected each day.
    - The time-schedule of the doctors who have several duties and responsibilities in the hospital can be better defined.
- **Quality improvement** of services offered:
    - A reminder system can be implemented based on the known appointment in order to improve the adherence to medical services; i.e. routine reminder call or sms
    - The possibility of early tracing of patients failing to come to medical appointment in order to reduce the number of lost-to-follow-up.

See annex 4

3.5 Tracing agenda

When patients are failing to come to the medical monotoring, they should be recorded in a specific agenda in which tracing activities, dates and name of defaulter tracer will be mentioned.

1) When the cause of defaulting is found out, it should be mentioned in the same agenda and in the patient file. If the patient died or was transferred to another ART center, it should also be recorded adequately on the "Patient administrative form" (see annex 2) and will be discharged from the active cohort.
2) When the cause of defaulting is NOT found out, the patient who **fails to come 2 months after the appointment date**, is considered as lost to follow-up (LFU). This information will be recorded on the "Patient administrative form" (see annex 2) and the patient will be discharged from the active cohort.
3) When a patient has been discharged from the active cohort because of LTF and the same patient comes back after some months or years, s/he should be registered as a new patient in the active cohort. Be careful of double counting. This is a new active patient in the HIV medical cohort, but s/he should not be recorded as a new HIV positive patient in the VCT or PITC report, as the patient was previously recorded in the national HIV record already. The returning patient will use the **same ID code** that was provided initially and his/her medical records will be retrieved from the archives and joined to his/her active medical file.

See annex 4

Chapter 4: WHO CLINICAL STAGING

WHO has developed tools in order to support the medical staff involved in HIV clinical care to assess the medical conditions and to orientate the decision in terms of immune-suppression. It should be used as an additional tool and does not replace the need of CD4 count.
There are 2 tables; one is developed for opportunistic infections in adults and adolescents, the 2nd one is developed for opportunistic infections in children.

The **purposes** of using the clinical tables are:

- To be used for assessment at baseline or entry into HIV/AIDS care to guide decisions on when to start CTX prophylaxis, start ART and other HIV related interventions;
- To be used to assess current clinical status of individuals in HIV/AIDS care, either on or off ART;
- To encourage clinical care providers to offer diagnostic testing for HIV in patients exhibiting the clinical events suggestive of HIV disease;
- To be used to guide clinicians in assessing the response to ART, particularly where CD4 count is not easily available, e.g. new or recurrent stage III/IV events may suggest failure of response to treatment.

Table 1: The WHO clinical staging of HIV infection in adults and adolescents[4]

Primary HIV infection	- Asymptomatic - Acute retroviral syndrome
Clinical stage I	- Asymptomatic - Persistent generalized lymphadenopathy (PGL)
Clinical stage II	- Moderate unexplained weight loss (<10% of presumed or measured body weight) - Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis) : current event plus one or more in last six months - Herpes Zoster - Angular cheilitis - Recurrent oral ulcerations (two or more episodes in last six months)

4 *Source*: WHO CASE DEFINITIONS OF HIV FOR SURVEILLANCE AND REVISED CLINICAL STAGING AND IMMUNOLOGICAL CLASSIFICATION OF HIV-RELATED DISEASE IN ADULTS AND CHILDREN, 2007

	- Papular pruritic eruptions - Seborrhoeic dermatitis - Fungal nail infections of fingers
Clinical stage III	- Unexplained severe weight loss (>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 - Current pulmonary tuberculosis (TB) - Severe-bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) - Acute necrotizing ulcerative somatitis, gingivitis or periodontitis - Unexplained anaemia (<8 g/dl), and/or neutropenia (<500/mm3) and/or thrombocytopenia (<50000/mm3)
Clinical stage IV	- HIV wasting syndrome - Pneumocystis pneumonia - Recurrent severe bacterial pneumonia (current episode plus one or more episodes in last six months) - Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration) or visceral at any site of any duration - Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) - Extrapulmonary TB - Kaposi's sarcoma - Cytomegalovirus infection (retinitis or infection of other organs) - Central nervous system (CNS) toxoplasmosis - HIV encephalopathy - Extrapulmonary cryptococcosis including meningitis - Disseminated non-tuberculous mycobacteria infection - Progressive multifocal leukoencephalopathy (PML) - Chronic cryptosporidiosis (with diarrhoed) - Chronic isosporiasis - Disseminated mycosis (e.g. extrapulmonary histoplasmosis, coccidiomycosis) - Recurrent non-typhoidal salmonella bacteraemia - Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV-associated tumours

	- Invasive cervical carcinoma - Atypical disseminated leishmaniasis - Symptomatic HIV-associated nephropathy or HIV-associated cardio-myopathy

Table 2: The WHO clinical staging of HIV/AIDS for children with confirmed HIV infection[5]

Clinical stage I	- Asymptomatic - Persistent generalized lymphadenopathy (PGL)
Clinical stage II	- Unexplained persistent hepatosplenomegaly - Papular pruritic eruptions - Fungal nail infections - Angular cheilitis - Lineal gingival erythema - Extensive wart virus infection - Extensive molluscum contagiosum - Recurrent oral ulcerations - Unexplained persistent parotid enlargement - Herpes Zoster - Recurrent oral ulcerations (two or more episodes in last six months) - Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)
Clinical stage III	- Unexplained moderate malnutrition or wasting not adequately responding to standard therapy - Unexplained persistent diarrhoea (14 days or more) - Unexplained persistent fever (above 37,5°C intermittent or constant, for longer than 1 month) - Persistent oral candidiasis (after first 6-8 weeks of life) - Oral hairy leukoplakia - Acute necrotizing ulcerative gingivitis or periodontitis - Lymphnode tuberculosis - Pulmonary tuberculosis (TB) - Severe recurrent bacterial pneumonia - Symptomatic lymphoid interstitial pneumonitis - Chronic HIV-associated lung disease including bronchiectasis - Unexplained anaemia (<8 g/dl), and/or neutropenia (<500/mm3) and/or thrombocytopenia (<50000/mm3)
Clinical stage IV	- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy - Pneumocystis pneumonia - Recurrent severe bacterial infections (such as empyema,

[5] *Source*: WHO CASE DEFINITIONS OF HIV FOR SURVEILLANCE AND REVISED CLINICAL STAGING AND IMMUNOLOGICAL CLASSIFICATION OF IV-RELATED DISEASE IN ADULTS AND CHILDREN, 2007

	pyomyositis, bone or joint infection or meningitis but excluding pneumonia) - Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration) or visceral at any site of any duration - Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) - Extrapulmonary TB - Kaposi's sarcoma - Cytomegalovirus infection (retinitis) or infection affecting another organ, with onset at age older than one month - Central nervous system (CNS) toxoplasmosis (after one month of life) - Extrapulmonary cryptococcosis including meningitis - HIV encephalopathy - Disseminated endemic mycosis (coccidiomycosis or histoplasmosis) - Disseminated non-tuberculous mycobacteria infection - Chronic cryptosporidiosis (with diarrhoed) - Chronic isosporiasis - Lymphoma (cerebral or B cell non-Hodgkin) - Progressive multifocal leukoencephalopathy (PML) - Symptomatic HIV-associated nephropathy or HIV-associated cardio-myopathy

Chapter 5: CLINICAL MANAGEMENT

5.1 First HIV Consultation

The **purposes** of the first visit is:

- To create a trustful relationship between the patient and the health provider,
- To evaluate the patient's condition and stage according to WHO clinical classification,
- To treat intercurrent opportunistic infection,
- To initiate prophylaxis if needed,
- To assess the need for antiretroviral therapy,
- To express support and explain the modalities of counselling and care.
  - . respect of confidentiality
  - . importance of having care-taker and the needs of disclosure
  - . patient decide if disclosure, not the counsellor nor the doctor
  - . present the peer group and its roles and give contacts

The **tasks** to perform are:

History taking	- Social and demographic history, household history, i.e. date first HIV test, partner informed, partner tested, partner on treatment, number of children, PMTCT intervention, children HIV tested, children on treatment - Medical history, e.g. TB history - Sexual and reproductive health background if appropriate, e.g signs and symptoms of STI, refer for PAP smear on annual basis - Allergies, e.g. to sulphonamides - Other medications, including ARVs in the past/herbal remedies/ drug or toxic addiction (alcohol and drugs use)/ food habits - History of recent acute illness (es) by using structured symptom checklist (see chapter 3) - Symptoms of active TB, i.e. fever, night sweats, loss of weight, chronic cough, chest pain, haemoptysis
Clinical examination	- Complete physical examination, even in the absence of symptoms, including temperature - Weight, height, Oedema and BMI or W/H% or MUAC - Signs of active TB, e.g lymph node, chest signs
WHO clinical staging	- Stage patients according to WHO clinical classification (see chapter 3) Start CTX prophylaxis (see chapter 4)

Diagnosis and treatment of intercurrent infections	- Treat any OI diagnosed in line with national protocols[6] - Refer for AFB smear (and x-ray) if suspicion of TB disease - Start nutrition supplement if needed (see chapter 9)
Samples for laboratory	- take blood samples for CD4 count (preferably if NO inter-current OI, as OI can decrease the level of CD4 even more than what it is in reality) - other blood tests according to protocol (RPR, HbsAg, HCV AB, Hb)
Counselling	- Offer health education to all patients on HIV/AIDS; its natural progression and importance of regular follow-up, on the availability and benefit of prophylaxis and treatment, on prevention of HIV transmission, on nutrition and on malaria prevention - Offer specific health education on ARV treatment (goals, benefits) to stage 3 and 4 patients - Offer information on/ or refer to/ family planning - Give date for next appointment.

5.2 Second HIV Consultation

Maximum 2 weeks after the 1st visit. Meanwhile the counsellor can be consulted as often as it is requested by the patient.

The **purposes** of the second visit are:

- To identify the patients in need of ART, mainly by reviewing WHO clinical stage and laboratory (CD4 count) results. Be aware that staging may not be accurate at first visit and may need to be revised at subsequent visits e.g. patient may complain of prolonged diarrhoea (suggesting Stage 4), but response to antibiotics at the following visit would indicate otherwise.
- To check CTX adherence and tolerance and to confirm CTX indication if CD4 available

5.3 Follow-up of Patients not eligible for ART

Since HIV/AIDS is a chronic illness and the natural history of HIV infection is one of progressive immunological decline, the aim of regular follow-up is:
-To help prevent missed opportunities to offer prophylaxis or treatment
-To allow recognition of clinical evolution and timely treatment interventions
-To support the patient in her/his choices re: prevention and in her/his positive living

[6] national protocols are mentioned further in this guideline (chapter 7), guidelines on opportunistic infections from MSF[6] (Medecins Sans Frontieres) was provided to all the doctors involved in HIV management.

Frequency of follow-up clinical review and CD4 count depends on WHO clinical stage and CD4 count

If CD4 not available	- Stage I: after 6 months - Stage II: after 3 months
If CD4 available	- Stage I, II and CD4 >350/mm3: after 6 months

- Always advise patients to return earlier if symptoms appear.
- Patients eligible but refusing ART will be followed monthly if they accept.

The **tasks** to perform are:

History taking	- Review household history, i.e. HIV status disclosure to the partner, partner and/or children tested - History of new acute illness (es) by using structured symptom checklist[7] - Occurrence of symptoms of active TB, i.e. fever, night sweat, loss of weight, chronic cough, chest pain, haemoptysis
Clinical examination	- Physical examination. In the absence of symptoms, at least check the mouth, the skin, the genitals for manifestations of STI and signs of active TB; listen to the lungs and palpate the abdomen. - Weight and temperature at EACH consultation - If children: take height at each visit - Height and BMI or W/H% or MUAC to be reviewed regularly
Samples for laboratory	- Take samples for complementary tests for OI diagnosis if needed - Take sample to re-assess immunological status (CD4 count if available, in absence of intercurrent OI) every 6 months
Diagnosis and treatment of intercurrent infections	- Treat any OI diagnosed in line with MSF protocols - Refer for AFB smear and x-ray if suspicion of TB disease - Start nutrition supplement if needed - Refer for ARV counselling if indications for treatment
Counselling	- Check CTX adherence and refill if needed - Prevention of HIV transmission, of OI and malaria - Family planning - Give date for next appointment.

[7] See section 5.4 key pointsfor clinical review of symptoms and signs

5.4 Key points for clinical review of symptoms and signs[8]

ASK

<u>If this is the first visit</u>:
Review medical history; particularly for TB, other opportunistic infections, and chronic problems.

<u>For all visits</u>:

- How have you been? What problems have you had?
- Have you had any of the following (investigate local names) ? If yes, ask for how long:
  - Headache? Fever? Night sweat?
  - Cough?
  - Nausea or vomiting? Poor appetite?
  - Mouth sores?
  - Abdominal pain?
  - Diarrhoea?
  - New skin rash?
  - Fatigue?
  - Signs of STI?
  - Tingling, numb, or painful feet/legs?
  - Any other pain? If yes, where?
- Have you needed urgent medical care? If yes, ask for record/diagnosis
- Which medications are you taking and how often?
- Assess adherence (if on opportunistic infection prophylaxis and/or ART)
- What problems have you had taking the medicines? How are you taking the medicines?
- Taking any other drugs (traditional remedies, TB, ARV, illicit drugs, etc.)?
- How are things at home?
- Who knows about your diagnosis and how do you feel about someone attending with you for appointments?
- Is there anything else you would like to talk about?
- Access to/ need for/ familiy planning ?

LOOK

<u>In all patients</u>:

- Look for pallor. If patient is pallid, check haemoglobin level.
- Look at whites of eyes: are they yellow?
- Look for oral candida/thrush
- Listen to the lungs and palpate the abdomen
- Weigh, calculate, and record weight gain or loss. If weight loss, ask for food intake.
- Take the height of adults at the first consultation and calculate BMI. Take the height of children at each consultation and calculate the ratio W/H.
- estimate adherence (pill counts, visual scale or other methods).
- If patient is sad or has lost interest, assess for depression

<u>If any news symptoms</u>:

- Examine the relevant system and do further assessment of symptoms
- Measure temperature.
- Check lymph nodes.
- Look for rash.
- Look for evidence of violence.

[8] Adapted from: *Chronic HIV care with ARV Therapy: Integrated management of adolescents and adults illness interim guide for first- level-facility health workers.* Geneva, WHO, December 2003.

Chapter 6 : PROPHYLAXIS

6.1 Cotrimoxazole Prophylaxis

Daily Cotrimoxazole (CTX) prophylaxis reduces mortality and morbidity in HIV/AIDS patients by reducing the risk of development and recurrence of PCP as well as by decreasing the incidence of toxoplasmosis, malaria and of some bacterial infections (the drug is active against streptococcus pneumonia, haemophilus influenza, salmonella, legionella, nocardia, methicillin-sensitive staphylococcus aureus and many Gram-negative bacilli). Also, CTX prophylaxis reduces mortality by 25-50% in TB/HIV coinfection.

1/ INDICATIONS

CTX prophylaxis should be initiated in **adults and adolescents** when:

- ***HIV infected adults with CD4 <350*** cells/mm3 irrespective of WHO stage or
- WHO stage[9] 2, 3 and 4 when CD4 count is not available
- ***Pregnant women*** with the criteria for CTX prophylaxis should be administered CTX prophylaxis regardless of the stage of the pregnancy
- ***Breastfeeding mother*** should continue cotrimoxazole prophylaxis following the usual recommendations of CTX prophylaxis

CTX prophylaxis should be initiated in **infants and children** for:

- ***All HIV exposed infants and children*** starting at 4-6 weeks after birth and maintained until cessation of risk of transmission and exclusion of HIV infection
- ***HIV confirmed infants < 1 year***: regardless of CD4 percentage or clinical status
- ***HIV confirmed children 1 - 4 years***: WHO stage 2, 3 and 4, regardless of CD4 percentage or any WHO stage and CD4 < 25%
- ***HIV confirmed children > 5 years***: follow adult recommendations

CTX prophylaxis should ideally be started 2 to 3 weeks before ART in order to assess tolerance to CTX and differentiate side effects due to CTX and ART.

2/ CONTRA-INDICATIONS

[9] See chapter 4: WHO clinical staging

Persons with a history of severe adverse reaction (grade 4) to cotrimoxazole or other sulfa drugs

3/ DOSAGE

Adults and adolescents: CTX 960 mg daily

1 double strength (DS) tablet daily (preferred) or 2 single strength (SS) tablets daily

1 DS = SMX 800 mg + TMP 160 mg
1 SS = SMX 400 mg + TMP 80 mg

Infants and children:

Age	weight	Dose in paediatric tablet (100/20 mg)	Dose in syrup (200/40 mg per 5 ml)	Dose in single strength tablets (400/80mg)
< 6 months	< 5 kg	1 tab	2.5 ml	Formulation not recommended in this age group
6 months - 5 years	5 – 15 kg	2 tab	5 ml	½ tab
6 years - 14 years	15 – 30 kg	4 tab	10 ml	1 tab
> 15 years	> 30 kg		N/A	2 tabs

4/ DURATION

- ***HIV exposed children***: discontinue CTX prophylaxis after exclusion of HIV infection

- ***Infants and children living with HIV***:

    - maintain CTX prophylaxis until 5 years old
    - children older than 5 can be reassessed and consideration of discontinuation will follow adults and adolescents recommendations

- ***Adults and adolescents***:

    - If CD4 not available: do not discontinue CTX prophylaxis
    - If CD4 available: due to high prevalence of bacterial infection and malaria in Timor-Leste, it is recommended to discontinue CTX prophylaxis only after CD4 increased to 350 cells/mm3 or above and after at least 6 months of ART.

5/ SIDE EFFECTS AND THEIR MANAGEMENT

Cotrimoxazole is usually well tolerated. If non severe adverse events (grade 1 and 2) occur, every effort should be made to continue prophylaxis with cotrimoxazole because of its superior efficacy compared with dapsone.

CTX prophylaxis should ideally be started 2 to 3 weeks before ART in order to assess tolerance to CTX and differentiate side effects due to CTX and ART.

No specific laboratory monitoring is required.

According to the "Division of AIDS table for grading the severity of adverse events" (December 2004), side effects may be divided in 4 grades of toxicity, and are described in the table below.

Grade Toxicity	**1**	**2**	**3**	**4**
SKIN TOXICITY				
Cutaneous reaction, rash	Localized macular rash	Diffuse maculopapular or morbilliform rash OR Target lesions	Diffuse maculopapular or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis
Pruritis (itching – no skins lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional	Itching causing inability to perform usual social & functional activities	N/A

		activities		
HAEMATOLOGICAL TOXICITY				
Haemoglobin (g/dL)	8.5 – 10.0	7.5 – 8.4	6.5 – 7.4	<6.5
WBC (/mm3)	2000 - 2500	1500 - 1999	1000 - 1499	<1000
Neutrophil count (/mm3)	1000 - 1300	750 - 999	500 - 749	<500

Risk of grade 3 and 4 neutropaenia is increased in patients taking CTX and AZT. In such patients, CTX should be discontinued first.

All patients starting CTX should be informed of potential adverse effects and of what to do should they occur (stop the drug and report to the clinic).
In case of
- **Grade 1 or 2 events:** attempts can be made to continue treatment with careful and repeated observation and symptomatic treatment (antihistamines, antiemetics). If the condition is worsening or the patient is very anxious, then CTX should be discontinued and desensitisation considered.
- **Grade 3 events:** CTX should be discontinued until the adverse event has completely settled. Then, CTX desensitisation should be considered.
- **Grade 4 events:** CTX should be permanently discontinued.

6/ PROTOCOL FOR COTRIMOXAZOLE DESENSITISATION

When desensitising (all grades 3, sometimes grades 1 and 2), treatment should be stopped for 2 weeks, and then the patient may be re-challenged with CTX in a gradually increasing dose by using syrup formulation (TMP 40/SMX 200 mg). For patient's misunderstanding reason, the patient could be hospitalized during the week of CTX desensitization.

Several protocols may be used. Below is the WHO recommended protocol.

Days 1	80 mg/16 mg = 2 ml (syrup 40/8mg)	OD
Days 2	160 mg/32 mg = 4 ml	OD
Days 3	240 mg/48 mg = 6 ml	OD
Days 4	320 mg/ 64 mg = 8 ml	OD
Days 5	400 mg/80 mg = 1 SS tablet	OD
From day 6 onwards	800 mg/160 mg = 1 DS tablet or 2 SS tablets	OD

Patient should be seen between day 6 and 10. If CTX is well tolerated, continue the prophylaxis at normal dosage. Inform the patient to return even if minor symptoms occur.

After desensitisation, up to 70% of patients may again tolerate CTX.

7/ ALTERNATIVE REGIMEN

Dapsone 100 mg OD, as the first alternative if the patient does not tolerate CTX. Dapsone is less effective than cotrimoxazole in preventing PCP and lacks the broad antimicrobial activity of cotrimoxazole. It is also not effective against Toxoplasmosis and therefore in case of previous documented Toxoplasmosis, Pyrimethamine 50mg/week and Folinic acid 25mg/week should be added (folinic acid counteracts the blockage of folate metabolism without affecting the antiprotozoal activity of pyrimethamine).

8/ PATIENT INFORMATION

Patients need to be clear that while CTX does not cure HIV, regular dosing is essential to prevent opportunistic infections. CTX does not replace the need for ART.

6.2 Fluconazole Prophylaxis

Fluconazole prophylaxis is prescribed to protect severely immune-compromised patients against cryptococcal infection.

Primary prophylaxis: fluconazole 400 mg once a week, if CD4 < 100 cells/mm3 and discontinue when CD4 > 100 cells/mm3 and at least 6 months on ART

Secondary prophylaxis: fluconazole 200 mg daily, until CD4 > 100 cells/mm3 and at least 6 months on ART

6.3 Isoniazide Prevention Therapy (IPT)[10]

Adults and adolescents[11] living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT for a period of 6 months:

- INH: 300 mg daily
- Pregnant women should also benefit of IPT and the best time for initiating IPT is left to clinical judgement. Pregnant women should receive pyridoxine (Vit. B6) together with INH.
- All adults and adolescents who have successfully completed their TB treatment should continue receiving INH for another six months.

Children[12] living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB and should be offered IPT regardless of their age:

- > 12 months and no active TB and **no contact** with TB case: IPT 10mg/kg/day for 6 months
- < 12 months and no active TB and **in contact** with TB case: IPT 10mg/kg/day for 6 months
- All children who have successfully completed treatment for TB disease should receive INH for an additional six months

[10] Guideline for intensified TB case finding and IPT for PLWHA in resources constrained settings, WHO 2010
[11] See annex 5.1
[12] See annex 5.2

IPT course starting or completion should not delayed the start of ART.

6.4 Valganciclovir Prophylaxis

Protects against relapse of cytomegalovirus infection in severely immune-compromised patients. All patients with CD4 < 100 cells/mm3 should undergo a fundoscopy and been screened for CMV retinitis. PCR for CMV could also be performed and is more accurate than fundoscopy as it can detect CMV viral load and therefore systemic CMV infections other than retinitis. CMV infection is a severe infection that gives irreversible vision impair if located in the eyes, but can also give severe pneumonia or gastro-intestinal infections leading to death if ART and adequate treatment aren't promptly administered. Increasing the immunity level is the best treatment against CMV, however for CMV disease, valgancyclovir or gancyclovir inj. should be prescribed for better outcome. Urgent treatment can be required for vision-saving or life-saving. Intra-ocular injection of gancyclovir should not be delayed when CMV retinitis is diagnosed.

Primary prophylaxis: Not applicable

Secondary prophylaxis: Valgancyclovir started as treatment and continued until CD4 > 100 cells/mm3

Induction:	Valgancyclovir 950 mg BID during 3 weeks
Maintenance:	Valgancyclovir 950 mg OD until CD4 > 100 cells/mm^3 at least for 3 months

Chapter 7: TREATMENT OF OPPORTUNISTIC INFECTIONS[13]

7.1 Opportunistic Infections and Conditions Frequently Causing Fever

Persistent or recurrent fever with no or limited findings	
Common causes	- Non-HIV related conditions: malaria, urinary tract infection, etc. - Mycobacterium: **TB**, mycobacterium avium complex - Bacteraemia, i.e. salmonella, streptococcus pneumonia - Systemic fungal infection: cryptococcosis - Other: CMV, HIV (with no other pathogen), drug reaction
Diagnosis	Look for the cause through: - History taking - Physical examination - Complementary investigations, i.e. malaria smear, urinalysis, AFB smear, chest x-ray, WBC and differential, CSF examination
Prophylaxis	- CTX also reduces the incidence of some bacterial infections, malaria and toxoplasmosis
Treatment	- According to findings

[13] For details and more information, plese refer to Clinical HIV :AIDS Care Guidelines for Resource-poor Settings, Médecins Sans Frontières, OCB, 2nd Edition, April 2006

7.2 Lymphadenopathy

Common causes of lymphadenopathy:

- HIV-related : progressive generalized lymphadenopathy (PGL) (usually no prognostic significance)
- Mycobacterial infections: **TB** (non-inflammatory, firm, cold and painless, single or multiple, usually bilateral, evolving in chronic mode towards softening and fistulization), mycobacterium avium complex
- Bacterial infections: syphilis, bartonella (e.g cat-sratch disease)
- Fungal infections: histoplamosis
- Viral infections: CMV, EBV
- Parasitic: toxoplasmosis, trypanosomiasis, filiariasis
- Neoplasm: lymphoma, kaposi sarcoma
- Immune reconstitution inflammatory syndrome
- STI : inguinal lymphadenopathy

Diagnosis:

- Rule out local or contiguous infection which might explain lymphadenopathy
- Chest x-ray and lymph node aspiration for AFB in case any of the following are present: fever, weight loss, asymmetrical nodes, tenderness, extra nodal foci such as skin lesions
- PGL: painless enlarged nodes , > 1 cm diameter, in two or more non-contiguous sites (excluding inguinal sites) for three or more months)
- RPR

Treatment:

- According to findings

7.3 Respiratory Problems

Opportunistic causes of respiratory problems:

- Tuberculosis
- Bacterial pneumonia
- Pneumonia due to Pneumocystis Jiroveci (PCP)
- Penicilliosis
- Cryptococcosis
- Histoplasmosis
- Coccidioidomycosis
- Aspergillosis
- Helminthic diseases
- Toxoplasma pneumonitis
- Mycobacterium Avium Complex (MAC)
- Pulmonary Kaposi Sarcoma

Diagnosis of respiratory symptoms :

1- based on clinical symptoms and findings,
2- sputum examination and
3- chest x-rays.

Tuberculosis (TB) stage 3 disease	
Symptoms	PTB is still the most common form of TB in HIV + patients. It may occur at any CD4 level (it is also frequent in patients under ART). The presentation depends on the degree of immunosuppression. In the early stages of HIV infection, when immunity is only partially compromised, the features are typical of PTB. As immune deficiency advances, HIV-infected patients present with atypical pulmonary disease or EPTB or disseminated disease. - Early HIV infection: chronic cough (> 2 weeks), sputum production, weight loss +/- fever, night sweats, loss of appetite, breathlessness, chest pain. - Late HIV infection: weight loss and fever. TB must be excluded in any patient presenting with wasting syndrome. - Cough and haemoptysis are less common in HIV+ PTB patients (less cavitation, inflammation and endobronchial irritation).
CD4 count	Any
Diagnosis (see chapter 8)	AFB smear: - Early HIV infection: result often positive - Late HIV infection: result often negative

	CXR findings: - Early HIV infection: upper lobe infiltrates, bilateral infiltrates, cavitation - Late HIV infection: interstitial infiltrates especially in lower zones, hilar adenopathy, no cavitation, no abnormality Other: needle aspiration of lymph node for AFB and/or lymph node biopsy, lumbar puncture for suspected TB meningitis (see section on headache, neurological symptoms), etc
Prophylaxis	- CTX prophylaxis: all TB/HIV patients should receive CTX prophylaxis regardless of CD4 count (see chapter 4) - INH prophylaxis (see chapter 4)
Treatment	- Follow protocol of national TB programme but... - ... MSF advocates for the 6-month rifampicin based regimen, proven to be more effective in HIV+ patients. See chapter 8 - TB treatment is the same for HIV-positive as for HIV-negative TB patients; with the exception that thiacetazone is contra-indicated in those who are HIV positive. - Prevention of INH neuropathy by pyridoxine (vit B6) 10 mg daily is recommended for all HIV positive patients whilst on anti-TB drugs. - suspicion of treatment failure : see chapter 8

Bacterial Pneumonia

Patients can develop serious pneumococcal infection despite a relatively preserved CD4 count. Recurrent pneumococcal pneumonia is common (up to 25% within 6 months).

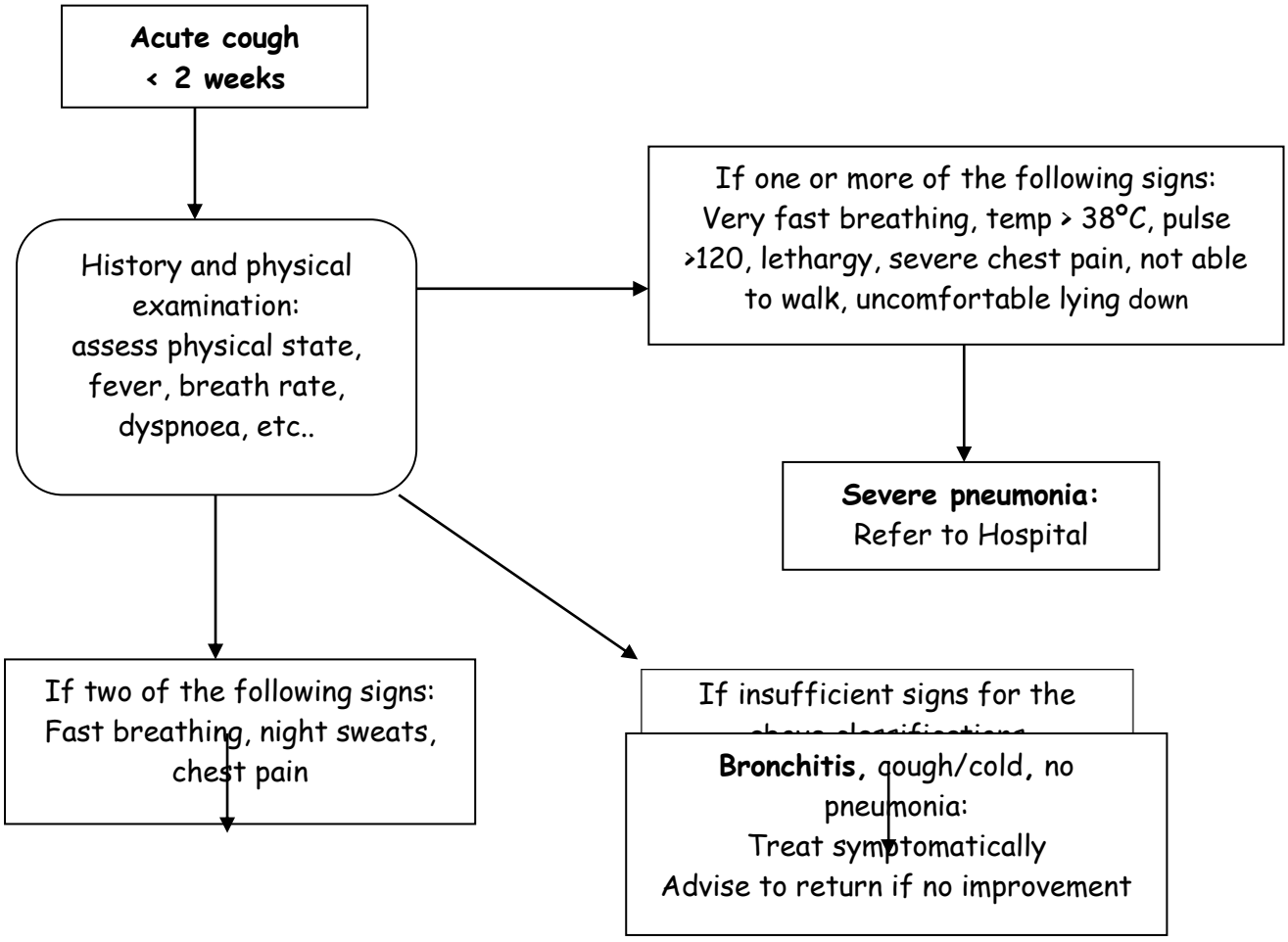
Symptoms	According to the presentation: - Typical bacterial pneumonia due to S. Pneumoniae, moraxella and H.Influenzae. Acute respiratory infection, which is often abrupt, with high fever, chills, productive cough of yellow/green sputum, unilateral pleuritic chest pain. Orthopnea, fatigue, and malaise are also common. Physical examination shows: fever, tachypnea, tachycardia, localised rales or ronchi. - Atypical pneumonia due to mycoplasma, chlamydia pneumoniae. Symptoms of lower respiratory tract infection with subacute

	onset, mild fever, productive or non-productive cough. Chest often clear. - Unusal bacterial organisms: S. aureus, other Gram – bacteria, Legionella. Acute severe pneumionia. Often in severely immune depressed patients.
Diagnosis	- Chest X-ray shows lobar consolidation. Atypical presentation includes multilobar, nodular, reticulonodular patterns - Sputum examination (Gram stain and AFB)
Prophylaxis	Daily CTX may reduce the incidence of bacterial pneumonia; see chapter 4
Treatment	Typical bacterial pneumonia: - 1st line: amoxicillin (50 mg/kg/day po divided over 3 doses x 7 days) - 2nd line: amoxicillin/clavulanate (625 mg po tid to qid x 7 days) Atypical pneumonia, and/or patient severely immune-depressed: Amoxicillin (50 mg/kg/day po divided over 3 doses x 7 days) with doxycycline (100 mg po bid x 7 days) or erythromycin (1000 mg po bid x 7 days) If severe and requires hospitalisation: Amoxicillin (+/- clavulanate) (1g IV tid to qid) or ceftriaxone (1 to 2 g IV od) with erythromycin (50mg/kg/day IV divided in 4 doses) or doxycycline (100 mg po bid), for one 1 week.

Pneumocystis jeroveci pneumonia (PCP) stage 4 disease	
Symptoms	Symptoms of PCP are insidious, subacute and slowly progress over the course of days to weeks. Most common symptoms are: low-grade fever, non-productive cough, progressive exertional dyspnea and chest discomfort that progressively worsen. Fever, fatigue, and weight loss may precede respiratory symptoms. Pulmonary examination is normal at rest.
CD4 count	< 200/mm3
Diagnosis	- A typical chest x-ray shows diffuse, bilateral interstitial or alveolar infiltrates ('ground glass' appearance). Sometimes there are nodules of cavities, but the x-ray can be misleadingly normal (25%). - Hypoxia and increased LDL are always present (usually not

	available). - Definitive diagnosis is given by broncho-alveolar lavage (BAL) and histopathology (usually not available).
Prophylaxis	- Primary prophylaxis by CTX, see section on CTX prophylaxis. - Secondary prophylaxis: everyone who has had PCP must continue with maintenance therapy: CTX 960mg daily until on ART for > 6months and CD4 >200.
Treatment	CTX (TMP 20mg/kg – SMX 100mg/kg/daily divided over 4 doses x 21 days). The patient should be checked daily in the first few days for tolerance and after the first week for efficacy. For the patient who is seriously dyspnoeic, or with a worsening condition, add oxygen and corticoid (prednisone 40 mg po bid x 5 days, then prednisone 40 mg po od x 5 days, then prednisone 20 mg po od x 11 days).

Management of acute cough



Pneumonia:

Treat with oral antibiotic: amoxicillin (50mg/kg/day over 3 doses x 7 days)

↓

If no improvement, worsening or recurrent condition:
Refer to Hospital

7.4 Oral lesions, Odynophagia and Dysphagia

The most common mouth problems in HIV/AIDS patients are trush, ulcerations, angular cheilitis and oral hairy leukoplakia.

Dysphagia (difficulties in swallowing) and odynophagia (pain in swallowing) are frequent symptoms in severely immune depressed patients and are mostly due to candidiasis infection, although other causes may be responsible.

The diagnosis of oro-oesophageal conditions is usually clinical.

Oral thrush or candidiasis *stage 3 disease*	
Symptoms	2 presentations are possible: - Creamy white pseudomembranous plaques: this is the most common presentation, covering areas of superficial ulceration on the gums, palate, buccal mucosa and tongue; are easily detached by a tongue depressor and cause taste disturbances. - Erythematous patches: which present as multiple, flat, red, non-removable plaques, mostly on the palate and the tongue, causing burning sensation.
CD4 count	< 500/mm3
Treatment	Topical treatment: miconazole nitrate (10 mg gum patch od x 7 days). Instructions for use are provided in the pharmaceutical note. Systemic treatment: fluconazole (200 mg po od x 7 days). - If no improvement is seen after 7 days of topical treatment or - If the oropharynx is involved or - If the infection is recurrent (i.e., >2 relapses, or 1 relapse if deeply

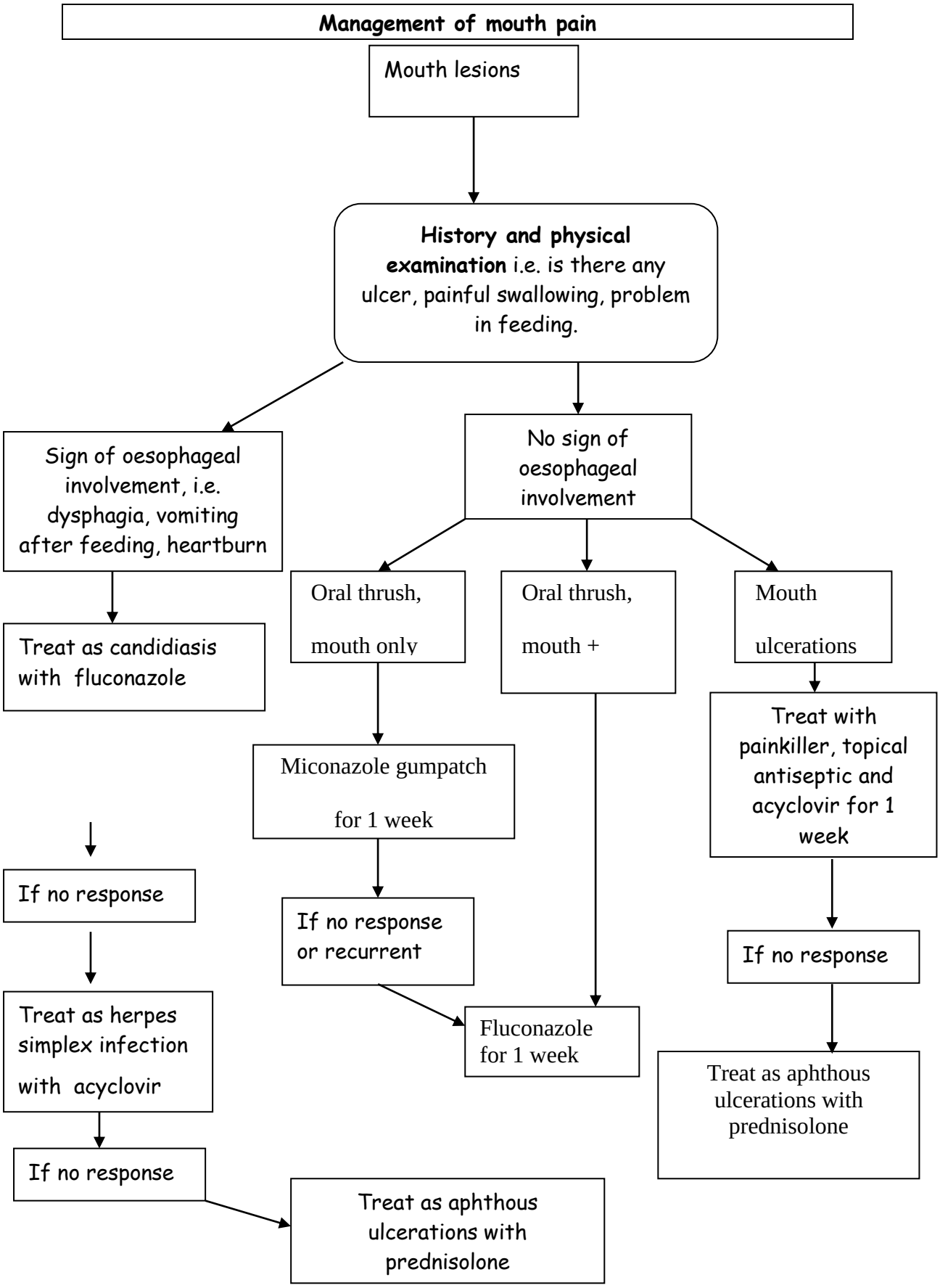
	immunosuppressed, within 3 months).
Oral hygiene	- Use of soft toothbrush, gently scrubbing the tongue and gums at least 3-4 times a day, and then rinsing the mouth with salt water or lemon water mix; - Rinsing the mouth with warm salty water or mouthwash after eating and between meals; - Increase fluid intake; - Modify food intake—eat more frequently, smaller meals.

Oral ulcerations *stage 2 disease if recurrent*	
Symptoms	There are 2 common causes of oral ulcerations. - Herpes Simplex stomatitis/ulcers due to HSV: vesicles with rupture that transform in pain and ulceration. Usually located on gums, hard plate, lips, and adjacent facial skin. - Aphthous ulcers (unknown aethiology): well-circumscribed lesions with a whitish covering surrounded by a reddish halo; small or large, single or multiple; anywhere in the mouth; usually deeper than herpetic ulcers but differential diagnosis is difficult. Ulcers can also be caused by CMV, deep mycosis, some bacterial infections and malignancies.
CD4 count	<100/mm3
Treatment	- Painkiller: paracetamol (500mg to 1g qid x 1 week) for mild pain, tramadol (50mg qid x 1 week) for severe pain. - Topical antiseptics: gentian violet mouth wash or diluted solution of povidone-iodine 0.5%, at least twice a day. - Acyclovir (400mg tid or 200mg 5 times daily x 10 days) is given systematically as clinical differential diagnosis between herpetic and aphthous ulcers is difficult. - In case of deep ulcers or no-response to acyclovir: try prednisone 20 mg po od x 7 days. - If secondarily infected: amoxicillin (50mg/kg/day po divided over 3 doses x 7 days) + metronidazole (400 mg po tid x 7 days)

Angular cheilitis	
Symptoms	Cracking, pain, and sometimes bleeding from the corners of the mouth. It is fungal in origin complicated by inflammation.
CD4 count	< 500/mm3
Treatment	Clotrimazole 1% cream 1 apply bid x until resolution of lesions

Oral hairy leucoplakia *stage 3 disease*	
Symptoms	Unilateral or bilateral adherent white or grey patches on lingual lateral margins. Patches are irregular folds and cannot be scraped off. It is caused by Epstein-Barr virus
CD4 count	< 500/mm3
Treatment	Rarely symptomatic and do not need treatment but is indicative of immune suppression (WHO stage III).

Oesophageal candidiasis *stage 4 disease*	
Symptoms	Severe candidiasis infection may extend into the lower pharynx and oesophagus. Symptoms may include dysphagia, odynophagia , substernal chest pain, vomiting after feeding, and feelings of obstruction and epigastric pain or heartburn. Patients may also be asymptomatic. Usually it presents along with oropharyngeal candidiasis, but it can also occur independently.
CD4 count	< 100/mm3
Diagnosis	Clinical.
Treatment	Fluconazole 200mg po od x 14 days. If no response, increase fluconazole up to 400 mg po od. If this treatment is not effective, underlying causes could be: - Herpes Simplex oesophagitis - Oesophageal aphthous ulcers - Oesophageal CMV infection. So as second alternative treatment, give acyclovir (800 mg po tid x 1 week); If no response: you may suspect aphthous ulcers and treat with prednisone (0.5 mg/kg/day x 2 weeks). If suspicion of CMV, give antacid and analgesics and Valgancyclovir


Management of mouth pain
Mouth lesions
History and physical examination i.e. is there any ulcer, painful swallowing, problem in feeding.
Sign of oesophageal involvement, i.e. dysphagia, vomiting after feeding, heartburn
Treat as candidiasis with fluconazole
No sign of oesophageal involvement
Oral thrush, mouth only
Oral thrush, mouth +
Mouth ulcerations
Miconazole gumpatch for 1 week
If no response or recurrent
Fluconazole for 1 week
Treat with painkiller, topical antiseptic and acyclovir for 1 week
If no response
Treat as aphthous ulcerations with prednisolone
If no response
Treat as herpes simplex infection with acyclovir
If no response
Treat as aphthous ulcerations with prednisolone

7.5 Diarrhoea

- Always assess hydration status in any patient complaining of diarrhoea

- Always provide nutritional advice such as continued diet with cooked food and frequent re-hydration with boiled water

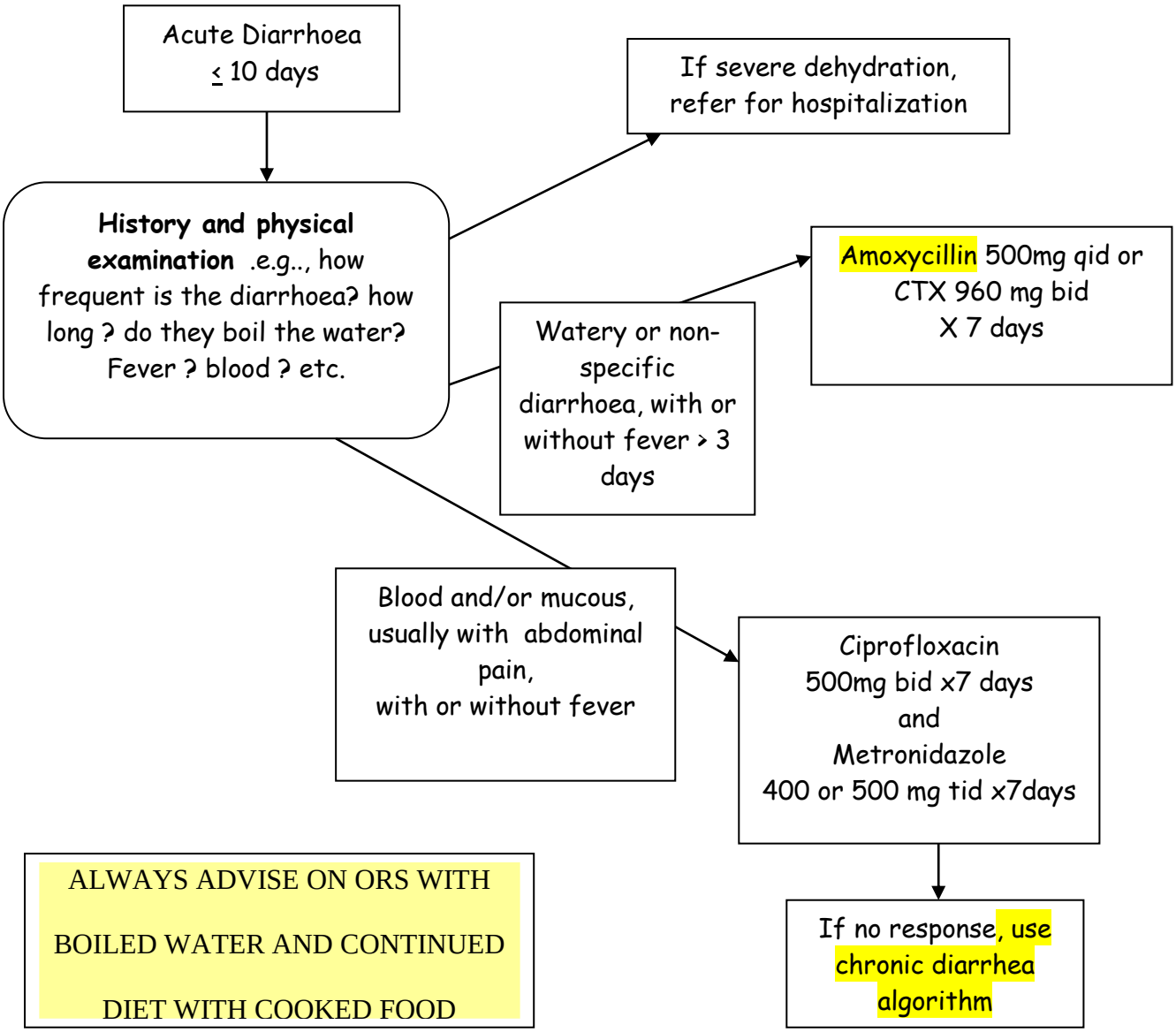
- Provide hygiene advice such as hand washing with soap to prevent recurrent diarrhoeal diseases

- If possible, take stool sample for laboratory examination (although this is rarely possible in practice)

Acute diarrhoea	
Definition	Acute diarrhoea is characterised by: - ≥ 3 loose stools daily for 3 to 10 days; - Most common in the early stages of HIV infection; - No weight loss or very slight weight loss, and disappears spontaneously or with appropriate treatment.
CD4 count	Any
Signs and symptoms	2 syndromes may be described: - Diarrhoea with blood and/or mucous in the stools (dysentery), with or without fever, usually caused by shigella, enterohaemorrhagic E. coli, salmonella non-typhi species, campylobacter or entamoeba histolytica; - Watery or non-specific diarrhoea, with or without fever, usually caused by viruses, E. coli, clostridium difficile, staphylococcus aureus or yersinia.
Treatment	- Assess hydration status. If moderate, treat with ORS and boiled water. If severe, refer for hospitalisation; - Assess the diarrhoea duration. If less than 3 days, do not give antibiotics; - In presence of blood and/or mucous: treat with ciprofloxacine (500 mg po bid) and metronidazole (400 or 500 mg po tid), for 7 days. Caution: anti-diarrhoeic are contra-indicated in this case; - In watery or non-specific diarrhoea: treat with CTX (960mg po bid x 7 days) if the patient is not under CTX prophylaxis or with amoxicillin (500mg po qid x 7days); - As anti-diarrhoeic, you may use codeine-phosphate (30 mg po tid to qid x 3-4 days with a maximum of 240 mg/day) or loperamide (4 mg as loading dose then 2 mg after each stools with a maximum of 16 mg/day). - If suspicion of helminthiasis: treat with albendazole(400 mg od for

	3 days).

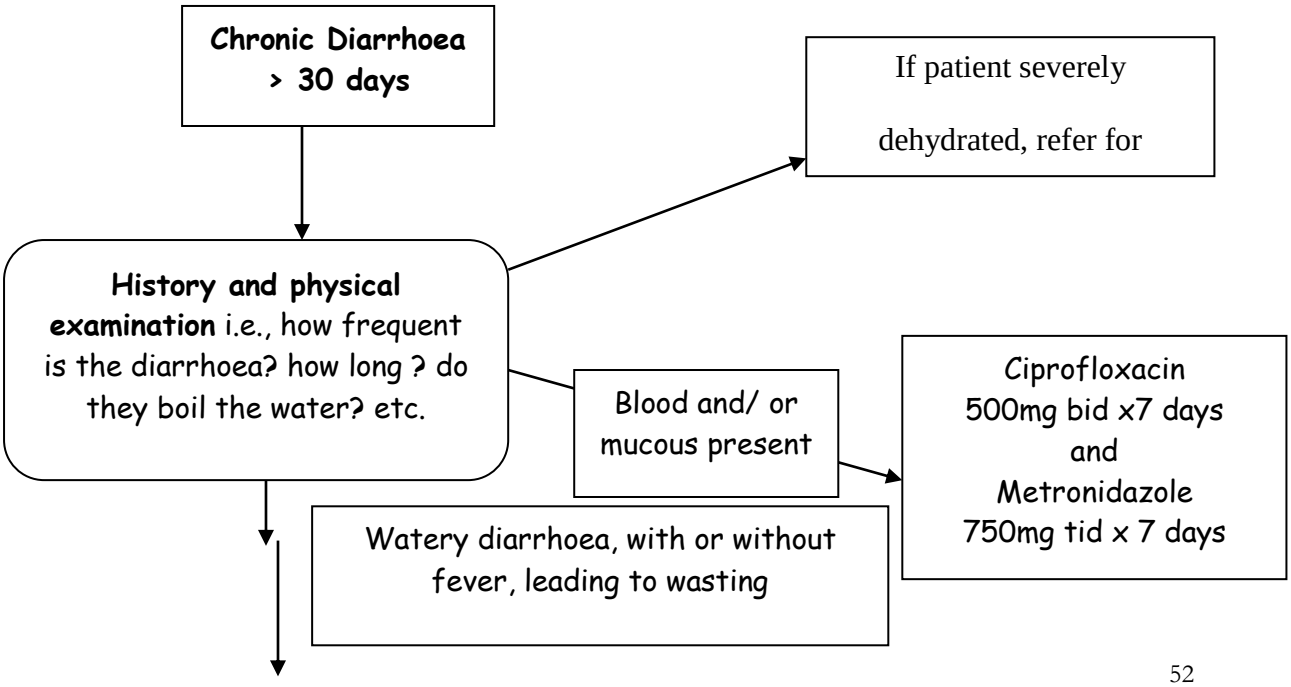
Management of acute diarrhoea

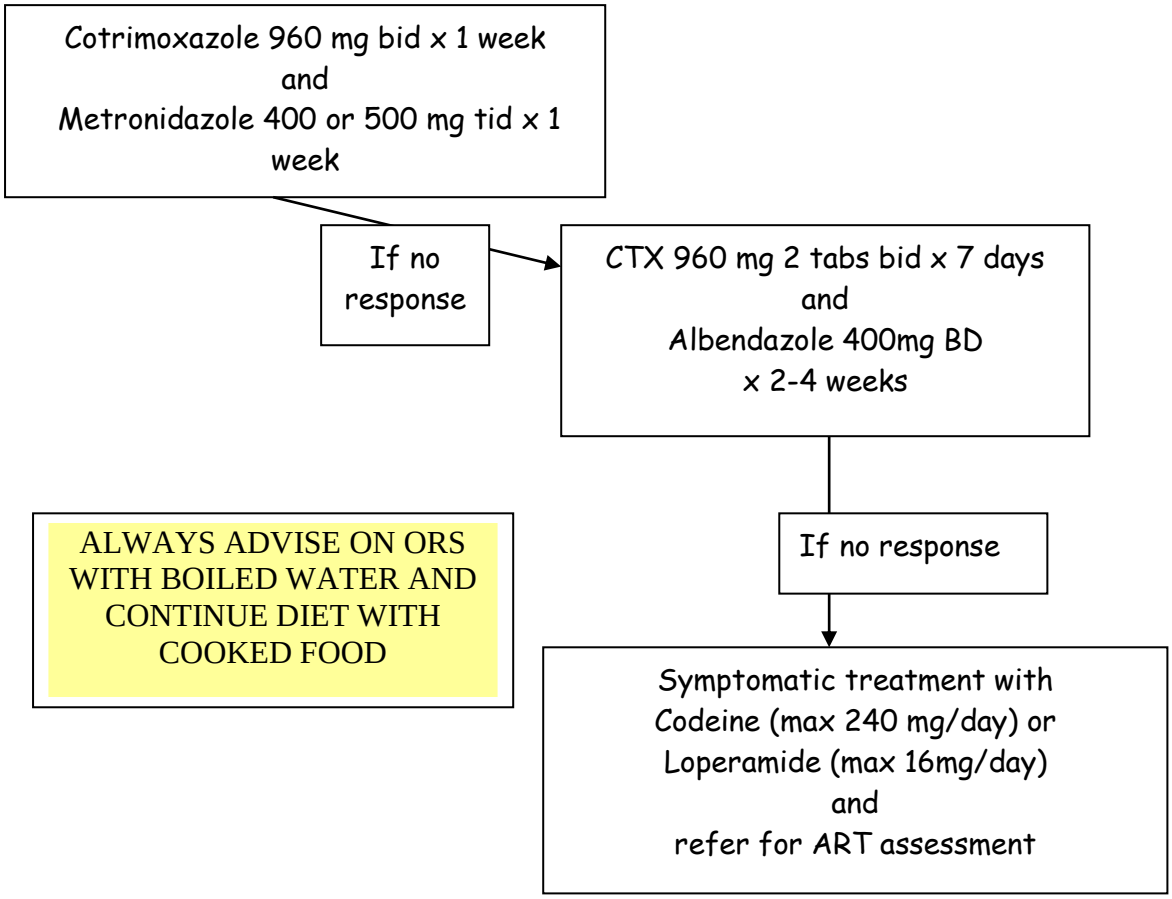


Chronic diarrhoea *stage 3 if unexplained*	
Definition	Chronic diarrhoea is characterised by: - ≥ 3 loose or watery stools/day for ≥ 30 days, continuously or episodically; - More common during the later stages of the HIV infection; - Leads to malabsorption and wasting syndrome.

CD4 count	< 200/mm3 (except for entamoeba histolytica and giardia where CD4 count may be higher)
Symptoms	- Usually watery, with or without fever, leading to malabsorption and wasting syndrome and caused by isospora belli, cryptosporidisosis, cyclospora, microsporidium species, mycobacterium avium complex, HIV itself; - Blood and/or mucous might be present if chronic infection by entamoeba histolytica or CMV; - Infection by giardia presents as non-specific diarrhoea with bloating and flatulence.
Treatment	- Not all causes may be treatable in resource limited settings (i.e. CMV, mycobacterium avium complex). - For some causes, the best results are obtained with immune reconstitution by ART (i.e. cryptosporidia, CMV). - Assess hydration status. If moderate, treat with ORS and boiled water. If severe, refer for hospitalisation. - If presence of blood and/or mucous, treat with ciprofloxacin and metronidazole as acute diarrhoea. - In presence of watery or non-specific diarrhoea, treat with: CTX 960mg bid + Metronidazole 400 or 500 mg tid for 1 week. If no response: increase CTX to 960mg - 2 tabs bid for 1 week + albendazole 400mg bid for 2-4 weeks. - Give anti-diarrhoeic and start ARV recruitment process

Management of chronic diarrhoea





Note: Clostridium difficile is recognised in USA as 57% causes of diarrhoea (Sanchez TH, CID 41: 1621-1627, 2005). Only 10% are bacterial infections, all together.

7.6 Skin lesions

The most common HIV- associated skin diseases are:

- Viral infections: herpes simplex, herpes zoster, molluscum contagiosum (poxvirus)
- Fungal infections: candidiasis, cutaneous ringworm
- Bacterial infections: folliculitis, furunculosis, pyoderma
- Parasite infections: scabies
- Neoplasm: Kaposi sarcoma
- Other dermatitis: papular pruritic infection (PPE), seborrheic dermatitis, xerosis
- Drug reactions: ARV (i.e. Nevirapine), antibiotics (i.e. CTX, streptomycin)

The diagnosis is usually clinical.

Skin manifestations usually occur at CD4 count < 500/mm3.

Herpes simplex	
Symptoms	HSV-1 or orolabialis on the mouth, face and skin HSV-2 or genitalis on the genitals, rectum, skin and meninges Sensory prodrome in the affected area rapidly followed by evolution of painful lesions from papules to vesicles, ulcer and crusting stages. In severely immune-depressed patients, extensive, deep, non-healing ulcers are seen in the mouth and on perineum/buttocks.
Treatment	Limited oral lesions: gentian violet topically, paracetamol (1g qid x 10 days) for mild pain, carbamazepine (200mg po od x 10 days) for moderate to severe pain; Genital lesions and extensive painful oral ulcers: Acyclovir (400 mg po tid or 200 mg po 5 times daily, x 7 days), plus painkiller.
Recurrent infections	Recurrence occurs frequently (more than 6/year): preventive therapy with acyclovir may be required (200 mg tid or 300 bid).
In HIV+ pregnant women	For pregnant women who report a history of genital herpes, acyclovir treatment is given from 36 weeks of gestation through to minimize risk of transmission to the baby.

Herpes Zoster (stage 2 disease)	
Symptoms	- Prodrome of headache, photophobia, and malaise, but usually no fever; followed by tingling or pruritis or pain that resembles a burn or muscle injury in the affected dermatome. A painful maculopapular rash appears that evolves to vesicles, pustules, and scabs over 3-5 days (dermatomal presentation) with healing over 2-4 weeks. - Complication: Post herpetic neuralgia after healing of scars.
Treatment	Topical treatment: gentian violet (no calamine lotion!). Systemic treatment - If patient presents within 72 hours of rash beginning: Acyclovir (800 mg 5 x/day x 7 days). - Paracetamol (1g qid) and carbamazepine (200mg po bid x 10 days) to prevent post-herpetic neuralgia.

Cutaneous or mucosal candidiasis	
Symptoms	- Cutaneous candidiasis: wet and itchy lesions with scaling and

	satellite papules - Also causes vaginitis: vaginal irritation, itching, burning and thick white discharge
Treatment	- Cutaneous: <u>Topical treatment</u> 1st line: gentian violet or Whitefield's ointment topically (x 2-4 weeks); 2nd line: Clotrimazole 1% cream topically (x 2-4 weeks). <u>Systemic treatment in severe cases</u> fluconazole 100mg weekly for 4 weeks or give 100mg daily for 7 days. - Vaginitis: Clotrimazole pessary (200 mg od nocte x 3 days or 100 mg od nocte x 6 days) or fluconazole if persistent or recurrent

Tinea pedis & Tinea corporis (cutaneous ringworm)	
Symptoms	- <u>Tines pedis</u> is characterized by peeling, cracking and scaling skin in the interdigital web areas, mainly between toes, along with occasional redness and blisters on the soles and sides of feet; - <u>Tines corporis</u> is characterised by a pruriginous annular, and erythematous lesion with a raised, erythematous active edge. It may be single or disseminated lesions of varying size.
Treatment	<u>Topical treatment</u> 1st line: Whitefield's ointment or gentian violet topically (x 2-4 weeks); 2nd line: Clotrimazole 1% cream topically (x 2-4 weeks). <u>Systemic treatment in severe cases</u> fluconazole 100mg weekly for 4 weeks

Folliculitis	
Symptoms	Presents as an eruption with papules and pustules on face, trunk, and extremities; usually very pruritic causing excoriations; multiple exacerbations and remissions.
Treatment	<u>Topical treatment</u> No supra-infection: C/C solution or ointment, topically (bid x 2 wks); Mild supra-infection: C/C ointment + Neomycin, topically (bid x 2 wks); <u>Systemic treatment if severe supra-infection</u> Cloxacillin (500 mg po qid x 7 days).

Scabies	
Symptoms	- Small red papules that are intensely pruritic, especially at night. Sometimes presentation is the "burrow," a 3-15 mm line that represents the superficial tunnel the female mite digs to lay eggs. - Usual locations are the interdigital webs of the fingers, the wrist, periumbilical area, axilla, thighs, buttocks, genitalia, feet, and breasts. - Presentation could be also hyperkeratosis of the knees, elbows and trunk (Norwegian scabies) - Scabies is usually atypical in advanced disease; it may be far more extensive than usual including areas above the neck
Treatment	Topical treatment: Benzyl benzoate 25% topically to whole body except face nightly for 3 nights. Systemic treatment: Ivermectin (0.2mg/kg stat) on empty stomach. Remember to also treat clothes, bed linen and all family members

Pruritic papular eruption (PPE)	
Symptoms	Chronic symmetric papular eruption, mostly on extremities, lower back, buttocks; very pruritic, and frequently secondarily infected. Lesions are at different stage of evolution: early blisters, inflamed papules, old inactive lesions. Might remain with post-inflammatory pigmentation.
Treatment	Topical treatment - Vaseline moisturizers mixed with Hydrocortisone 1% ointment (x 2 wks) - Povidone-iodine solution 0.5% (x 2 weeks) - C/C ointment plain (x 2 weeks) Systemic treatment if supra-infection: Cloxacilline (500mg qid x 1 week) Responds to ART

Seborrheic dermatitis	
Symptoms	Erythematous or yellowish plaques with greasy scales and indistinct margins. May resemble a fungal infection. The most common locations are in the hairline, eyebrows, nasolabial folds, and chest.
Treatment	Clotrimazole 1% cream topically with Hydrocortisone 1% ointment

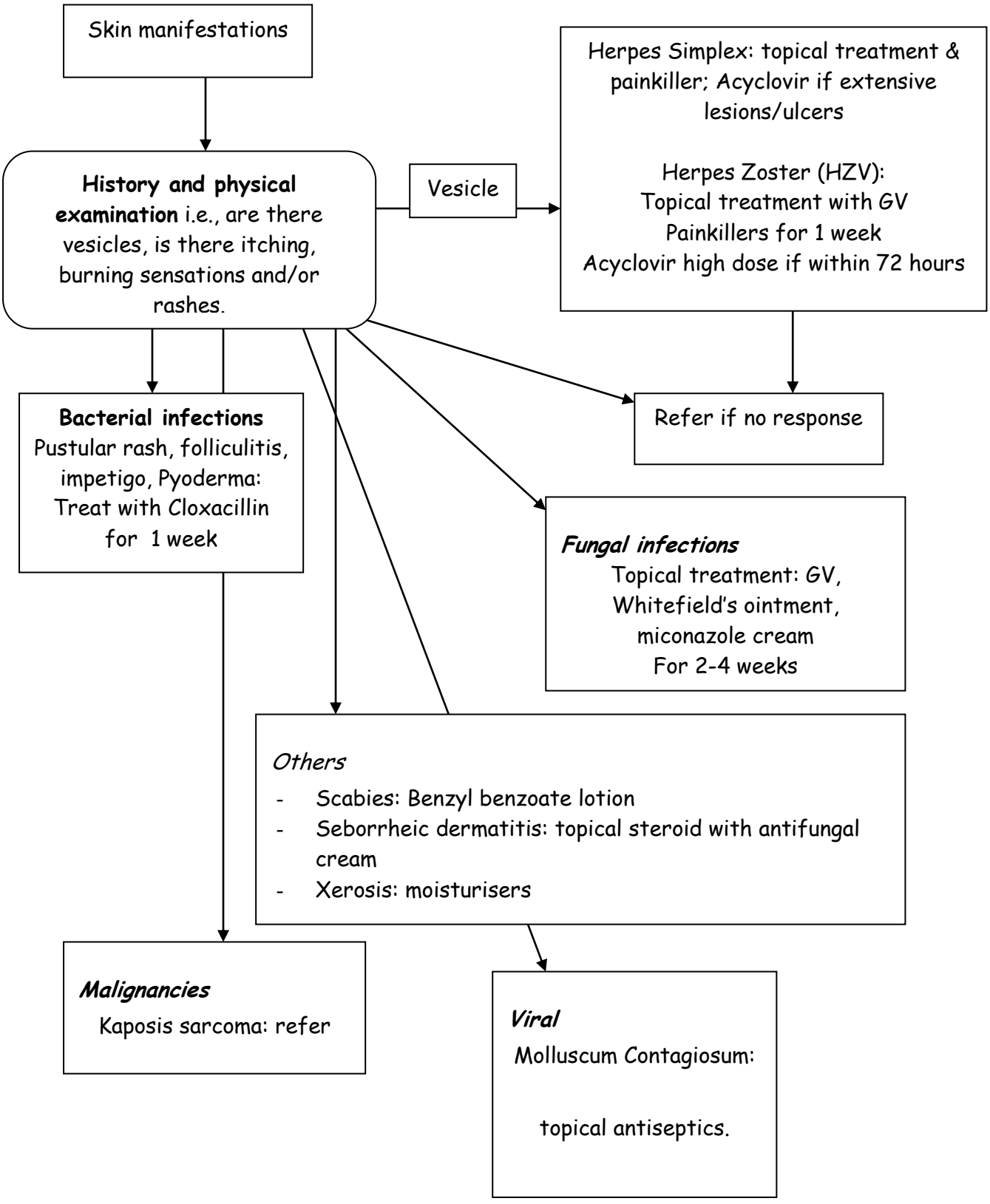
	topically (x 2-4 weeks).

Xerosis	
Symptoms	= Dryness of the skin. Caused by HIV itself. Due to lack of oil. Presents as a persistent, slight to severe scaling; it affects mostly the limbs and back, but can involve the whole body. Itching.
Treatment	Use only moisturizers, e.g., Vaseline, if no supra-infection or PPE/folliculitis.

Molluscum contogiosum	
Symptoms	Centrally umbilicated, non-pruritic papules on the face, neck and ano-genital areas
Treatment	- Usually does not require treatment - prick the centre of the lesion with a needle dipped in iodine

Psoriasis	
Symptoms	Extensive severe psoriasis is often observed in AIDS patients
Treatment	-exposure to sun -for thick plaques, use keratolytic (e.g. salicylic acid 5%) in combination with topical steroids class III or IV (e.g bethametasone 0.1% crème)

Management of skin manifestations



7.7 Neurological Disorders

The assessment of the patient with headache should include the presence or absence of neurological symptoms, including:

- Evidence of meningeal irritation or raised intracranial pressure (neck stiffness, photophobia, vomiting, and bradycardia in the presence of fever) due to bacterial and fungal meningitis
- Seizures and focal neurological deficits (paresis, cranial nerve palsies, movement disorders, ataxia, aphasia) due to toxoplasmosis, tuberculoma, cryptococcoma, lymphoma, PML);
- Changes in mental status (loss of concentration, personality change, confusion, cognitive impairment) and dementia due to TB meningitis, cryptococcus meningitis, HIV dementia
- Visual disturbances due to CMV (floaters, scotoma, flashing lights)

Some of these conditions require advanced investigations for diagnosis but the most common seen in resources limited settings may be clinically strongly suspected (toxoplasmosis) or diagnosed only with CSF examination (meningitis).

Wherever malaria is endemic it should be ruled out at the earliest opportunity.

Note that a CD4 is very useful in narrowing the differential diagnosis. Patients on ARV's and cotrimoxazole prophylaxis may be at lower risk of some of infections such as malaria and toxoplasmosis but they should still be considered.

Toxoplasmosis is the most common cause of focal brain disease in HIV patients. It is therefore worth treating any HIV positive patient presenting with focal neurological signs, with or without fever.

Toxoplasmosis ***(stage 4 disease)***	
Symptoms	- Constellation of severe headache, fever and focal neurological signs (such as hemiparesis) is typical. Can also cause altered mental status (confusion, change in behaviour), seizures, coma, eye pain and reduced vision. - Physical examination demonstrates focal neurological abnormalities.
CD4 count	< 100/mm3
Diagnosis	Clinical diagnosis based on symptoms.

Prophylaxis	- Primary: CTX, see section on CTX prophylaxis - Secondary: CTX 960mg od daily or Sulfadoxine-pyremithamine (Fansidar) 2 tabs stat weekly.
Treatment	The first choice treatment usually described is: pyremithamine (100mg loading dose, followed by 50mg od) and sulfadiazine (1 to 2 g qid) and folinic acid (10 mg od) for 6 to 8 weeks. Unfortunately, this treatment is often not available in the field. As an alternative administer CTX (10mg/kg/day TMP + 50 mg/kg/day SMX po divided over 2 doses x 3 to 6 weeks). Clinical improvement is expected within one to two weeks. Patients who do not respond should be referred to specialist facility.

Bacterial Meningitis	
Symptoms	- High pyrexia, violent headache, photophobia, vomiting, and sometimes decreased level of consciousness. - On clinical examination, neck stiffness (can be absent in some aetiologies), positive Kernig and Brudzinski signs, and petechial lesions (if meningococcus)..
CD4 count	Any
Diagnosis	CSF examination: - Turbid appearance, - PMN > 500/mm3, - Low glucose - Increased protein usually > 1g/l.
Treatment	Ceftriaxone 2g IV od x 7 days.

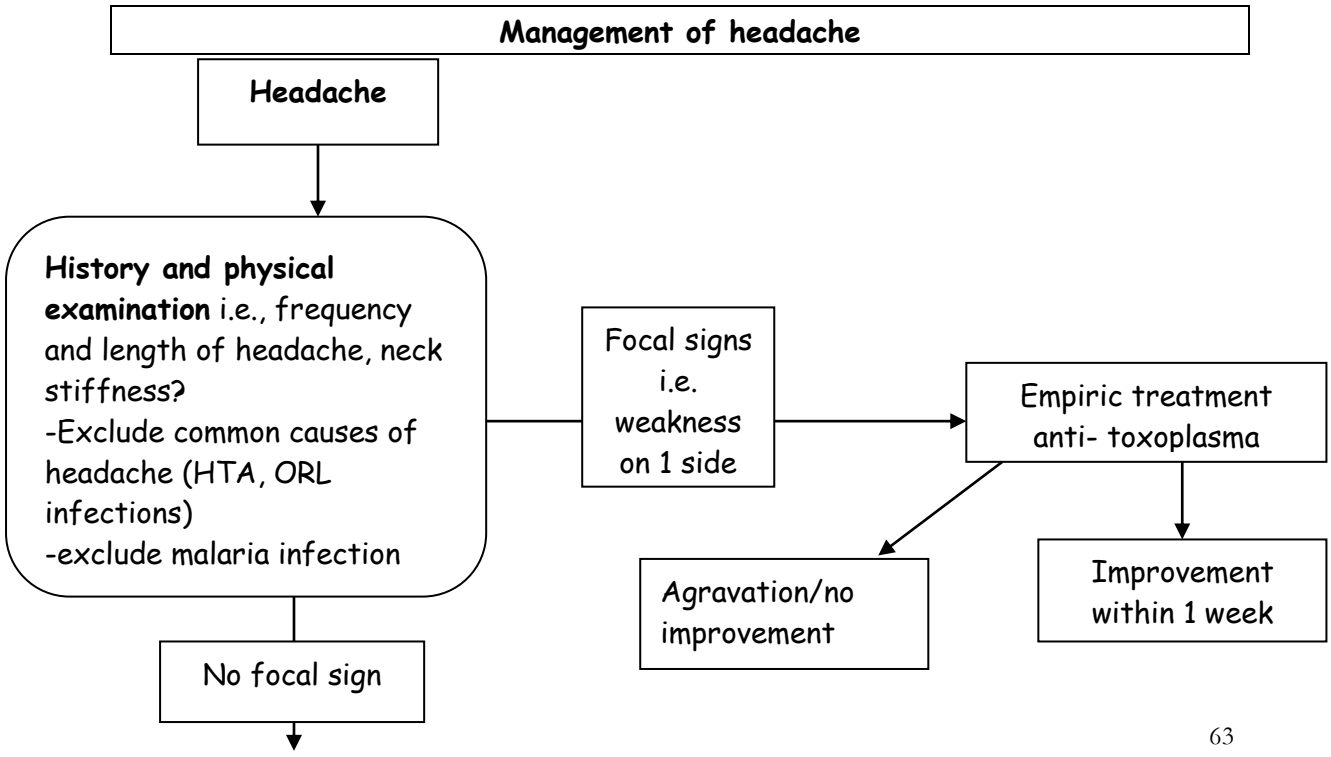
Cryptococcus meningitis *stage 4 disease*	
Symptoms	Sub-acute onset with very mild symptoms including general malaise, tiredness, low grade fever, anorexia, sub-pyrexia, and headache. It generally affects patients in late stage HIV disease. There is often disorientation, confusion, or seizures and is one of the causes of chronic fever in HIV infection.
CD4 count	< 100/mm3
Diagnosis	CSF examination: - Appearance : clear - Elevated opening pressure, - Protein increased but < 500 - Glucose normal or slightly decreased - WBC increased but < 800 (Lymphocytes > granulocytes) - Indian ink positive in most case (+ 85%) Cr Ag + (sensitivity 92%, highly specific).
Prophylaxis	- Primary: not recommended (except in high prevalence areas e.g. Asia; consult with HQ). - Secondary: fluconazole 200mg od daily. Can be discontinued if CD4>100 and on ART for > 6 months. -
Treatment	Preferred regimen: - Amphotericin B given by slow IV infusion (0.7mg/kg/day) in G 5% (never use saline solution) for 14 days followed by fluconazole (400mg po od for 8 weeks). - Test dose of amphotericin B of 1 mg can be given over an hour. If tolerated (no nausea, vomiting, chills, headache), full dose is infused over a 4 hours period. - Premedication by paracetamol (1g po) and promethazine (25mg po) is given 30 to 60 minutes before infusion. - Pre-treatment salt loading with Normal Saline (500ml) over 2 hours should be given to avoid nephrotoxicity. Alternative regimen: In patient with less severe disease, oral fluconazole treatment alone may be sufficient: 400mg po od for 10 weeks, after an initial loading dose of 800 mg for 3 days. Repeat evacuatory LP (up to 30 ml daily) is indicated to control

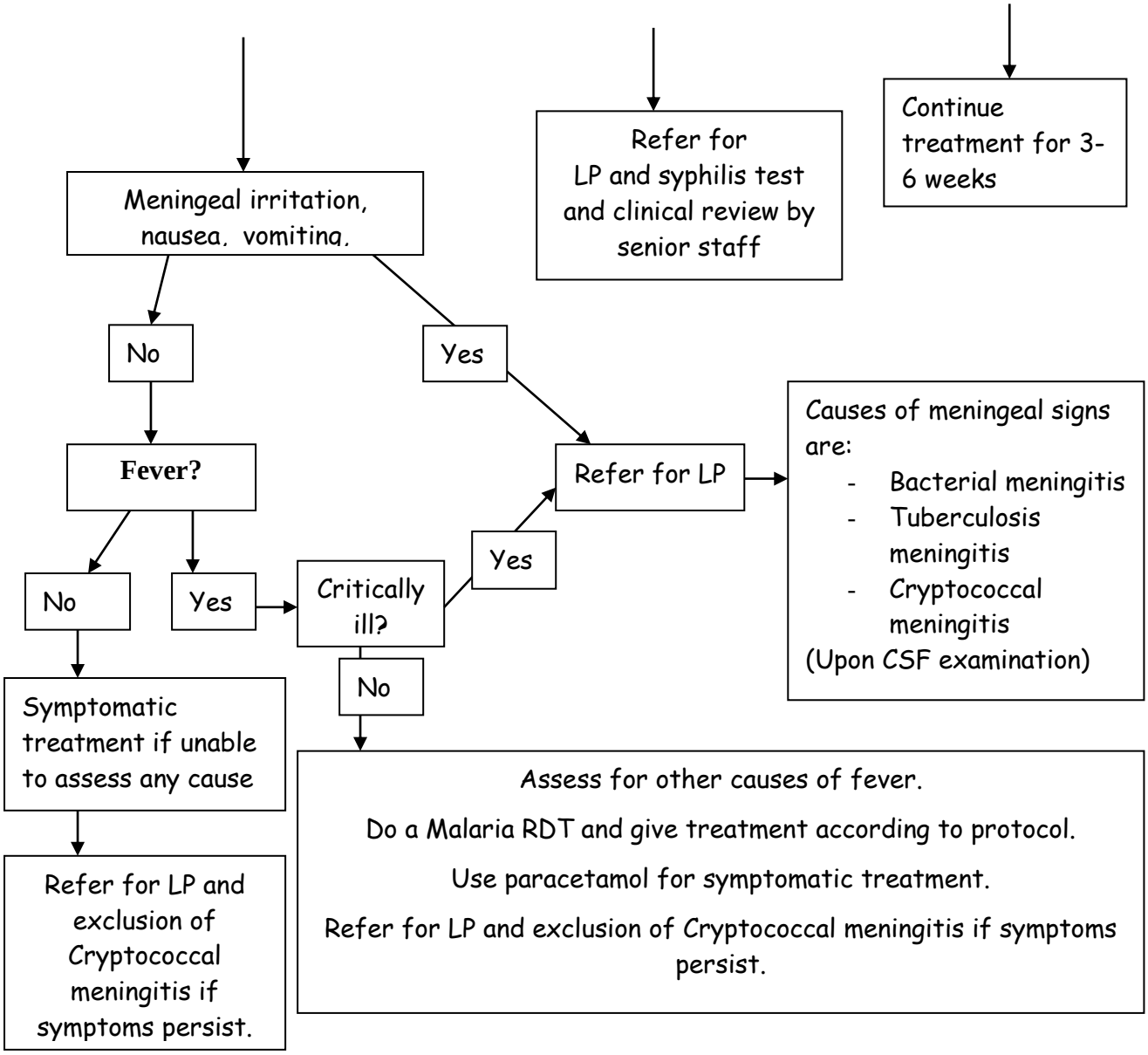
	elevated intracranial pressure if there is failure to respond or with new symptoms after > 2 weeks of therapy.

TB Meningitis *stage 4 disease*	
Symptoms	- Gradual onset and progression of headache and decreased consciousness. Commonly neurological symptoms are mild but may be focal signs. Other symptoms as hyperthermia, lymphadenopathy; cough may be present. - Examination often reveals positive Kernig's sign.
CD4 count	Any
Diagnosis	CSF examination: - Elevated opening pressure, - Lymphocytes >, - Glucose < (or normal), - Protein >, - AFB +/-. (sensitivity about 10%)
Treatment	- Follow protocol of national TB programme but... - effective in HIV+ patients. See section on TB/HIV co-infection. - TB treatment is the same for HIV-positive as for HIV-negative TB patients. - Streptomycin is recommended during the intensive phase as ethambutol does not cross the meningeal barrier (2SRHZ instead of 2RHZE). - Prevention of INH neuropathy by pyridoxine (vit B6) 10 mg daily is recommended for all HIV positive patients while on anti-TB drugs. - Adjuvant corticoid therapy should be given in TB meningitis (prednisolone 60 mg od for 4 weeks then decrease over several weeks). Note that is NOT indicated for Crypotcoccus meningitis.

Patients may also present with peripheral nervous system disorder, the most common being distal and predominantly sensory neuropathy. It can be caused by HIV itself or by other viral infections such as Herpes zoster or CMV. Nutritional deficiencies, alcohol or drug toxicities (Isoniazid, D4T) may also be responsible of peripheral neuropathy.

Peripheral neuropathy	
Symptoms	- HIV-related neuropathy presents as sensory loss, pain and numbness in the extremities (toes and feet). Ankles, calves and fingers are involved in more advanced cases. - Sharp, stabbing pain, "shooting electrical feeling", in post-herpetic herpetic neuralgia. - Burning, tingling, pins and needles, in drugs associated PNP.
CD4 count	Usually < 200/mm3
Diagnosis	Clinical
Treatment	- Treatment is usually disappointing in absence of HAART. Try: amytriptylin (25 to 75 mg po) at bedtime (can increase up to 200 mg if necessary). - For post-herpetic neuralgia: carbamazepine (200 mg po bid). - In case of INH toxicity: Pyridoxine (100 to 200mg po od). - In case of D4T toxicity: see section of D4T side effect algorithms.
Advices	- Educate patients to identify early signs of PNP - Recommend good foot care, comfortable shoes, and walking aids; - Recommend balanced diet to avoid vitamin deficiencies; - Recommend exercise or massage to improve circulation of feet.





7.8 Kaposi Sarcoma Disease

- Kaposi Sarcoma disease is the most common HIV-1 associated malignancy. The disease is due to a Human Herpes Virus called Kaposi Sarcoma Herpes Virus (KSHV, previously named HHV8).
- The main mode of transmission is sexual but some cases in children suggest a transmission during pregnancy or labour.
- Iimmuno-depression due to HIV plays an important role in the development of the disease. For the patients under ART, there is a correlation between the decrease in the size of the lesions and the increase of CD4 count. However KS may also be seen in patients with still good immunity.

1/ SYMPTOMS

- Skin: the typical skin lesions are multifocal vascular plaques or nodules, purple-to-brown in colour with firm consistency. Localized lesions are usually painless. Extensive KS skin lesions are usually painful. The lesions can be associated with oedema (especially for the lower limbs) or ulceration. The progression can be either slow either slow or fast.
- Mucous membrane: usually involves the oral cavity with the soft palate or the pharynx.
- Visceral: digestive (usually asymptomatic) or pulmonary, lymph nodes.

2/ STAGING AND PROGNOSIS

Staging is based on whether lesions are confined to the skin or if there is mucosal and visceral involvement (T), and whether patients have constitutional symptoms (S).

ACTG staging of AIDS KS:

	Good risk (0) - All the following	Poor risk (1) - Any of the following
Tumour (T)	Confined to the skin and/or lymph nodes and/or minimal oral disease (flat lesions on the palate)	Tumour associated oedema or ulceration Extensive oral KS Gastro intestinal KS KS in other non-nodal viscera
Immune system (I)	CD4 ≥ 200/mm3	CD4 < 200/mm3
Systemic illness (S)	No history of OI or thrush No B symptoms (unexplained fever, night sweats, weight loss >10%, diarrhoea persisting > 2 weeks) Karnofsky score ≥ 70	History of OI or thrush B symptoms Karnofsky < 70 Other HIV related illness (e.g. neurological disease, lymphoma)

2 categories of AIDS KS patients on ART can be identified:
- A good prognosis category: T0S0, T1S0, T0S1 (respective 3-years survival of 88, 80 and 81%)
- A poor prognosis category: T1S1 (3-years survival of 53%).

3/ DIAGNOSIS

Usually clinical. The best is to realise a biopsy (preferable on old lesions) for histology, unrealistic in most of developing settings.

4/ TREATMENT

Indications

T0S0, T0S1:
ART alone. No indication for chemotherapy.
Normal recruitment process and start ART whatever the CD4 count (stage IV patient)

T1S0, T1S1:
ART + chemotherapy.
Because the response to chemotherapy is slow in KS and because ART is an essential part of KS treatment, it is good practice to start ART soon after or concurrent with the chemotherapy, especially in patients with advanced immune deficiency.

Treatment protocols

According to the KS stage and underlying conditions:

Stage	Underlying condition	Regimen	Comments
T0SO/T0S1	All patients	ART alone	
T1S0, T1S1	- Neuropathy or patient on D4T, DDI, INH - Poor bone marrow reserve or patient on AZT	- Bleomycin alone (15 mg single dose IM every 2-3 weeks) - Bleomycin alone (15 mg single dose IM every 2-3 weeks) or bleomycin (10mg/m2) /Vincristine (2 mg) IV every 2 weeks	- Start ART as soon as possible

Treatment response

4 categories of response to KS treatment are considered:
Complete response: absence of any detectable residual lesion, including tumour-associated oedema, persisting for at least 4 weeks.
Partial response: A 50% or greater decrease in the number and/or size of previously existing lesions lasting for at least 4 weeks without the appearance of new skin or oral lesions or new visceral sites of involvement, and without the appearance or worsening of tumour-associated oedema or effusions, and without an increase of 25% or more in the product of bi-dimensional diameters of any indicator lesions.
Stabilization: any response not meeting the criteria for progression or complete/partial response.

Progression: Increase of 25% or more in the size of previously existing lesions and/or the appearance of new lesions or new sites of disease and/or a change in the character of 25% of more of the skin or oral lesions from macular to plaque-like or nodular. The development of new or increasing tumour-associated oedema or effusion is also consider as disease progression.

Duration

After 3 months of chemotherapy (+ ART):
- If complete or partial response: stop chemotherapy, continue ART;
- If stabilization or progression: continue chemotherapy for 3 more months (if tolerated) + ART. Check ART adherence.

At 6 months of chemotherapy (+ ART):
- If complete or partial response: stop chemotherapy, continue ART;
- If stabilization or progression: assess ART adherence, ART treatment failure.

Side effects

Bleomycin:
- Pulmonary fibrosis. The risk increases with cumulative doses. A total dose of more than 400 mg must not be given.
- Stomatitis, chills and fever.

Vincristine:
- Neuropathy and ileus.

7.9 In-Patient Department

Some severe OI will request the patient's hospitalisation, mainly:
- Meningitis: Cryptococcus, bacterial or TB meningitis
- Severe bacterial pneumonia
- Pneumocystis pneumonia with severe dyspnoea
- Diarrhoea with severe dehydration
- TB
- Life-threatening KS

Clinical presentations are already described in specific sections on OI. Below are summarized the complementary investigations and drugs needed to diagnose and treat the OI in IPD.

1/ MENINGITIS

Differential diagnosis will be made by cerebro-spinal fluid analysis. Remember that lumbar puncture is hazardous in the presence of focal neurological deficit (cerebral space-occupying lesion).

CSF examination:

Cryptococcus meningitis	Bacterial meningitis	TB meningitis
- Elevated opening pressure - Protein >> - Glucose low or normal - Lymphocytes >> - Indian ink +/- - Cr Ag +	- Turbid appearance - PMN >500/mm3 - Glucose < - Protein more than 1g/l	- Elevated opening pressure - Lymphocytes >> - Glucose < (or normal) - Protein >> - AFB +/- (sensitivity 10%)

Treatment: see also specific sections on OI

Cryptococcus meningitis	Bacterial meningitis	TB meningitis
<u>Preferred regimen</u>: Amphotericin B IV (0.7/mg/kg) for 14 days followed by fluconazole (400mg po od) for 8 weeks. <u>Alternative regimen</u>: Fluconazole (400mg po od) for 10 weeks with a starting loading dose of 800 mg od for 3 days. <u>Repeated LP</u> is indicated to control elevated intracranial pressure if there is failure to respond or with new symptoms after > 2 weeks of therapy.	Ceftriaxone (2g IV od) x 7 days.	- According to national protocol but - Best treatment is (and should be advocated for): 2SHRZ/7RH (eventually 2 ERHZ/7RH). See section on TB/HIV co-infection.

Use of Amphotericin B

Side effects	Most of the time, patients present with moderate reaction: fever, chills, vomiting, diarrhoea, epigastric pain, phlebitis, neurological disorders. In some cases, it can be severe: - Anaphylactic shock (very rarely): prevention relies on test-

	dose and pre-medication before infusion. - Nephrotoxicity (more common): increases when the patient is dehydrated and when the total cumulative dose given reaches 2 to 3 g. Diuresis must be monitored carefully. In case of oliguria or anuria, Amphotericin B treatment must be stopped without delay. Doing so, kidney failure improves and resolves in most of the cases.
Pre-medication	- Salt loading with 500ml of Normal Saline over 2 hours to avoid nephrotoxicity; - 1g po Paracetamol and 25mg po Promethazine is given 30 to 60 minutes before infusion.
Test-dose	- 1 mg of Amphotericin B over 1 hour. Then stop infusion and wait 30 minutes. - During test-dose, drip must be stopped if the following symptoms of allergic skin rash with generalized itching or fall of the blood pressure.
Administration	- Reconstitute each vial of 50 mg with 10 ml of water for injection, then shake immediately and gently to dissolve. - The daily dose for each patient shall not exceed 1mg/kg. - Dilute the daily dose inside 500ml of Glucose 5%. - Let it run over 4 hours.
Monitoring	- If oliguria or anuria: stop Amphotericin B, increase fluid intake (normal saline IV or oral drinks), and give Furosemide I.V.and Spirolactone (aldactone). - If anaphylactic reaction: stop infusion, give Dexamethasone IV 10mg, Adrenaline SC 1 mg (to repeat 5 to 10 min later if no improvement) and colloids (500 cc to run over 30 min only until the systolic B.P. comes up to at least 80 mm Hg)
Caution	Avoid concomitant use of other nephrotoxic drugs (e.g. amino-glycosides, NSAIDs)

2/ <u>SEVERE BACTERIAL PNEUMONIA</u>

Signs of serious respiratory illness

- Cyanosis (examine the lips, the buccal membranes and finger nails) - Nasal flaring

- Intercostal or subclavical in drawing - Respiratory rate >30/min - Heart rate > 125/min - Altered level of consciousness (drowsiness, confusion)

Complementary investigations

- Chest X-ray: it shows lobar consolidation in typical pneumonia and multilobar, nodular or reticulonodular patterns in atypical ones
- Sputum examination: ask for gram stain and AFB.

Treatment

Antibiotic therapy (7 days)	- Amoxycillin (+/- clavulanate) (1g IV tid to qid) or ceftriaxone (1 to 2 g IV od) - With (if atypical bacteria) erythromycin (50mg/kg/day IV divided in 4 doses) or doxycycline (100 mg po bid)
Adjuvant therapy	- Paracetamol against fever: 3 to 4 g to be divided in 3 to 4 doses per day (po or IV) - Oxygen at a rate of 1 liter/min - Maintain adequate hydration and nutrition

3/ PNEUMOCYSTIS PNEUMONIAE

Patients presenting with suspected Pneumocystis pneumonia may be managed as outpatient or be hospitalised (hypoxia and severe dyspnoea).

Complementary investigations

- A typical chest x-ray shows diffuse, bilateral interstitial or alveolar infiltrates ('ground glass' appearance). Sometimes there are nodules or cavities, but the x-ray can be misleadingly normal (25%).
- Hypoxia and increased LDL are always present (usually not available).
- Definitive diagnosis is given by PCO stain on broncho-alveolar lavage (BAL) aspirates and histopathology (usually not available).

Treatment

CTX (TMP 20mg/kg – SMX 100mg/kg/daily divided over 4 doses x 21 days).
The first few days of antimicrobial treatment are critical since the decomposition of many dead parasites exacerbates the pre-existing inflammatory process and aggravates pneumonia. In patients whose arterial oxygen tension is less than 70 mmHg (usually not measured in practice but patient severely dyspnoeic or with worsening condition), prednisolone should be

added at a dose 40 mg po bid x 5 days, then 40 mg po od x 5 days, then 20 mg po od x 11 days.

4/ DIARRHOEA WITH SEVERE DEHYDRATION

Hydration status
It should always be assessed in a patient complaining of diarrhoea. Clinical evaluation of dehydration may be done as described in the following table:

Clinical features	Mild dehydration	Moderate dehydration (2 signs present)	Severe dehydration (2 signs present)
General appearance	Thirsty, alert	Thirsty, alert	Generally conscious, anxious, cold extremities, clammy, cyanosis, wrinkled skin of fingers, muscle cramps, dizzy if standing
Pulse	Normal	Rapid	Rapid, thready, sometimes absent
Respiration	Normal	Deep, sometimes rapid	Deep and rapid
Systolic BP	Normal	Normal	Low, sometimes immeasurable
Skin elasticity	Normal: fold of pinched skin disappears at once	***Decreased***	Fold disappears very slowly (> 2 seconds)
Eyes	Normal	***Sunken***	***Severely sunken***
Tears	Present	Absent	Absent
Mucous membranes (test mouth with a clean finger)	Moist	Dry	Very dry
Urine output	Normal	***Reduced, dark urine***	Anuria, empty bladder
% of body weight loss	1 – 5 %	6 – 9 %	10 % or more

Estimated fluid deficit	10 – 50 ml/kg	60 – 90 ml/kg	100 ml/kg

Hospitalization is always indicated for severe dehydration.

Rehydration protocol

Degree of dehydration	Type of liquid	Volume to give	Rate
Mild	ORS	50 ml/kg	In 4 hours
Moderate	ORS	100 ml/kg	In 4 hours
Severe	Ringer 's lactate solution (Hartmann's solution)	110 ml/kg	In 4 hours: at first as rapidly as possible until a radial pulse is palpable

Note: If ringer's lactate is not available, use

- Half strength Darrow' s solution (also called lactate potassic saline solution; this is prepared by diluting full strength Darrow's Solution with an equal volume of 5% or 10% glucose solution).
- Normal saline (also called isotonic or physiological saline) with sodium bicarbonate and potassium chloride added
- Normal saline diluted to half – strength with 5 % glucose (Dextrose)

None of these solutions is as effective as ringer's lactate solution.
Plains glucose (dextrose) should not be used.

Fluid maintenance therapy:

After the re-hydration protocol above, cater for ongoing losses. For every stool lost give as much fluid as desired. Thirst is the best guide for maintenance fluid therapy. Patients should drink as much ORS (and other liquids) as they desire.

Treatment of diarrhoea is described in section on OI – diarrhoea.

5/ TUBERCULOSIS

Decision to hospitalize TB/HIV co-infected patients depends on their clinical status. They may also suffer from other OI, which leads to deterioration of their general state (e.g. oesophageal candidiasis leading to poor food intake).
Some national programmes require that all newly diagnosed TB patients be hospitalized during a part or all the intensive phase. For others, there is a move away from an inpatient intensive phase towards outpatient management, which helps to decrease the burden in already crowded adult medical and TB wards.

Infectious TB in-patients require isolation. Patients are generally infectious for the first 10 days – 2 weeks following initiation of treatment.

6/ KAPOSI SARCOMA

Life-threatening lesions may require hospitalization until regression of the lesions is seen and patient's life is not in danger anymore.

Life-threatening lesions include:
- Pulmonary KS: dyspnoea without fever, occasionally haemoptysis, association with severe mucocutaneous lesions of KS, sometimes a sero-hematic pleural effusion, and in all cases absence of PTB.

- And/or facial Kaposi with skin lesions AND oedema of the face, or eye localization or oral cauliflower like lesions.

Complementary investigations:
A pleural puncture will help to make a differential diagnosis between pulmonary Kaposi sarcoma and TB, as the analysis will reveal a sero-hematic effusion if KS origin and a straw-coloured one if due to TB. Both effusions are exudates.

Treatment
- Treatment KS disease is described in section on OI-Kaposi sarcoma disease.
- For pain management and palliative care for terminally ill patients, see below. .

7.10 Palliative Care

Palliative care is the provision of appropriate relief from physical and psychological discomfort in the absence of cure.

In the current era of ART, there should be very few circumstances when medical care is no longer effective, or the side effects outweigh the benefits of treatment. These would include end stage liver or renal diseases.

Palliative care includes:
- Pain relief,
- Appropriate nursing care to keep the person comfortable

- Psychological support
- No aggressive treatments.

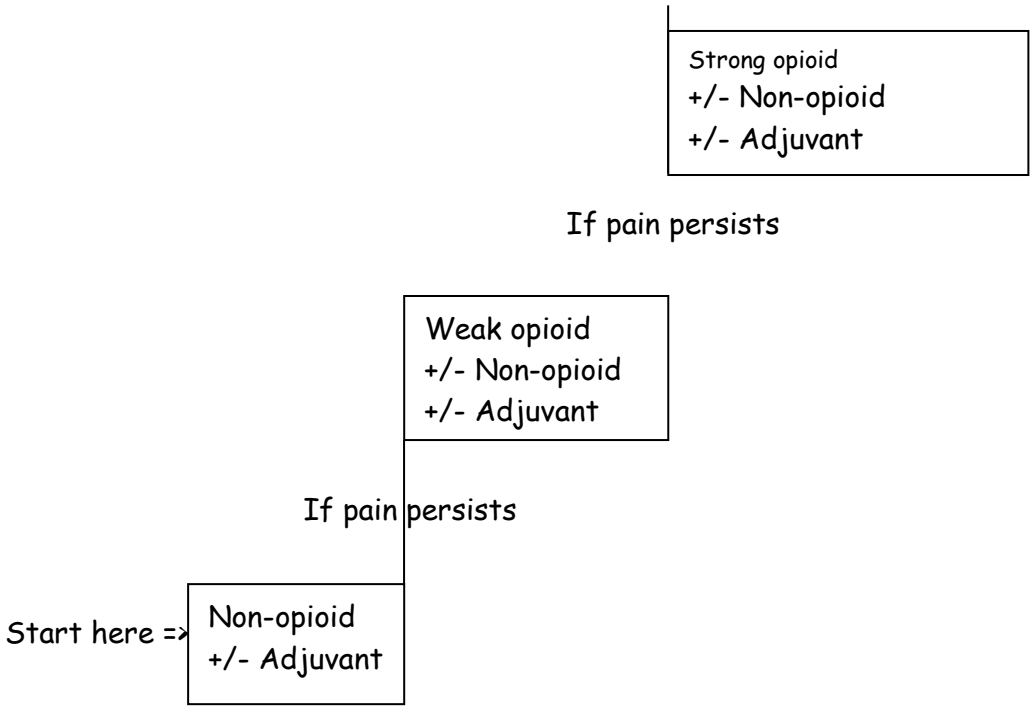
Pain relief, for acute or chronic pain

- If possible give oral painkillers
- Give painkillers at fixed time intervals
- Start with low dose and increase until the patient is comfortable
- Give next dose before previous dose wears off (specifically in chronic pain)
- Treatment must be individualised (see below)

An initial assessment of the patient's pain includes believing the patient's complaint, establishing the severity of the pain preferably by using a visual scale (pain quoted from 0 to 10, 0 being no pain at all) and assessing the restriction it causes. A physical examination that includes a psychological assessment is important to rule out any treatable causes of the pain.

The analgesic ladder (WHO) defines three level of pain with adapted painkillers for each level:
- Non-opioids such as aspirin, paracetamol and ibuprofen,
- Weak opioids such as codeine and dextropropoxyphene,
- Strong opioids such as morphine and tramadol.

To enhance the efficacy of these drugs, adjuvants that can be used are: carbamazepine, diazepam, amitriptyline, prednisolone.



The side effects of both analgesic and adjuvant medications should be kept in mind and drugs to counteract these side effects should be prescribed (e.g. antinausea, anxiolytic, antidepressant, laxative)

Adequate nursing care

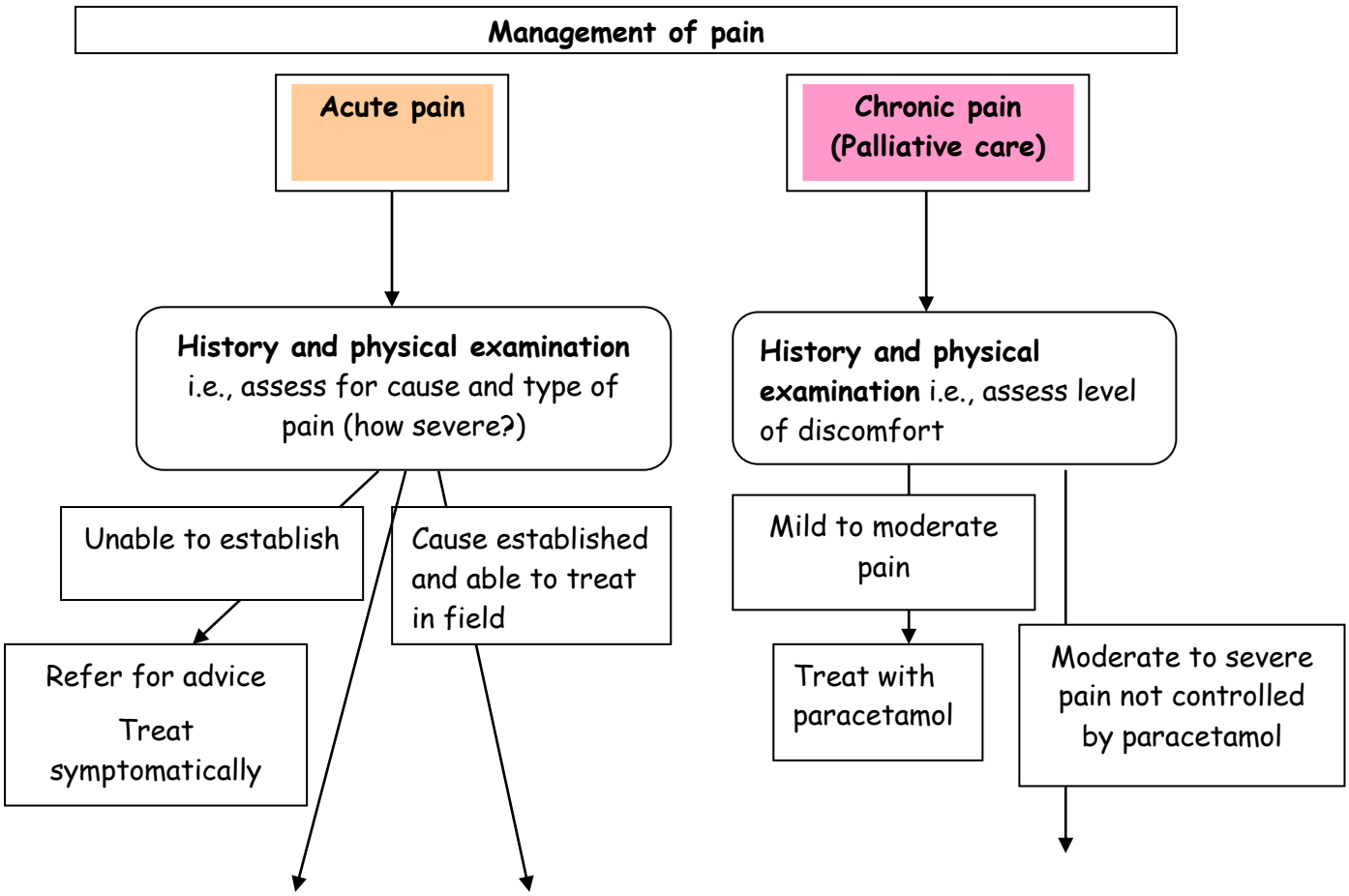
- For chronic pain, provide medications regularly and not episodically,
- Use relaxation measures such as deep breathing, back rubs, body massage,
- Good hygiene of all bedridden patients: keep the patient clean and dry,
- Maintain skin integrity and prevent bedsores.

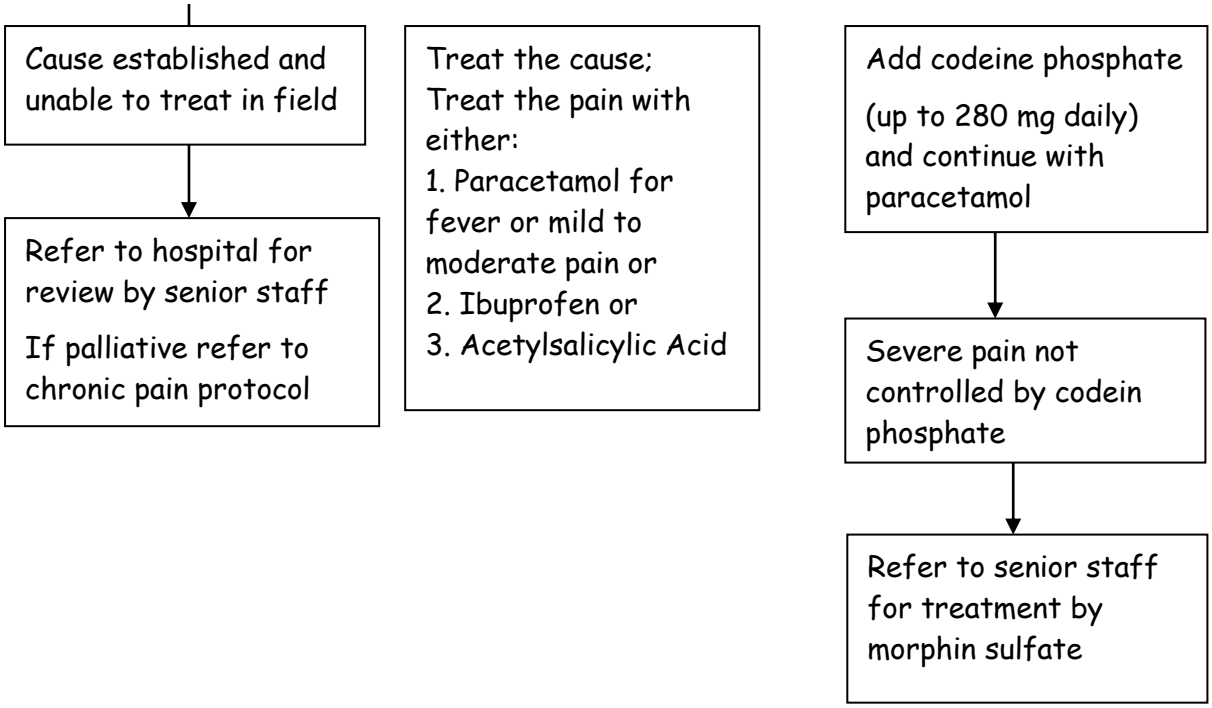
Psychological support

This consists of:

- Assisting the patient in grieving for and coping with the continuing losses they are experiencing consequent to the impact of HIV infection,
- Helping the person, their relatives and carers to organize their lives, orient them to the forthcoming issues and concerns about dying,
- Preparing the person and their loved-ones for death.

In hospital settings, most of the care will be undertaken by a nurse. If possible, encourage the relatives to provide palliative care at home after being taught the interventions that can be applied to help care for the dying.





7.11 Drugs & Basic Investigations Needed for OI Manangement

The table below summarizes the drugs and minimum complementary investigations needed to treat opportunistic infections linked to HIV/AIDS disease.

OI	Drugs	Investigations
Fever	According to findings. If no cause, ciprofloxacin	WBC and differential, malaria smear, urinalysis, AFB smear, chest x-ray, CSF examination
Lymphadenopathy	According to findings	Lymph node aspiration for AFB, RPR chest x-ray
TB	6-month rifampicin based regimen prednisolone pyridoxine	AFB smear (sputum, CSF, fine needle aspiration) Chest X-ray Protein tests: Pandy (CSF) and Rivalta (body fluid)
Bacterial pneumonia	Amoxicillin	Sputum examination (Gram stain)

	Amoxicillin/clavulanate Doxycycline or erythromycin Ceftriaxone (IV)	Chest X-ray
PCP	CTX Prednisolone Dapsone	Chest X-ray
Toxoplasmosis	Sulphadiazine Pyrimethamine Folinic acid CTX	
Oral conditions: thrush, ulcerations, OHL, angular cheilitis	<u>Topical:</u> Miconazole gum patch Clotrimazole cream GV or povidone-iodine <u>Systemic:</u> Fluconazole Acyclovir Prednisolone Painkiller	
Oesophageal conditions	Fluconazole Acyclovir Prednisolone Painkiller	
Acute diarrhoea	ORS Ampicilline	Stool examination if possible

	Ciprofloxacin Metronidazole Albendazole Codein-phosphate or loperamide	
Chronic diarrhoea	ORS Ciprofloxacin Metronidazole CTX Albendazole Codein-phosphate or loperamide	Stool examination if possible
Skin conditions	<u>Topical:</u> GV Povidone-iodine Clotrimazole cream Clotrimazole pessary Whitefield's ointment C/C ointment or solution C/C + neomycin ointment Benzyl benzoate Hydrocortisone ointment <u>Systemic:</u> Acyclovir fluconazole	

	Cloxacillin Carbamazepine Painkiller	
Bacterial meningitis	Ceftriaxone	CSF examination: Gram stain, cell type/count/aspect, Pandy test (protein)
Cryptoccocus meningitis	Amphotericin B Fluconazole Paracetamol Promethazine	CSF examination: Indian ink/ CRAG, cell type/count/aspect, Pandy test (protein)
PNP	Amytriptyline Carbamazepine Pyridoxine	
KS	Vincristine Bleomycin	
Pain management	Paracetamol or aspirin or ibuprofen Codeine or dextropropoxyphene Morphine or tramadol Carbamazepine, diazepam/amitriptyline, prednisolone	

Chapter 8: ANTIRETROVIRAL THERAPY

8.1 Inclusion Criteria

- Inclusion criteria includes the eligibility criteria, both medical and psychosocial, and the recruitment process.
- Once medically eligible to start ART, the patient will need to be stabilised for any acute OI and educated on ART issues and especially adherence.
- Decision to treat with ARV drugs will be taken by multidisciplinary team at the clinic level.

Patient considered to be enrolled in antiretroviral treatment (ART) should meet both medical and psychosocial criteria. The process should not delay the start of ART. **But the prompt start of ART should not occult the minimal medical and counselling management required prior to ART**. Usually, 2 weeks are the average time needed to prepare the patient to start ART.

- **MEDICAL CRITERIA**

1. **Patient confirmed HIV+** : see HIV testing protocol for Timor-Leste

2. **All opportunistic infections should be stabilized**: all candidates for ART must be carefully screened for evidence of active OI (especially TB) before ART is commenced to minimize the risk of immune reconstitution syndrome (see Chapter 9: Immune Reconstitution Inflammatory Syndrome).

3. **CD4 count or WHO clinical stage**:

✓ **adults and adolescents**:

- CD4 < 350 cells/mm3 for WHO clinical stage 1 and 2
- WHO clinical stage 3 and 4, irrespective of CD4 count
- TB/HIV co-infection, irrespective of CD4 cells count
- HBV/HIV co-infection, in need of treatment for HBV, irrespective of CD4 cells count.

✓ **children and infants**:

- < 24 months: start immediately after HIV confirmation (clinical staging is not relevant for children less than 24 months)
- > 24 months: WHO clinical stage 3 and 4, treat irrespective of CD4

- If Stage 1 & 2: (don't treat if no CD4)
  - 24 months to 59 months: start ART when CD4% <25% or CD4 count < 750 cells/mm3
  - 5 years and above: start ART when CD4 < 350 cells/mm3

Important notes on CD4 count:

CD4 count is an indicator of immunosuppression more reliable than WHO clinical stage. CD4 count is important in identifying patients who are eligible for antiretroviral therapy.

However, **CD4 count is not a pre-requisite** for providing HIV/AIDS care and ART in HIV + confirmed patients in WHO stage 3 and 4. Once patients have reached clinical stage 3 or 4 of disease progression, they have a high short-term mortality, and delay in waiting for CD4 counts can result in significant mortality.

If ART is started on clinical basis, the clinician should objectify non-specific conditions of stage 3 such as unexplained loss of weight, chronic diarrhoea and fever.

CD4 count is also helpful in the clinical management of OI and in the follow up of ART.

- **PSYCHO-SOCIAL CRITERIA**[14]

Adults

- All medically eligible patients should receive ART as soon as they are ready to start. Criteria to define readiness to start are given below. They should not be used as exclusion criteria. They do not help to decide if the patient is entitled to receive ART but when (s)he is thought to be ready to start. They also help to identify the type of adherence support that should be organized for this patient.

- Patient must be educated on the benefits and constraints of ART, how to take it, the relevant potential side effects, the importance of good adherence to a successful outcome, and the need for ongoing clinical +/- laboratory monitoring. Counselling or "adherence " sessions should be offered to the patients, individually or preferably in a group as well as written IEC material (in patient's own language if possible).

- It is recommended that patients disclose their HIV+ status to at least one friend or family member. However, disclosure should not be a pre-requisite and treatment should not be delayed initiation while waiting for disclosure or a suitable treatment assistant. Instead these should be continually encouraged even after starting ART, for these exceptional cases.

-Patients should be able to attend regular visits for clinical +/- laboratory follow-up and cotrimoxazole prophylaxis.

[14] See section on ART adherence, section 8.10

-Problems of alcohol abuse, illicit substance addiction and active mental illness should be addressed and treated if possible, as they adversely affect adherence capability.

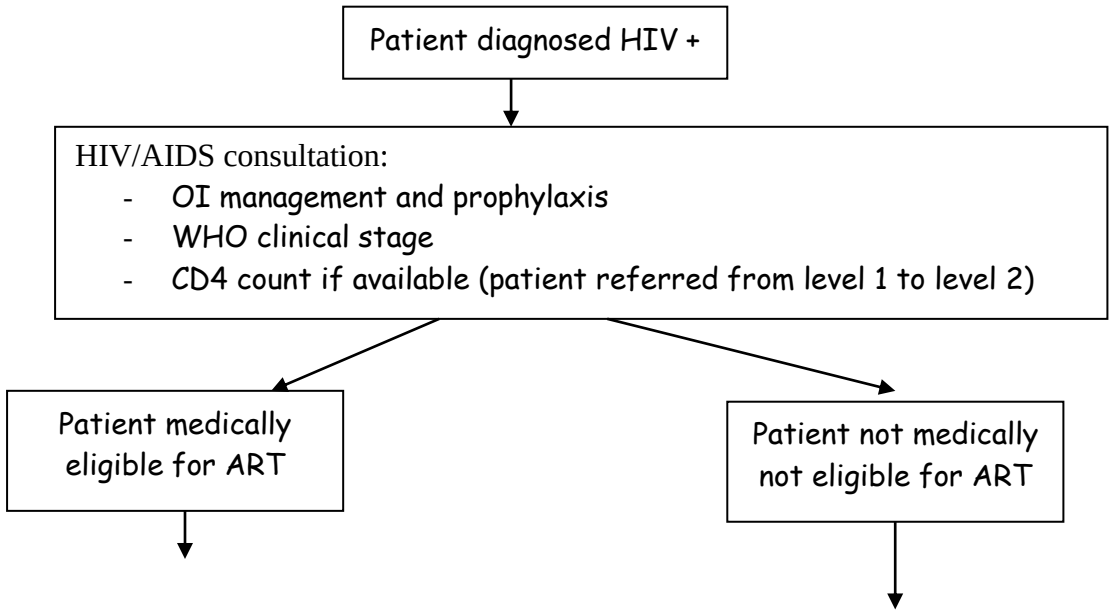
Adolescents

Adolescents are part of a specific group that needs its own and adapted attention. Adolescents are in opposition and need to prove their independency.
Special adolescent counselling session or individual support need to be provided according the needs. ***Competencies should be developed in Timor-Leste to answer to this specific patients group***.

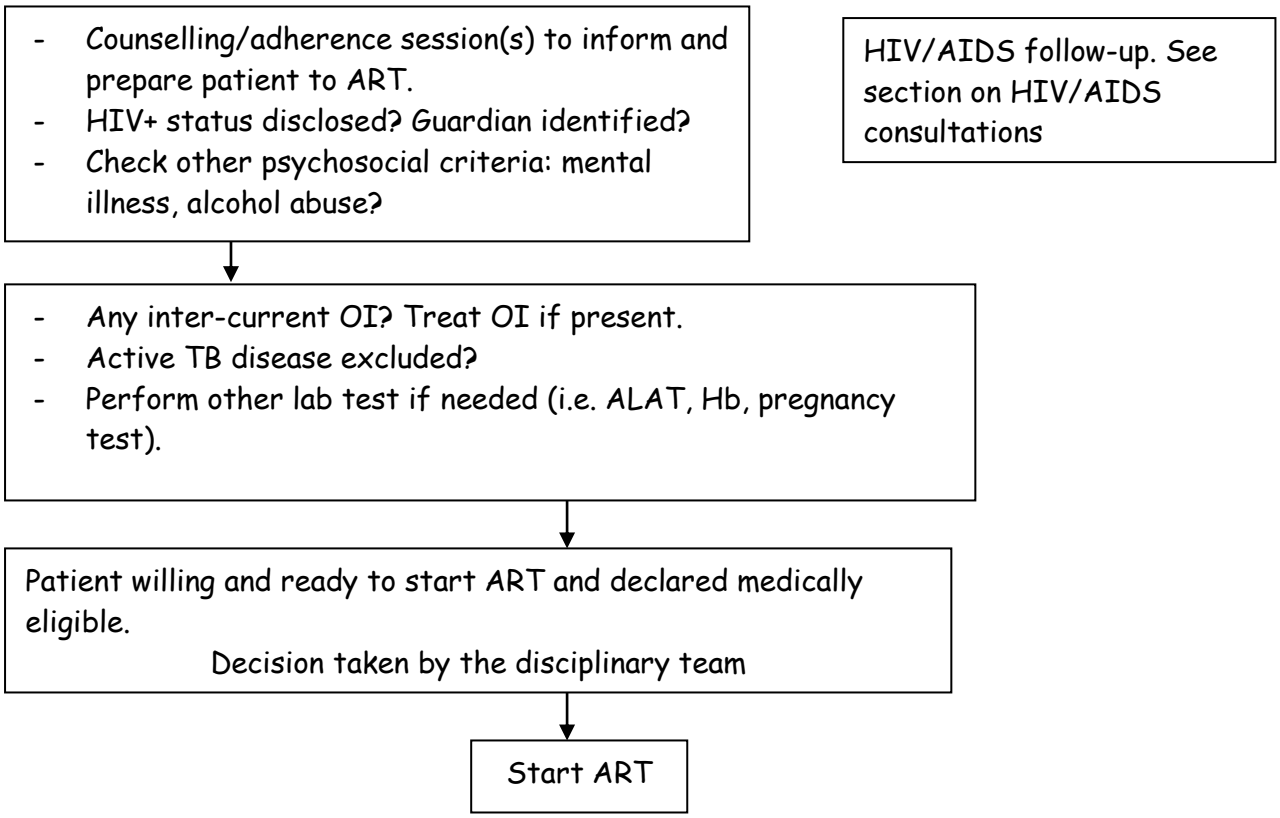
Infants and children

Usually if parents are still alive, they are also benefiting of the HIV care and treatment program. However, due to HIV infection, many children are orphans and are taken care of by members of family or care givers who are not HIV positive. Specific attention should be given to orphans as they are more vulnerable to drop out the program and not being properly taken care off (stigma, less attention, no priority for sick children).
Special support group with adapted information to children should be available at each ART center or at least at the national referral hospital (HNGV) and specific competencies need to be developed in Timor-Leste for addressing HIV positive children counselling and support needs.

8.2 Inclusion Process15



[15] Cf section 8.9



8.3 ART ELIGIBILITY DECISION

If possible, the decision to start a patient on ART should not be confined to a single individual namely the clinician. Direct exchange of information at the clinic level between the clinician and adherence support counsellor should be in place to ensure that all elements have been taken into account before the patient is enrolled in ART program.

Clear documentation of the counsellor's important findings and concerns will be recorded in the patient file. It can be very helpful and the clinician will take an interest to read these details. Frequently information obtained by the counsellor does not reach the clinician, adversely affecting true understanding of a patient's situation.

Regular team meeting (weekly or fortnightly) will be organized in ART centers where ART initiation and failure management take place for case review and therapeutic decision-taken.

8.4 REASONS TO DEFER ART

A patient may have antiretroviral therapy postponed due to:

- Not fulfilling clinical +/- immunological criteria for ART,
- Not have gone through the preparation process to ART
- Being an unreliable clinic attendee, i.e. patient has not respected appointments for adherence counselling session or to pick up CTX drugs (unless there is specific valid explanation for individual circumstances),
- An acute opportunistic infection that requires immediate management,
- Acute or uncontrolled depression or alcohol (or other substance) abuse.

Patients are "treatment ready" when:

- They show understanding of what can be expected on ART,
- They have understanding of the possible side effects they may experience and what to do if severe,
- They recognise the importance of timely daily therapy,
- They have accepted their HIV status and preferably disclosed to a friend or family member able to support them.

8.5 Recommended First Line Regimens in Timor-Leste

2 NRTIs + 1 NNRTI
Recommended first line regimens are a combination of two nucleosides (NRTI) and one non-nucleoside (NNRTI) reverse transcriptase inhibitors

8.5.1 Adults and Adolescents

TABLE 1: ADULTS AND ADOLESCENTS

Regimen	Indications	Contra-indications
TDF-3TC-EFV (1 tab OD)	Preferred 1st line	Renal functions impairment < 15 years old Pregnancy
AZT-3TC-EFV (1 co-blister daily: AZT/3TC BID + EFV OD)	Alternative 1st line: • TDF intolerance • Pregnancy and CD4> 250 cells/mm3	1st trimester of pregnancy Hb < 7,5g/dl
AZT-3TC-NVP	Alternative 1st line:	Female with CD4> 250

(1 tab BID)	• Already on this regimen • Pregnancy during 1st trimester	cells/mm3 TB/HIV coinfection with rifampicine based regimen Hb < 7,5g/dl

First line regimen might be adapted to pre-existing conditions: i.e.

- TB & HIV co-infection: EFV based regimen is preferred, NVP should not be administered concomitantly with rifampicine
- Pregnancy: refer to PMTCT protocol, EFV should not be administered during the 1st trimester of pregnancy
- Hepatitis B coinfection: TDF/3TC based regimen is recommended

D4T (stavudine) is not recommended anymore by WHO, due to its severe and definitive side-effects. All patients on d4T based regimen should be switched to one of the recommended 1st line options as soon as possible.

TABLE 2: DOSAGES OF FIRST LINE REGIMENS IN ADULTS AND ADOLESCENTS

1st line regimen	Dosage
AZT-3TC-NVP	- AZT 300 mg twice daily - 3TC 150 mg twice daily - NVP 200 mg daily first 2 weeks (leading dose), then 200 mg twice daily
AZT-3TC-EFV	- AZT 300 mg twice daily - 3TC 150 mg twice daily - EFV 600 mg at night
TDF-3TC-EFV	- TDF 300 mg daily - 3TC 300 mg daily - EFV 600 mg daily

First line regimens should preferably be given as a fixed dose combination (FDC). FDC have considerable advantages over individual drugs to prevent dual or mono-therapy and to facilitate adherence due to the decrease pill burden. FDC exist for AZT/3TC/NVP, AZT/3TC, AZT/3TC+EFV (co-blister), TDF/3TC/EFV, TDF/3TC, ABC/3TC, ABC/3TC/AZT

8.5.2 Children and Infants[16]

Most of the paediatric ARV drugs are available as fixed dose combinations. The FDCs are preferable to the syrups as soon as the child can swallow properly (usually at 1 year old). The dosage adapted to the

[16] See Annexes 8.1 and 8.2 for paediatric dosages

body weight is more accurate with tablets than with syrups. Therefore the risk of subdosage (resistance) is lower with tablets.

TABLE 3: CHILDREN AND INFANTS

Regimen	Indications	Contra-indications
AZT+3TC+NVP	Preferred 1st line	TB/HIV coinfection with rifampicine based regimen
AZT+3TC+EFV	Alternative 1st line: • TB/HIV coinfection (rifampicine based regimen)	< 3 years old or < 10 kg
ABC+3TC+AZT	Alternative 1st line: • TB/HIV coinfection (rifampicine based regimen) and less than 3 years old or < 10 kg • Intolerance to NVP and < 3 years old or < 10 kg	
ABC+3TC+NVP	Alternative 1st line: • Anaemia on AZT	
ABC+3TC+EFV	Alternative 1st line: • Anaemia • TB/HIV coinfection	< 3 years old and < 10 kg
AZT or ABC + 3TC + LPV/r	• Exposed to NNRTI during PMTCT	

8.6 ARV DRUGS CONTRA-INDICATIONS

TABLE 4 : ARV DRUGS CONTRA-INDICATIONS

AZT	- Hb level < 7.5 g/dl - Association with D4T
NVP	- Severe clinical pre-existing hepatic failure or baseline ALAT grades 3 /4
EFV	- EFV is contra-indicated during the first trimester of pregnancy; it may be considered during 2nd and 3rd trimester if no alternative exists. - Severe clinical pre-existing hepatic failure or baseline ALAT grades 3/4
TDF	- Creatinine clearance < 50 mg/ml - Co-administration with DDI or ABC - Children < 15 (unknown affects on bone mineral density) - Pregnant women

ABC	- Co-administration with TDF - Previous hypersensitivity reaction to ABC. In case of HPS, ABC must be ceased immediately and NEVER recommenced as this can result in death.

8.7 ARV FOOD AND DRUGS INTERACTIONS

- There is no food interaction with the first line regimens described above. The drugs may be swallowed with or without food.
- NNRTI drugs (and protease inhibitors used in 2nd line regimen) interact with the cytochrome P450 liver enzyme system, resulting either in inhibition or induction of these enzymes. Co-administration of other drugs metabolised by the same system results in potential increased of toxicity because of elevated drug concentrations or drug failure attributable to sub-therapeutic drug concentrations.

TABLE 5: DRUGS INTERACTIONS

Drug	Interaction
Rifampicine	NVP (and all PIs) cannot be co-administrated because of reduced ARV drug concentrations. Therefore, EFV will be the drug of choice in case of co-administration of rifampicine-containing TB treatment. No increase of the EFVdose is needed.
Oral contraceptive pills	Their effectiveness is reduced if taken with NVP, EFZ and any of the PIs. Women should be informed to use a barrier contraceptive method, i.e. condom (standard recommendation for all HIV+ patients: avoid infecting others; avoid new infection from other HIV-infected people).
Ketoconazole	Blood levels are significantly lowered with use of NVP. In addition, fluconazole should be the systemic anti-fungal of choice as ketoconazole bioavailability is decreased by gastric hypochlorhydria, which is common in AIDS patients (while Fluconazole also causes some hepatic enzyme induction, routine dose modification is not recommended).
Carbamazepine	Because of alteration of drug plasma concentrations, the co-administration of carbamazepine with EFV and LPV/r should be avoided.
Benzodiazepines	Should be avoided with EFV due to increased risk of sedation. Only diazepam might be used in case of sleep disturbances.

Herbal or traditional treatments	Over-the-counter and traditional herbal treatments should be avoided with all ARV drugs as they might lead to inadequate ARV drug concentrations. E.g. garlic supplement or St John's Wort (millepertuis), which is a popular herbal remedy for treating mild depression, reduces the plasma concentration of all ARV drugs.

8.8 Management of Treatment Interruption of NNRTI Containing Regimens

Elective treatment interruption is not recommended. However if for any reason, it is necessary to interrupt an ART regimen containing NVP or EFV, the two associated NRTIs should be prolonged for 7 days after NVP or EFV has been stopped.

In case of unplanned treatment interruption of a NVP containing regimen (e.g. because the patient has not been able come to the consultation before running out of drugs) and of subsequent re-initiation of the treatment,
- the NVP should be restarted at the full dose (ie 200mg bid) if the interruption lasted less than 7 days
- half the dose of NVP (ie 200mg od) should be given for the first 2 weeks if the interruption lasted more than 7 days.

8.9 Objectives and Tasks of ART Consultations

1/ FIRST ART ASSESSEMENT CONSULTATION

This first part has already been developed in the section "HIV organization".

➔ See section on Objectives and tasks of HIV/AIDS consultations

The **purpose** of this first screening is:
- To evaluate the medical qualification criteria to receive antiretroviral treatment,
- To diagnose and treat any intercurrent opportunistic infection (especially TB),
- To assess adherence on CTX prophylaxis,
- To perform additional laboratory tests if required
- To provide the initial education session (basic HIV and ARV information), done by the adherence counsellor,
- To discuss the benefit of HIV status disclosure, the choice of a treatment support person and to ask for that person to attend next visit if possible

TABLE 6: TOOL FOR THE 1ST ART CONSULTATION

History taking	- Review WHO clinical stage and CD4 count result (if available) - History of recent acute illness by using structured symptom checklist: see section on clinical management - Symptoms of active TB, i.e. fever, night sweats, loss of weight, chronic cough, chest pain, haemoptysis - History of previous antiretroviral treatment (including PMTCT) - History of peripheral neuropathy (for patients who might receive D4T)
Clinical examination	- Complete physical examination, even in the absence of symptoms, including complete skin survey (e.g. for early KS lesions), examination of the mouth, the abdomen (hepatomegaly?), the reflexes (if complain of PNP) - Temperature - Weight, height and BMI or W/H% or MUAC - Signs of active TB, i.e. lymph node, respiratory signs
Diagnosis and treatment of intercurrent infections	- Treat any OI diagnosed according to MSF protocols - Refer for AFB smear and x-ray if suspicion of TB disease
Samples for laboratory	- According to ARV first line regimen, take additional blood samples for laboratory tests: Hb if AZT use, ALAT if NVP use, creatinine if TDF.
Counselling	- Give first education session on basic HIV & ART, individually or in group (counsellor) - Encourage patient to disclose HIV+ status and to bring a treatment support person to the next visit (counsellor) - Explain recruitment process for ART and scheduled visits before and after starting - Explain the limit in time of MSF activities.

2/ SECOND ART ASSESSMENT CONSULTATION

The second visit should occur around 2 weeks after the initial one. Consider a closer visit for patients who are severely ill or with a CD4 count <100/mm3 (e.g. after 1 week).

The patient might only see the counsellor (except if there is a medical problem). The patient has normally had time to consider the implications of ART, to disclose his/her HIV status (possibly with the counsellor's help) and to identify a treatment support person.

The **purpose** of the second visit is:
- To evaluate the patient's understanding and expectations regarding ART: goals, benefit, side effects, adherence issues,
- To clarify all questions about HIV or ART and to reinforce on adherence issues,
- To adapt the ART schedule to the patient's lifestyle
- To explain to the treatment support person his/her role in enhancing adherence to ART,
-To review laboratory results if any (patient doesn't need to be seen by the clinician if all results are within acceptable range.)

3/ ART COMMENCEMENT VISIT

1. **OI has been treated/stabilized**:
    a. If yes, go to next step
    b. If the patient is acutely ill with an opportunistic infection or has been diagnosed with active TB, treat the infection or start TB treatment before initiating ART; you may need to postpone the commencement of ART accordingly

2. **Patient is ready for ART therapy[17]?**

- Patient understands ART, possible side effects, limitations, adherence schedule, etc. and wants treatment; - Patient ready for treatment adherence; - Patient actively involved in own care; - Family and/or social support available (treatment supporter if possible); - Barriers to adherence have been addressed.

    a. If the patient is ready, go to the next step
    b. If the patient is not ready, provide repeat counselling and education; you may want to postpone the commencement of a few days, to allow the patient to understand and reach a better commitment;

3. **Prescription and therapeutic education**
    a. Medical / Clinical assessment

[17] See section on adherence

b. Review the laboratory results of pre-ART laboratory assessment
c. To start the patient on antiretroviral treatment with a detailed description of drug dosing, preferably using a **treatment chart**[18]
d. To re-explain the potential side effects of ARV drugs and what do to do if adverse reactions occur.

4. Data record

a. Update the medical record of the patient with the new prescription
b. Enrol the patient in the ART cohort and data collection according to the national data record and collection

4/ ART FOLLOW-UP VISITS

TABLE 7: FREQUENCY OF VISITS WITH THE MEDICAL DOCTOR AND THE ADHERENCE COUNSELLOR

Timing	ART visit with medical assistant/doctor or nurse	Counselling session with counsellor
1st ART assessment	x	x
2nd ART assessment		x
ART commencement	x	x
2 weeks follow-up	x	x
1 month follow-up	x	x
2 months follow-up	x	x
3 months follow-up	x	x
4 months follow-up	If patient not yet stable (or not yet adherent)	Optional
5 months follow-up		Optional
6 months follow-up	x	x
3 monthly	x	x

- For Laboratory monitoring: See section on laboratory monitoring

5/ FOLLOW-UP consultations

Checklist[19] to detect ARV side effects, as the example below, may be used.

Patients should be told to visit the doctor if the side effect happens very often or in permanence and if it disturbs the patient moderately or a lot.

Specific actions may be taken depending on the signs and symptoms presented by the patient under ART. They may be due to side effect of ART[20], new opportunistic infection, and immune reconstitution syndrome.

[18] See annexes 9.1, 9.2 and 9.3
[19] See annex 6

TABLE 8: LIGHT OR MILD SIDE-EFFECTS MANAGEMENT[21]

Signs or symptoms	Response
Headache	Give paracetamol. Assess for meningitis especially in severely immune-depressed patient (stage III or IV and/or CD4<200). If on AZT or EFV, reassure that it is common and self-limited. If persists more than 2 weeks, check intensively for untreated CNS infection, IRIS, then consider switching ARV drug if still persistent. Refer to HNGV
Fever	Look for possible causes of fever. Control fever.
Fatigue	This commonly lasts 4 to 6 weeks especially when starting AZT. If severe or longer than this, refer to HNGV.
Pallor	If possible, measure Hb. If severe pallor or symptoms or Hb <8.5g/dL, take appropriate decision (blood transfusion (see national guideline for blood transfusion), prescribe supportive ferrous sulphate, switch AZT to TDF or ABC)
Anxiety, nightmares, depression, insomnia	This may be due to EFV. Give it at night. Counsel and support (usually lasts < 3 weeks). EFV should be interrupted if symptoms are persistent or severe depression or suicidal or psychosis. EFV may need to be interrupted and switched to NVP or LPV/r if NVP can't be prescribed. Refer to HNGV.
Rash	If on NVP, assess carefully. If wet, generalized or peeling associated with fever or mucosal involvement, stop drugs and refer to HNGV. (See appropriate flowchart for rash management)
Nausea	Take the drugs with food. If on AZT, reassure that it is common, usually self-limited. Treat symptomatically. If vomiting, hospitalisation may be needed for appropriate support. Refer to HNGV.
Diarrhoea	Hydrate. Follow diarrhoea guidelines. Reassure the patient that if due to ART, it will improve in a few weeks. Follow-up in 2 weeks. Meanwhile, look for other causes of diarrhoea.
Jaundice or abdominal pain	Stop drugs. See appropriate hepatotoxicity flowchart. Refer to HNGV.
Tingling, numbness,	If new or worse on treatment, sign of mitochondrial

[20] See section on side-effects in this chapter
[21] See annexes 10.1 to 10.10 for Side Effects grading and management

pain in the feet/legs	toxicity. Refer to HNGV.
Cough or difficulty in breathing	Look for respiratory infections: TB, PCP, bacterial pneumonia, cryptococcosis, cytomegalovirus infection… and manage accordingly. Refer to HNGV.

8.10 Antiretroviral Treatment Education & Adherence

Strict adherence to treatment with ARV drugs is very important. Poor adherence leads rapidly to the development of viral resistance and hence, to treatment failure. This means a patient should not miss taking pills more than three times a month in case of a twice-daily regimen.
ART should be adapted to patient's lifestyle. Adherence problems should be anticipated and solutions explored with the patients. It is necessary to not underestimated the importance of emotional support given to the patient and his/her family.

1/ MEASURES TO OPTIMISE ADHERENCE TO ART

Ensure free and simplified treatment with uninterrupted supply of ARV	- Provide free ARV drugs: see section on access to HIV/AIDS care - Ensure no stock-out of ARV drugs - Simplify treatment minimizing pill burden with fixed dose combinations (FDC).
Prepare health facilities and set up PLWHA groups for adherence support	- Make health facility user-friendly and trustworthy: respect confidentiality, overcome stigma and discrimination. All the staff of the health centre should be trained on confidentiality. - Train all health workers for adherence support and ensure that the same adherence messages are given by all health workers to patients - Promote and facilitate peer support groups of PLWHA introduced trough the health facility (if large number of patients, organize groups according to ART duration, gender, adults/children, etc) - Mobilize community volunteers for treatment education and adherence support (information about HIV and its treatment) in the community

Prepare patients before initiating ART	- Establish a trusting relationship with health workers and provide necessary information (see below) - Encourage participation of PLWHA to support groups. - Assess factors that help determine capability for follow-up, i.e. regular attendance to the clinic, transportation difficulties, adherence to CTX prophylaxis - Encourage patients to identify a treatment assistant, ideally a household member or a friend, who can accompany them to clinic appointments and help to support them with adhering to treatment on a day-to-day basis.
Monitor adherence and provide ongoing support and education	- Develop an appointment schedule with possibility of access to services between planned visits for advices and care if needed. An organized appointments record will also help the health providers to identify patients missing appointments and hence not picking up the drugs - Give buffer stock for a few days (e.g. give 1 box of 30 days and ask the patient to come back after 28 days). - Assess adherence to treatment in a supportive manner (see below).

2/ PREPARE PATIENTS BEFORE INITIATING ART

The most important issues regarding adherence are:

- A good understanding by the patient of ART requirement and a strong motivation to take the ART;
- An inclusion process that maintains a strong focus on treatment education. Two to three education sessions may be enough, although some patients will need more time.

Key advice points to prepare patient for ART:

HIV/AIDS infection and its natural progression
ART: - Life-saving, but requires a lifelong commitment from the patient - The ARV drugs do not cure HIV/AIDS infection - The ARV drugs do not prevent HIV transmission to others: patients need to practice prevention, i.e. condom use
Need for complete adherence: - Must be taken evening, at the right time (every 24 hours) in case of once-daily regimen such as TDF/3TC/EFV, without interruption

- Must be taken morning and evening, at the right time (every 12 hours) in case of twice-daily regimen such as AZT/3TC/NVP, without interruption - If the patient forgets more than 3 times a month, treatment may fail in the long-run - If a patient forgets a dose, do not take a double dose; instead take the forgotten dose if within 4 hours of usual time; beyond four hours wait until the next usual dose; in both cases report event to counsellor at next visit. - Drugs must not been shared with the family members or friends, patients must take full doses
Side effects and interaction: - Warn patients about common expected side effects, i.e. headache, nausea, fatigue, skin rash and what to do if side effects occur (but do not overload patients with information, or frighten them) - Explain food interaction with ARV drugs if any
Importance of HIV status disclosure for support from others - Support from family or friends - Support from other PLWHA, or peer support by joining PLWHA support group
Importance of testing partner(s) and children

3/ ASSESSMENT OF ADHERENCE TO TREATMENT

Adherence assessments should be done on a monthly basis at least for the first 6 months of ART. The goal is to identify patients who are having difficulty with adhering to treatment so that extra assistance can be offered to these individuals.

Review the medications with the patient, with/without the treatment assistant	If poor adherence, determine problem
Ask in a respectful and non-judgemental way: - "Many patients have trouble taking their medications. What trouble are you having?" - "Can you tell me when/how you take the pills?" - "When is it the most difficult for you to take the pills?" - "It is sometimes difficult to take the	- Side effects? - Simply forgot? - Falling asleep in the evening? - Ran out of pills? - Which dose missed: morning or evening? - Remind you of HIV? - Misunderstood? - Changed work situation? - Not comfortable taking the

pills on time. How many have you missed in the last four days and the last month?" Ask about the common important factors that may interfere with adherence. Ask about stigma related to taking the pills. Count pills: The health worker counts the number of pills remaining in the bottle or box, and compares it to the number of pills that should be remaining if adherence had been 100% since the last visit. The monthly adherence % may be calculated: (tablets dispensed to be taken – tablets returned that were supposed to be taken) /(tablets prescribed) x 100. E.g.: (28-5) / 28 x100= 89% of adherence.	pills around others? - Stigma? - Different timing when away from home or holiday, travel, weekend? - Seldom at home and disorganized? - Problem with diet (food availability)? - Another medical problem? - Screen for alcohol use, depression - Others

-Self-reporting by patients (they are asked to report their own adherence using open-ended questions as mentioned above) and pill counts are routinely used to monitor adherence. The methods based on self-reporting or auto-evaluation tend to overestimate adherence.
-Specific tools may be used and may be particularly useful during the first months of treatment, such as pill boxes, agenda, calendars, booklets, flipchart, flyers, alarm clock, etc.

-Good clinical evolution (especially weight gain and improvement of general status) also indicates adherence to treatment, as a patient taking properly his/her treatment will respond better to ARV drugs.

The main reasons for missed doses are:

- Forgetting
- Being too busy
- Being away from home
- Change in daily routine
- Being depressed
- Having adverse side effects
- Being too ill.

4/ FACTORS THAT MAY INFLUENCE ADHERENCE

Factors	Promote adherence	Reduce adherence
Patient factors	- Motivated patient - Good understanding of HIV/AIDS disease and therapy - Education given in patient's own language prior to and during therapy - Participation in support group Treatment supporter identified	- Alcoholism or other substance abuse - Depression - Poor understanding of the disease or therapy - Fear of stigmatisation - Non- disclosure of HIV status to family member or friend - Poor social support, living alone
Disease factors	- Late or symptomatic HIV/AIDS disease	- Early, asymptomatic disease - No change in health status
Therapy factors	- Small number of tablets to swallow - Few adverse events - Empathic health staff - Friendly environment in the health facility	- Large and frequent (more than twice a day) number of tablets - Severe or ongoing minor side effects - Food requirement - Treatment at cost - Follow-up visits too frequent and transportation problems - Too long time to spend in the clinic

5/ PRACTICAL ORGANIZATION

Treatment education and adherence sessions are usually conducted by counsellors or nurses trained in counselling skills. PLWHA should also be involved in facilitating such sessions as they will share their own experience in taking the drugs and better motivate their peers.

Sessions may be organized individually or in a group. This will depend on the workload linked to HIV/AIDS activities. Group sessions have advantages over individual ones such as time saving (particularly in setting with high workload) and exchanges of questions, experiences, difficulties encountered, etc. among patients.

Written information should also be provided with posters and pamphlets, preferably in patients' own language. The therapeutic educating material will have to be developed for Timor-Leste and translated in adequate dialect according the districts.

It is advised to report adherence issues in the medical file, for the medical staff to be aware of the problems if any.

8.11 ARV Side Effects and Toxicity

1/ TYPES OF SIDE EFFECTS

Minor side effects	- Unpleasant side effects such as nausea, headache, malaise, dizziness, nightmares and insomnia are common when starting on ARV drugs and all patients should be warned to expect them. - They are distressing but usually tolerable, can be managed symptomatically and tend to improve within a few weeks in most of the cases. - They can affect adherence but patients should be encouraged to persist taking the ARV drugs and should be followed up regularly to support adherence. - However, these distressing side effects might be severe enough to warrant stopping the drug responsible completely and switching to another one.
Potentially serious side effects	- Disabling and even life-threatening side effects do occur with patients on ARV drugs, though fortunately they are infrequent. - Some toxicities are drug-specific while other are class-related, overlapping between all drugs in a class.

2/ MAIN SIDE EFFECTS BY DRUG AND BY CLASS

Tenofovir (TDF)	- (potential effects on foetal bone if taken during pregnancy) - renal insufficiency (rare)
Zidovudine (AZT)	- Haematological toxicity: anaemia, neutropaenia - Lipoatrohy (less frequent than with d4T) - Myopathy including cardiomyopathy

Abacavir (ABC)	- severe hypersensitivity reaction (2 to 5%)
NRTI drugs	- Lactic acidosis
Nevirapine (NVP)	- Hepatotoxicity - Skin toxicity
Efavirenz (EFV)	- CNS disturbances (dizziness, headache, insomnia, depression, impaired concentration, agitation, disturbing dreams, nightmares and somnolence) - Teratogenic toxicity - Hepatotoxicity (less frequent than with NVP) - Skin toxicity (less frequent than with NVP)

3/ DESCRIPTION OF SIDE EFFECTS

DRUGS SPECIFIC SIDE EFFECTS

Zidovudine

- AZT is responsible for severe macrocytic anaemia. Haematological toxicity is dose-related and it is more common with advanced AIDS disease. Patients on AZT and CTX may develop neutropenia; stop cotrimoxazole first in these patients.
- AZT has also been associated with reversible myopathy, with symptoms of myalgia, proximal weakness (accompanied by increased creatinine phosphokinase).
- AZT use is also associated with lipoatrophy but to a lesser extent than D4T.

Tenofovir

- Generally well tolerated
- Deterioration in renal function in those with baseline renal dysfunction. In those with normal baseline renal function it is unclear if deterioration in renal function occurs more frequently than with other ARVs.

Abacavir

- associated with severe hypersensitivity in approximately 2-5% of patients (limited data from resource limited settings). Symptoms occur in 90% within 6 weeks of starting and are non-specific: fever, rash, nausea, abdominal pain, lethargy, fatigue, dyspnoea, myalgia.

Nevirapine

- NVP given at half-dose during the first 14 days decreases the risk of intolerance.

- NVP associated side effects usually occur within the first 12-18 weeks of ART.
- NVP associated rash is usually erythematous, maculopapular, confluent and most prominent on the body and arms; it may be pruritic and can occur with or without fever. Life threatening Stevens-Johnson syndrome and toxic epidermal necrolysis has been reported in about 0.3% of individuals receiving NVP.
- Hepatotoxicity: in MSF settings, the hepatic tolerance may only be assessed clinically. Risk factors are: baseline elevated transaminases, history of alcohol abuse, older ages, female gender, low body mass index, co-infection with hepatitis B and C and elevated baseline CD4 count (>250/mm3 in women and >400/mm3 in men).

Efavirenz

- Adverse effects on the central nervous system have been reported in 30-50% of patients treated with EFV e.g. nightmares and psychological disturbances, usually appearing early and resolving within the 1st month of treatment. The administration of EFV at bedtime can improve the patient's tolerance of these side-effects.
- EFV has teratogenic toxicity as congenital abnormalities of the CNS. EFV is contra-indicated during first trimester of pregnancy; it may be considered during 2nd and 3rd trimester if no alternative exists. Contraception should be ensured in women in childbearing age receiving EFV.
- Skin and hepatic adverse reactions may occur also on EFV although they are less frequent.

CLASS SPECIFIC SIDE EFFECTS

NRTI

- The initial symptoms of lactic acidosis are variable. A clinical prodromal syndrome may include generalized fatigue and weakness, gastro-intestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia and/or unexplained sudden weight loss), respiratory symptoms (tachypnea or dyspnoea) or neurological symptoms (including motor weakness).
- Risk factors include female gender, high body mass index, and prolonged NRTI use.
- It usually occurs usually after 6 months of treatment but cases have occurred as early as one month after the commencement of ART.
- All ARV drugs should be stopped when lactic acidosis occurs (no continuation of NRTI backbone to prevent emergence of NVP resistance strains).
- AZT, D4T, DDI should never be reintroduced. NRTI drugs with less propensity of lactic acidosis (like Abacavir, Lamivudine, Tenofovir, Emtricitabine) may be considered but not reintroduced until lactate levels return to normal. If lactate measurement is not available, then NRTIs should not be reintroduced for at least one month.

Toxicity is related to the effect of harmful or poisonous metabolites of a medication, which can lead to intolerable side effects and significant organ dysfunction. This can be monitored clinically on the basis of patient reporting and physical examination, and there may also be a limited number of laboratory tests, depending on the specific combination regimen used.

4/ GRADING OF SIDE EFFECTS

Adverse reactions are graded according to the "Division of AIDS table for Grading the Severity of Adult and Paediatric Adverse Events", December 2004.

Grades 1 and 2	The patient remains on therapy. The patient should be reassessed clinically within 2 weeks. If the adverse reaction is a laboratory abnormality, then the test should be repeated.
Grade 3	The management will depend on the nature of the toxicity and the drug involved. Discontinuation of drugs will not necessarily be done. Attention should be paid to: rapidity of occurrence, risk of progression to a grade 4 event, overall tolerance of the patient, possibility of close follow-up, association with drugs of similar toxicity, etc.
Grade 4	Stop all the drugs immediately and wait for the symptoms to resolve. Appropriate change to ART needs to be made. See section on ARV side effects algorithms.

In case of grade 3 and 4 side effects, refer the patients immediately to the medical assistant/doctor.

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Clinical				
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater then minimal interference with usual social & functional activities	Sensory alteration or parsethesia causing inability to perform usual social & functional activities	Disabling sensory alteration or parsethesia causing inability to perform basic self-care functions
Neuromuscular weakness (including neuropathy & myopathy)	Asymptomatic with decreased strength on exam or minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions or respiratory muscle weakness impairing ventilation
Myalgia	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Pancreatitis	N/A	Symptomatic and hospitalisation not indicated	Symptomatic and hospitalisation indicated	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Lipodystrophy (abnormal fact accumulation or fat loss)	Detectable by patient	Detectable on physical exam by health care provider	Disfiguring or obvious changes on casual visual inspection	N/A
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences or aggressive intervention indicated (e.g. tube feeding)
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral	Persistent nausea resulting in decreased oral intake for < 72 hours	Persistent nausea resulting in minimal oral intake >72 hours or aggressive rehydration indicated	Hospitalization required Life-threatening consequences (e.g. hypotensive shock)

	intake		(e.g. IV fluids)	
Vomiting	Transient or intermittent vomiting (2 to 3 episodes per day) lasting < 1 week with no or minimal interference with oral intake	Frequent episodes of vomiting (4 to 5 episodes per day) with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration (e.g. IV fluids)	Life-threatening consequences (e.g. hypotensive shock)
Cutaneous reaction - rash	Localized macular rash	Diffuse maculopapular or morbilliform rash OR Target lesions	Diffuse maculopapular or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis
Altered mental status	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater then minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium or obtundation or coma
Laboratory				
Haemoglobin (g/dL)	8.0 – 9.4	7.0 – 7.9	6.5 – 6.9	<6.5
Neutrophil count (/mm3)	1000 - 1500	750 - 999	500 - 749	<500
ALT	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	If normal at baseline 5.1 – 10.0 x ULN If increased at baseline 3.6 – 5 x baseline value	Of normal at baseline >10.0 x ULN If increased at baseline > 5 times baseline value

5/ RECOMMENDED SUBSTITUTIONS FOR SPECIFIC SEVERE SIDE EFFECTS

Regimen	Toxicity	Drug substitution
AZT/ 3TC/NVP	- AZT: severe anaemia	- Switch AZT/3TC -> TDF/3TC (ABC/3TC)
	- NVP: grade 3 and 4 hepatotoxicity or grade 4 skin toxicity	- Switch NVP -> LPV/r
	- NVP: grade 3 skin toxicity	- Switch NVP -> EFV if patient can be hospitalized; if not -> PI
TDF/3TC/EFV	- TDF: renal failure	- Switch TDF/3TC -> AZT/3TC (ABC/3TC)
	- EFV: grade 3 and 4 hepatotoxicity or grade 3 and 4 skin toxicity	- Switch EFV -> LPV/r
	- EFV: persistent CNS toxicity	- Switch EFV -> NVP
D4T/3TC/NVP or EFV	The d4T based 1st line regimen is not recommended anymore in Timor-Leste and therefore, all patients remaining on d4T based 1st line regimen should be switched as soon as possible to one of the following 1st lines: - AZT/3TC/NVP	The switch needs to take into consideration - the level of Hb - previous reaction to NVP or EFV - HBV status

	- TDF/3TC/EFV	- Concomitant rifampicine based TB treatment - Renal function

Chapter 9 : IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

The immune reconstitution inflammatory syndrome (IRIS) describes some inflammatory disorders associated with paradoxical worsening of pre-existing infectious processes following the initiation of ART. Pre-existing infections may have been previously diagnosed and treated or they may be sub-clinical, undiagnosed and later unmasked by the host's regained capacity to mount inflammatory response.
IRIS does not indicate a failure of ART as it shows an immunological and virological response to ART.

9.1 Diagnosis Criteria

Most or all of the following features should be present in order to make the diagnosis of IRIS:
- The presence of stage (2), 3 and 4 symptoms that have developed after the commencement of ART, or had improved with ART and have since worsened
- Symptoms consistent with an inflammatory condition than cannot be explained by an acute drug resistant infection, a bacterial super infection, drug adverse reactions, treatment failure due to obvious lack of adherence or drug malabsorption.
- Evidence of good response to ART with immune reconstitution (e.g. increase from baseline of CD4 and undetectable VLs).
- The timing of onset is variable. Most of IRIS developed within the first 2 months after ART initiation (in 2/3 of patients). IRIS can also occur within a few days after initiating ART or as late as 3 years after ART commencement.

9.2 Pathogens Involved

The most frequently reported associated infections are: mycobacterium tuberculosis, Cryptococcus, Kaposi sarcoma, localised herpes zoster, mycobacterium avium complex, CMV.

The clinical features of IRIS are strongly related to the type of pre-existing opportunistic infection.

9.3 IRIS Prevention

- Aim to treat and stabilise known OIs prior to initiation of ART, unless severely immunocompromised or unwell where delay in ART may result in increased mortality from the current OI or the development of other OIs in the interim.
- Clinician awareness of IRIS is very important so that it can be identified quickly and managed correctly.

9.4 IRIS Management

- Treat the underlying OI;
- Continue ART despite IRIS;
- If severe treat with NSAIDs or corticosteroids to decrease the inflammatory syndrome. Treatment with corticosteroids must be an individualized decision as such treatment could be harmful. Initiate with prednisolone 1mg/kg/day (maximum 60 to 80mg/day) then decrease the dose over 4-6 weeks;
- ART may be interrupted if the patient is experiencing life-threatening IRIS despite the initiation of corticosteroids. Patients should then be treated for a period of time for the underlying infection before resuming ART.

9.5 TB & IRIS

Early IRIS	Tends to occur within the first few weeks of starting ART. The great majority of cases develop in patients with a diagnosis of TB that antedated the commencement of ART or TB undiagnosed prior to ART commencement (either not symptomatic, or inadequately investigated). Symptoms are: - Severe fever, malaise, weight loss - Peripheral and intra-thoracic lymphadenopathy, - Pulmonary infiltrates with transient worsening of radiographic abnormalities - Extra-thoracic disease is less common and includes pleural effusion, HSM, ascitis, cerebritis, meningitis, tuberculoma. The most commonly reported manifestations are: fever, lymphadenopathy and worsening respiratory symptoms. Management: - Continue or start, if TB diagnosis confirmed, anti-TB drugs; - Evaluate discontinuation ART if life-threatening condition; - Add corticosteroids for severe IRIS especially if CNS involvement or severe respiratory symptoms (i.e. lymphadenopathy causing airway obstruction). Prevention: To avoid IRIS in patients with known TB, ART should be delayed for 2 weeks to 2 months after initiation of anti-TB treatment, depending

	on CD4 count. See section on TB/HIV co-infection.
Late IRIS (less frequently)	It results from an immune response against the antigens of non-viable pathogens. It does not require re-introduction of TB treatment if it has been already completed and if TB re-infection has been ruled-out. In practice, ruling out TB is difficult in resource-limited settings and one has to assume that this is re-infection and re-treat.

Chapter 10: HIV 2

There are two main strains of HIV:

1- **HIV-1** that has caused the majority of infections and AIDS cases and
2- **HIV-2**, which is primarily found in West Africa. HIV-2 prevalence is > 1% in the general population in Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria and Sierra Leone. HIV-2 is also found in Angola, Mozambique and India.

HIV 1 & 2 co-infection is frequent in countries where both are prevalent.

10.1 HIV 2 clinical presentation

Compared with HIV-1, HIV-2 is less transmissible, is associated with a lower viral load and a slower rate of both CD4 cell decline and clinical progression.

HIV-1 and HIV-2 diseases cause the same clinical illness at corresponding levels of immunosuppression (CD4 counts) and thus treatment of opportunistic infections should be approached in a similar manner.

10.2 Medical management

HIV-2 is intrinsically resistant to the NNRTI class of ARV. Therefore, in case of HIV-2 infection:

Recommended 1st line for HIV 2
AZT/3TC /ABC

Recommended 1st line for HIV 1 and HIV 2 co-infection
AZT/3TC + LPV/r

10.3 Laboratory

Available commercial VL assays do not measure HIV- 2 viral load. Specific HIV-2 viral load assays are required to monitor HIV-2 VL.

10.4 PMTCT[22]

Regarding PMTCT, the rates of mother to child transmission of HIV-2 are between 0% and 4% among breastfed infants in the absence of any interventions. As the risk is much lower for HIV-2 than HIV-1, standard PMTCT recommendations also apply in settings with coexisting HIV-1 and HIV-2 infection.

[22] See National PMTCT guidelines for Timor-Leste, MoH, 2011

Chapter 11: MANAGEMENT OF TREATMENT FAILURE and SECOND LINE TREATMENT

11.1 General Principles[23]

The decision of when to switch from a first-line to a second-line ART regimen is critical. If the decision is made too early the months or years of potential survival benefit from any remaining first-line effectiveness is lost; if it is made too late, the effectiveness of second-line therapy may be compromised as resistance mutations accumulate overtime and the patient is put at additional and appreciable risk of death if remaining on a failing first-line regimen with significant immunosuppression (ie CD4 < 200).

Treatment failure may be measured in three ways:
1°- **clinical failure**: disease progression (occurrence of opportunistic infections),
2°- **immunological failure**: using trends in CD4 counts over time[24],
3°- **virological failure**: by measuring HIV viral load (VL).

In general virological failure occurs first, followed by immunologic failure and finally by clinical progression. These events may be separated by months to years[25].

In Timor-Leste, clinical or immunological failure should be confirmed with a viral load measurement prior to changing to a second-line regimen.

When failure is expected?

1- Failure in adherent treatment-naïve patients will very rarely occur before 12 to 24 months of ART[26]. There is usually a history of improvement on the first line regime, prior to subsequent deterioration.
2- Lack of any improvement from the start of ART, is more suggestive on
   a. an untreated OI
   b. the patient is not taking drugs at all.

How to handle failure on poor adherence?

[23] See annex 7.1: Flowchart for diagnosis of 1st line regimen failure and management

[24] Ideally the CD4 percentage (or fraction) should be followed in adults (as well as in children), since the variability of CD4 percentage is much less than the variability in absolute CD4 counts. Most CD4 machines available on the field to day do not provide CD4%. Therefore this requires a total lymphocyte count be available from the same blood draw as the CD4 count. The TLC will be obtained from an automated WBC differential count.

[25] Some patients show discordant responses in virological, immunologic and clinical parameters.

[26] 95% undetectable viral load at 24 months in MSF project in Phnom Penh; 85% after 36 months in Kenya; 86% after 24 months in Arua, Uganda.

If failure is due to poor adherence, then changing therapy will have no benefit. Thus before changing to a second-line regimen problems of adherence should be addressed.

Even if immunological failure is present, if the CD4 count is > 200 cells/ml, the patient is not at risk of life-threatening AIDS-related illnesses, and will usually remain clinically well on the short term. There is no urgent need to change to second-line therapy in these cases but an intensive work on adherence should be started and the patient should be closely monitored.

Other potential reasons for failure and confounding problems should always be considered:
- Drug interactions (i.e. with rifampicin) or inadequate drug absorption (i.e. due to diarrhea) leading to sub therapeutic ARV levels
- The initially undiagnosed presence of HIV-2 (as the first-line regimen contains an NNRTI to which HIV-2 is intrinsically resistant) in patients infected with both the HIV 1 and HIV2 virus.
- clinical manifestation due to IRIS (and therefore not a sign of treatment failure).

People at higher risk of treatment failure include:
- non-naive patients at inclusion in the program
- women previously exposed to a single dose of nevirapine for PMTCT particularly if started on a NNRTI based first-line regimen within six months after NVP exposure.
- patients with a confirmed history of poor adherence or of treatment interruption during the first months of treatment, particularly if taking NNRTI.

Switching to 2nd line in coordination:
The ***decision to shift should be collegial*** and taken after the case has been reviewed with colleagues from the project or the coordination.

The patient needs to be informed on the medical situation and the therapeutic options. When the patient agrees and commit, s/he has to follow an ***intensive program of adherence counselling***[27] if not already. The patient will be inform about the non-availability of a 3rd line regimen "yet" in Timor-Leste and that the 2nd line regimen has to remain active (non-resistant) as long as possible due to no other options for the time-being. At each visit, the patient on 2nd line will spend time with the counsellor and/or the doctor and assessment of difficulties in taking the medicines, side-effects and how the patient takes his/her medicines will be done. Therapeutic education will be repeated as long the patient needs it.

Information regarding ***reasons for changing regimen should be properly recorded in the individual medical file***:
- a specific form[28] where information regarding criteria about the switch should be completed and use as a support for decision-taking when to suspect failure.

[27] See Chapter 8, sub-chapter 8.10: Antiretroviral treatment Education and Adherence
[28] Annex 7.2 : 6 monthly assessment of failure and check-list for decision on viral load request

- the VL and CD4 values should be recorded in the patient file.
- any other relevant information

IN TIMOR-LESTE CD4 IS AVAILABLE FOR ROUTINE MONITORING (every 6 months) AND VL IS USED TO CONFIRM A TREATMENT FAILURE

VL will be considered for routine monitoring (every 3 to 6 months) when it will be available in the country.

Treatment failure should be suspected if the following criteria are met[29]:

- Patients presenting with a new episode of a stage III or IV disease, after the first 6 months on ART[30] [31] and/or one of the following immunological criteria :
- > 30% fall from on therapy CD4 peak level[32]
- if CD4 drops back to a level at or below the pre-therapy CD4 baseline after at least 6 months of ART.
- If CD4 fails to increase by 25-50 above the baseline count after the first six to twelve months of therapy
- If CD4 remains < 100 at 12 months of therapy[33].

The viral load test should be performed as soon as possible after the patient has met one of these criteria except in the case of

- concurrent infection (should be treated first)
- recent vaccination (wait for one month)

Management of virological failure

A VL below 1,000 copies/ml mandates that ART should not be switched, irrespective of CD4 level and presence of clinical symptoms.

If the VL is more than 1,000 copies/ml, the first steps should be to :

- re-assess systematically potentially confounding problems and

[29] note that criteria used are more open than the ones used to define immunological failure in settings where viral load is not available

[30] OI episodes occurring during the first 6 months are considered to be due to IRIS or to a still insufficient immune reconstitution.

[31] Including TB that may occur at any CD4 count level; (TB episodes after 6 months may not be taken into account in the strategy in order to reduce its sensitivity).

[32] If the access to viral load is difficult, perform a second CD4 one month after the first one to confirm the CD4 drop, before asking a VL.

[33] Very sensitive in case of very low baseline CD4

- initiate an intensive counselling program[34] for three months after which VL should be measured again. Clinical judgement should be used here; if the patient is sick and in a bad condition after 12 months on first line, AND adherence is assessed not to be a problem, the second viral load can be performed earlier - from 4 weeks onwards. Intensive counselling should continue to support the patient with the burden of second line treatment, but a delay in these cases may be life-threatening.

If the second viral load is

- below 1,000 copies/ml : do not switch; re-check VL after 6 months if possible

- Between 1,000 and 10,000 copies/ml: consider a switch to second-line after taking into account factors such as: the patient's clinical state and CD4 count, the patient's preparedness and ability to adhere to the proposed second-line regimen, and the availability of a robust second-line regimen. If a switch is not made the VL should be repeated in 3 months and the patient reassessed at that time.

- over 10,000 copies/ml : switch to second line

IF VL IS NOT AVAILABLE

When to decide to switch to second line

The diagnosis of treatment failure will be made if one of the following criteria is met after at least 12 months on ART[35] :

- > 50% fall from on therapy CD4 peak level
- in case of return of CD4 cell count to pre-therapy baseline or below
- persistent CD4 levels below 100 over the first year of therapy

- Before switching to second line, systematically re-assess adherence and initiate an intensive adherence counselling program. In case of adherence problems, do not start the second line treatment until this is solved.
- In general, patients meeting the above criteria but who have a single CD4 above 200 and are asymptomatic or presenting with a single new stage III clinical event, should not switch therapy. CD4 should be rechecked after 3 months.
- Patients with a very low baseline CD4 and with persistent CD4 levels below 100 over the first year of therapy who are asymptomatic and gaining weight should not switch therapy

- Shift should not be based on a single CD4 measurement; always perform a second CD4 to confirm the initial value and exclude any technical error[36]. Check that there is no

[34] intensive counselling program may consist of specific individual or group counselling sessions for patients in treatment failure only

[35] Cfr 6 months according to WHO guidelines for antiretroviral therapy, 2006 revision, but in practice 12 months are needed to have at least 3 CD4 measurements (MO, M6, M12)

[36] See section on ART monitoring for more information on CD4

concomitant infection (or recent vaccination) that could explain the transient CD4 decrease. Treat it before (re)measuring CD4 count. Measuring CD4% may be useful if there is a suspicion that the total number of lymphocytes is being modified by other factors.

11.2 Recommended Second Line Regimens

Adults and adolescents:

If 1st line failing	2nd line preference
AZT or D4T/3TC/NVP or EFV	**TDF/3TC + LPV/r**
TDF/3TC/EFV or NVP	**AZT/3TC + LPV/r**

Drug	Formulation	Dosages
LPV-r heat-stable	Tablets Lopinavir : 200 mg + Ritonavir : 50 mg	2 tablets twice daily (400/100 mg twice daily)[37] no food restrictions

- LPV-r : fixed dose combination of lopinavir/ritonavir, where ritonavir is acting as a booster. A heat-stable formulation is preferred for its room temperature storage requirement.

- 3TC is continued in the setting of treatment failure despite the likely emergence of resistance to this drug in a patient failing on a standard first line regimen. The viral strain carrying the 3TC-induced mutations is less fit than the wild strain and is more sensitive to AZT and TDF. 3TC may also have some residual activity despite the resistance.

- In case of HBV co-infection, the discontinuation of TDF/3TC may be associated with hepatitis B flares and rapid clinical deterioration. TDF/3TC should be maintained with 1 new NRTI (AZT) and 1 new PI (LPV/r).

- In case of TB co-infection, LPV/r dosage should be increased to 800 mg/200 mg twice daily when prescribed concomitantly with rifampicine.

Children and infants:

1st line failing	2nd line preference
AZT/3TC/NVP or EFV	**ABC/3TC + LPV/r**
ABC/3TC/NVP or EFV	**AZT/3TC + LPV/r**

For dosage of ARVs, please refer to the table in annexes 8.1, 8.2, 8.3.

[37] same dosage if combined with EFV or NVP

With the development of the HIV program in Timor-Leste and the boost given to the PMTCT activities, there will be most likely more infants and children with HIV infection who would have been exposed previously to ARVs for prevention. For those children, the choice of ARVs is very crucial as they may have developed resistance during the prophylaxis prescription. The table below will help the ART health provider to make an appropriate choice according to each individual situation:

Situation	**Preferred 1st line**	**Preferred 2nd line**
Infants and children < 24 months		
Not exposed to ARV	NVP + 2 NRTIs	LPV/r + 2 NRTIs
Exposed to NNRTI	LPV/r + 2 NRTIs	NNRTI + 2 NRTIs
Unknown ARV exposure	NVP + 2 NRTIs	LPV/r + 2 NRTIs
Children		
Children > 24 months	NNRTI + 2 NRTIs	LPV/r + 2NRTIs

11.3 Side effects of Lopinavir boosted ritonavir

- Generally well-tolerated
- Most common adverse effects : nausea and diarrhoea
- increase of hepatic transaminases
- Class adverse reactions : insulin resistance, fat accumulation and hyperlipidaemia
- Advantages of the thermo-stable formulation LPV-r compared to the non stable one : lower pill burden, no food restriction.

Chapter 12: LABORATORY MONITORING OF ANTIRETROVIRAL THERAPY

12.1 Minimal and Basic Requirements

Laboratory monitoring tests are mainly useful to help identify patients in need of ART, to monitor the response to and monitor the adverse events from ARV drugs.

In Timor-Leste, health facilities function with a microscope and minimal laboratory possibilities: malaria smear, tuberculosis smear, haemoglobin, white cells count and differential, parasitology and urine analysis.
In Dili, the laboratory of the national hospital (HNGV) and the National referral Laboratory have larger facilities as biochemistry tests such as liver function, micriobiology, serology…

The availability of laboratory monitoring is important to increase ART efficacy and safety but should not restrict the commencement of HIV/AIDS activities if not available.

Table 1 : Summary of routine laboratory monitoring

Regimen containing	**AZT**	**TDF**	**ABC**	**NVP/EFV**	**LPV/r**
CD4	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
Pregnancy test		Baseline		Baseline	
Hb	Baseline, month 1, 3, 6, 12, 18…	Baseline, month 12, 24…	Baseline, month 12, 24…		
Creatinin		Baseline, day 15, month 1, 6, 12, 24 …			
LFT				Baseline, day 15, month 1, 6, 12, 24 …	
LDH	If lactic acidosis symptoms				
Glycemia					Baseline, month 6, 12, 24…
Lipids & Cholesterol					Baseline, month 6, 12, 24…

12.2 CD4 Count

CD4 cells count mobile equipment (point-of-care (POC)) will be made available in Timor-Leste by 2011. The POC CD4 will enable ART centers to have fast access to CD4 and take adapted medical attitude and will allow easy CD4 monitoring at the districts level.

The enumeration of CD4+ T-lymphocytes in peripheral blood is a helpful tool in monitoring the immunological status of HIV infected patients.

CD4 count is used to:
- Assess the degree of immune deterioration and speed of progression towards AIDS,
- Define, together with clinical information, decision points to initiate ARV treatment,
- Orientate the differential diagnosis in OI care,
- Decide the timing for starting and stopping prophylaxis of opportunistic infections,
- Monitor the efficacy of antiretroviral treatment.
- On ART help distinguish IRIS from other conditions eg poor adherence, ART failure, ARV side-effects etc

Importantly, the unavailability of CD4 count should not prevent to initiate HIV/AIDS care and antiretroviral treatment.
Patients can be assessed clinically and the time to start prophylaxis and ART may be decided only on clinical grounds (WHO clinical staging).

➔ See sections on objective and tasks of HIV consultations, CTX prophylaxis, ART goals and indications.

Table 2: What to know in practice about CD4 cells count

Normal value	Reproductibility	Influencing factors	Response to ART
500-1400 cells/mm3	• Depends on methodology • Inconsistent results with previous results indicate the need for a repeated test	• WBC, % lympho, % CD4 • 6-15% of CD4 variation for the same individual • Diurnal changes: lower CD4 in the morning, higher in the evening => measure CD4 at the same time of the day • TB, OI, viral infections, malaria…	• > / = 50 cells/mm3 at 4-8 weeks after viral suppression with ART • > 50-100 cells/mm3/year on ART • Despite good virological response, there may be a delay in CD4

		decrease CD4 level temporarily; do / repeat CD4 outside infection event • Vaccination: perform CD4 1 month after a vaccination	response that cannot be explained • With infrequent monitoring, the true peak of the CD4 cells count can be missed

12.3 HIV Viral Load

Viral load is a blood test that measures the amount of active HIV in your blood. The higher the value of the viral load test the more active HIV is present.
The goal of HIV treatment is to suppress HIV replication (reproduction) in order to bring the HIV viral load measurement as low as possible. People with higher viral loads have a greater risk for immune system damage that in turns leaves the body at risk for opportunistic infections.

In Timor-Leste the viral load is used for treatment failure confirmation.
The viral load reflects the level of response to ART and will be the earliest to rebound in cause of treatment failure.

Ideally, the viral load should be followed every 3 months, as part of the routine monitoring. However, in case of low resources setting, as for Timor-Leste, VL will be requested to confirm treatment failure according to the protocol developed in chapter 11.

The blood sample will be referred abroad according to the procedure agreed between the international laboratory identified and the MoH.

Once VL for HIV will be available in TL, the schedule of routine monitoring will be revised accordingly.

The resistance profile will be requested for all detectable VL and done in agreement with the international reference laboratory.

Chapter 13: TUBERCULOSIS AND HIV

13.1 TB Diagnosis and Treatment[38]

1/ HIV & TB

HIV is the most powerful known risk factor for reactivation of latent TB infection to active disease. In people living with HIV/AIDS, there is also a higher risk of rapid TB progression to active disease soon after infection with *Mycobacterium tuberculosis.* A person infected with HIV has a 10 times higher risk of developing TB than those who are uninfected. TB can occur at any point in the course of progression of HIV infection but the risk of developing TB rises sharply with worsening immune status.

HIV status	Lifetime risk of developing TB
Negative	5 – 10%
Positive	50% (or 10%-30% per year[39])

HIV positive patients with TB, who are not receiving ART, have a higher case-fatality both during and after anti-TB treatment. Also HIV+ smear-negative pulmonary TB cases and extrapulmonary TB (EPTB) have a worse prognosis than HIV+ smear positive PTB cases. The high case fatality rates are due in a large part to TB but also attributable to other HIV-related infections that might be present at the same time. In addition, failure, recurrence and relapse rates after TB treatment are higher in HIV co-infected patients.

In an individual infected with HIV, the presence of other infections, including TB, may allow HIV to multiply more quickly due to additional weakening of the immune system. This results in more rapid progression of HIV disease. TB is also one of the leading causes of mortality in the HIV+ individual.

2/ DIAGNOSIS OF TB in HIV positive patient

Pulmonary TB (PTB) is the commonest form of TB in HIV + patients. The presentation depends on the degree of immune-suppression.

In the early stages of HIV infection, when immunity is only partially compromised, the features are typical of PTB.

[38] Refer to National TB program Manual, Ministry of Health, Timor-Leste, 3rd Edition, July 2008
[39] Maartens G & Wilkinson RJ. Tuberculosis. *Lancet online* Aug 2007 : www.thelancet.com.

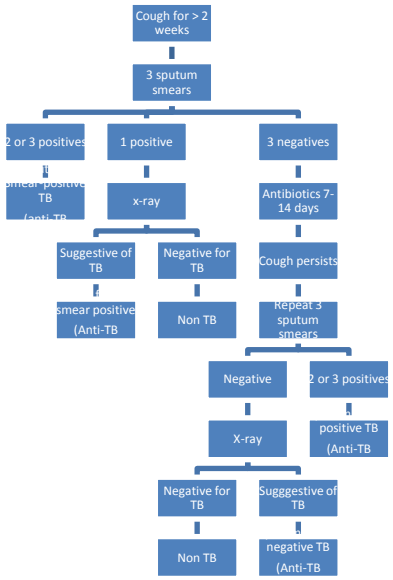
As immune deficiency advances, HIV-infected patients present with atypical pulmonary disease resembling primary TB or EPTB or disseminated disease. Bacterial co-pathogens are frequent in HIV co-infected patients.

Features of PTB	Stage of HIV infection	
	Early	Late
Clinical picture	Chronic Cough (> 2 weeks) Sputum production Weight loss +/- fever, night sweats, loss of appetite, breathlessness, chest pain, haemoptysis	Weight loss and fever -> TB **must be excluded** in any patient presenting with wasting syndrome.
	Cough and haemoptysis are less common in HIV+ PTB patients as immunodeficiency increases (less cavitation, inflammation and endobronchial irritation), however chronic cough lasting more than 2-3 weeks is also highly predictive of TB disease in PLWHA	
Sputum smear result	Often positive	Often negative
CXR findings	- Upper lobe infiltrates - Bilateral infiltrates - Cavitation	- Interstitial infiltrates especially in lower zones - Hilar adenopathy and/or pleural effusion - sometimes miliary - No cavitation - No abnormality

Differential diagnosis of PTB in HIV infected adults patients

Acute bacterial pneumonia	- Shorter history - All clients with cough > 2 weeks should be referred to exclude TB (i.e. sputum smear microscopy for AFB, chest X-ray) - Chest x-ray: lobar infiltrate or maybe negative
Pneumocystis pneumonia	- Sub-acute and insidious onset - Latter stage of HIV infection (CD4 count < 200/mm3) - Dry cough, mucoid sputum (if any), progressive dyspnoea - Chest x-ray: bilateral diffuse infiltrates (ground glass appearance) or maybe normal or may have findings of spontaneous pneumothorax
Kaposi's sarcoma	- Typical lesions found on the skin and mucous membranes (oral cavity) - Cough, haemoptysis and dyspnoea - Pleural fluid is blood-stained

Diagnosis of pulmonary TB[40] in HIV + patient



The timing of decision is very important. It is recommended not to loose time as the prompt decision can safe patient's life.

The following schedule will help in decision taking:

In patient with NO danger signs:

1st visit with cough > 2 weeks:
- Smear 3 samples
- Antibiotics
- Cotrimoxazole prophylaxis (see chapter on prophylaxis)

2nd visit:after 5-7 days
- Smear positives: treat for TB
- Smear negative: X-ray, repeat smear + culture, clinical assessment
    - If clinical assessment and x-ray suggestive of TB
        - treat with anti-TB

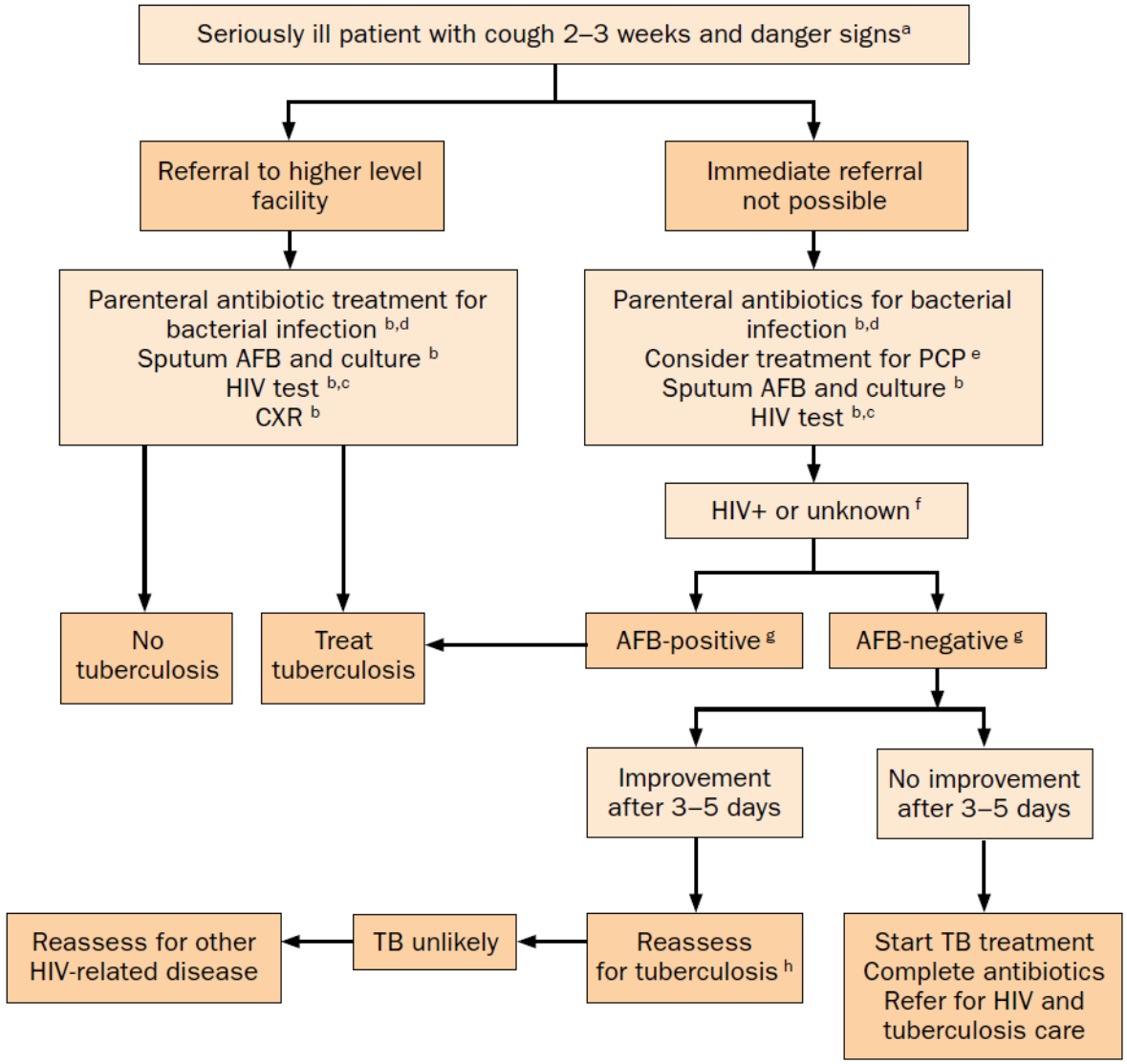
3rd visit:after 1 week
- Results of smear and culture:
    - Positive for TB: treat for TB
    - Not suggestive of TB => clinical assessment in favour of:
        - Treat for PCP
        - Or Treat for bacterial infection

4th visit:after 1 week
- Responsive to Antibiotics
    - continue same treatment
- Non responsive to antibiotics

[40] Manual National Tuberculosis Program control, MoH timor-Leste, July 2008

- Reassess for TB

In patient with danger signs[41]:



[a] The danger signs include any one of: respiratory rate >30/min, fever >39 °C, pulse rate >120/min and unable to walk unaided.
[b] The investigations within the box should be done at the same time wherever possible in order to decrease the number of visits and speed up the diagnosis.
[c] For countries with adult HIV prevalence rate ≥1% or prevalence rate of HIV among tuberculosis patients ≥5%.
[d] Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.
[e] PCP: *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia.
[f] In the absence of HIV testing, classify HIV status unknown into HIV-positive depends on clinical assessment or national and/or local policy.
[g] AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.
[h] Reassessment for tuberculosis includes AFB examination and clinical assessment.

[41] WHO 2010, Guidelines for intensified TB case finding and IPT for PLHIV in resource constrained settings

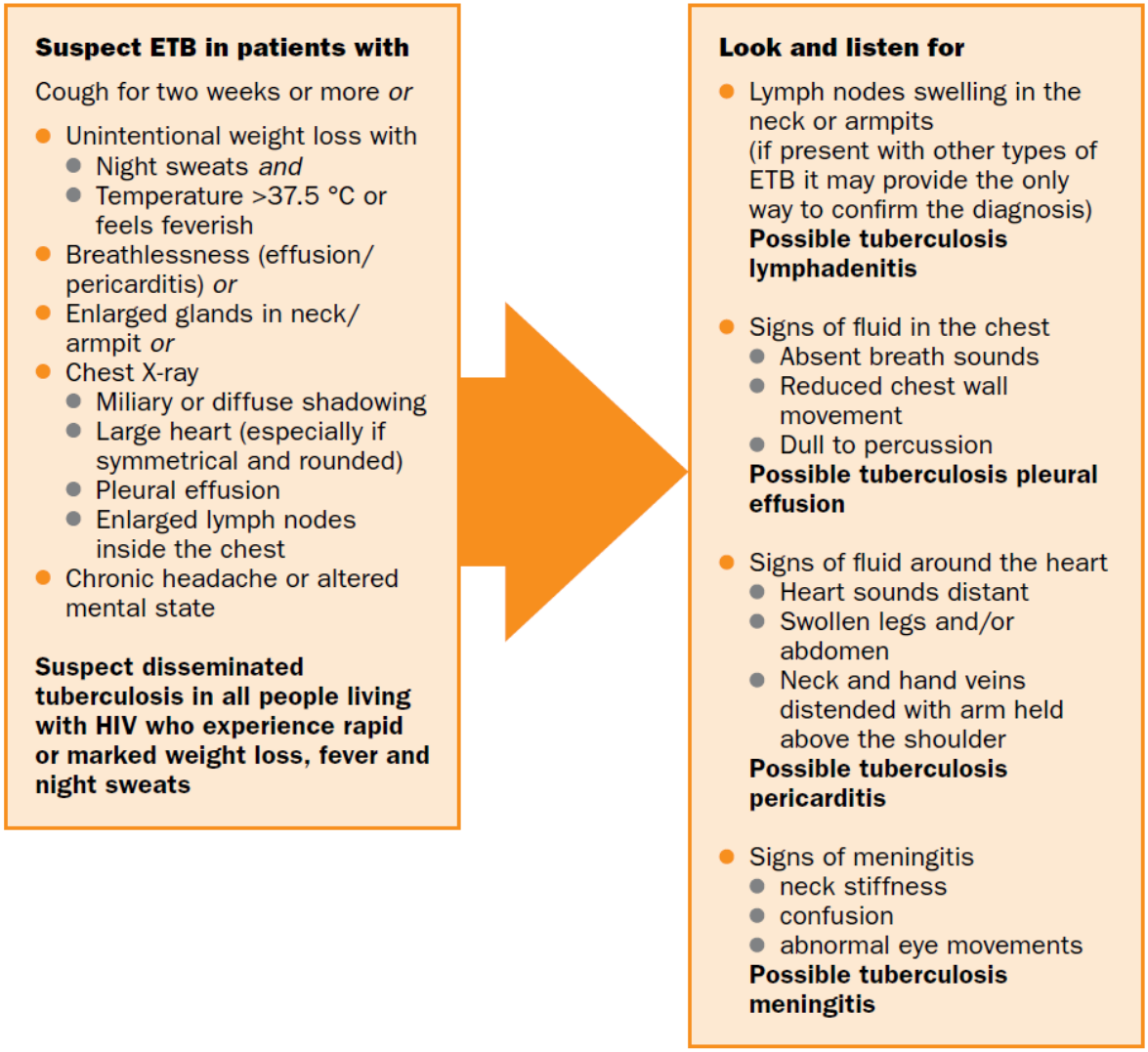
Diagnosis of extra-pulmonary TB (EPTB)[2]

Tuberculosis may infect any tissue or organ system of the body.

The commonest forms of EPTB in HIV+ patients are: lymphadenopathy, pleural, peritoneal and pericardial effusion, miliary and meningeal TB.

Presentation of EPTB in HIV + patients is generally not different from that in HIV negative ones. Suspect disseminated TB in all HIV infected people who experience rapid or marked weight loss, fever and night sweats[42].

When to suspect EPTB



TB lymph nodes are difficult to distinguish clinically from other causes of enlarged nodes. Therefore, needle aspiration should be carried out at the first visit[43].

[42] About one-third of deaths in HIV infected Africans are due to disseminated TB but only about half of HIV positive patients who die from disseminated TB are diagnosed before death.

Differential diagnosis of EPTB in HIV infected adults patients

	High suspicion of TB if	Probably not TB if
Lymph node TB	2cm or more in size asymmetrical/localized painless swelling firm/fluctuant/fistulated cervical location weigh loss, night sweats and fever	-KS in skin or mouth : KS nodes -Symmetrical : Lymphoma or HIV lymphadenopathy -Tender, inflamed, purulent : bacterial or fungal -Site other than cervical (although EPTB lymphadenopathy may be anywhere)
Pleural effusion	Unilateral Aspirate of fluids is - clear and straw coloured & - clots on standing in a tube weight loss nights sweats and fever - Rivalta +	Bilateral : heart failure, pneumonia Clinical KS/other malignancy Aspirate or fluid is - cloudy/pus - fails to clot[44]
Disseminated TB	Weight loss, fever & cough Abnormal CXR (including military pattern) Large spleen/liver Night sweats anaemia	DD with Salmonella, malaria, Cryptococcus, Kala-Azar, Lymphoma : Rigors, very breathless (RR>30/min), severe diarrhoea, blood in stool, positive Cryptococcal antigen, malaria smear or likley pathogen isolated from blood culture
Pericardial effusion	Lung fields clear (but may have bilateral pleural effusion) Weight loss, night sweats, fever Evidence of TB elsewhere	-Non infectious cardiac problems -Rigors : bacterial pericarditis - murmur : probable valvular disease - High blood pressure

[43] WHO 2007 smear negative or EPTB guidelines: The technique is described page 19 http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf

[44] Does not exclude TB but send fluid for protein and differential cell count, and consider heart failure

TB meningitis	Weight loss, night sweats, fever CSF clear with high protein, low glucose & lymphocytes and negative for Ag crypto or Indian ink Evidence of TB elsewhere	-Cryptococcus (more likely than TB in HIV patients; cryptococcal antigen positive) -Bacteria

3/ TB TREATMENT REGIMENS[45]

There are several possible regimens depending on the patient's diagnostic category:

TB diagnostic category	TB patients	TB treatment regimens	
		Intensive phase	Continuation phase
I	All new patients: - PTB smear positive - PTB smear negative - EPTB	- 2 HRZE or	- 6 HE - (4 HR)**
II	All previously treated TB patients: - Relapse - Treatment after default - Treatment failure*** - Others	2 SHRZE /1 HRZE	5HRE****

* For TB meningitis, streptomycin is recommended during the intensive phase as ethambutol does not cross the meningeal barrier. Note that streptomycin injections are really painful in wasted HIV-infected TB patients. Corticoids are recommended during the first two months of treatment for tuberculous meningitis.

** 8-months regimen (with HE) is the current choice for TB management in Cat. I for Timor-Leste. Timor-Leste will consider switching to 6-months rifampicine-based regimen later in the development of its NTP. Note that 4 HR is the latest WHO recommended regimen for TB management in HIV and non HIV patients.

*** Failure of category 1 should preferably be confirmed by culture before starting category 2 treatment.

****Patients who have previously received 5 or more months of ethambutol should continue pyrazinamide throughout the continuation phase, e.g. 5RHZE

4/ FAILURE TO IMPROVE

Some TB/HIV patients fail to improve, or even deteriorate, during anti-TB treatment. They continue to have, or develop new, respiratory problems. In any case, TB treatment must not be interrupted. First check adherence to TB treatment. Then consider the following possibilities:

[45] WHO 2009 TB treatment guidelines http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

Original Diagnosis	Possibilities
Sputum smear – PTB	Incorrect diagnosis e.g.: - Other pathogens (pneumocystis pneumonia, bacterial pneumonia, mycoses e.g. cryptococcus, Kaposi's sarcoma, CMV), - Heart failure, - Chronic obstructive airways disease - Drug resistant TB - IRIS
Sputum smear + PTB	- Superimposed infection with other pathogens - Drug resistant TB - Lung abscess (empyema) - IRIS

For a patient with suspected EPTB who is started on anti-TB treatment without bacteriological or histological confirmation, the clinical response to treatment should be assessed after two months. If there is no improvement, a clinical reassessment should be performed and an alternative diagnosis sought. TB treatment should be continued and completed unless TB is excluded (culture). If it is confirmed that TB is not present the TB treatment should be ceased (see algorithm).

13.2 Isoniazide Preventive Therapy[46][47] (IPT)

Timor-Leste has decided to provide IPT for PLHIV as part of the NTP. The HIV health care provider is in charge of screening PLHIV for TB and the clinician providing HIV care is given the responsibility to rule out TB infection. Once TB is ruled out, IPT will be initiated.

Adults and adolescents living with HIV should be screened for TB with a clinical algorithm (see below) and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT:

- Primary Prophylaxis:
  - INH 10 mg/kg/day for a period of 6 months
  - Pregnant women should also benefit of IPT and the best time for initiating IPT is left to clinical judgement.

[46] IPT: Isoniazide Preventive Therapy
[47] WHO 2010, Guidelines for intensified TB case finding and IPT for PLHIV in resource constrained settings

- Secondary Prophylaxis: All adults and adolescents who have successfully completed their TB treatment should continue receiving INH for another six months.

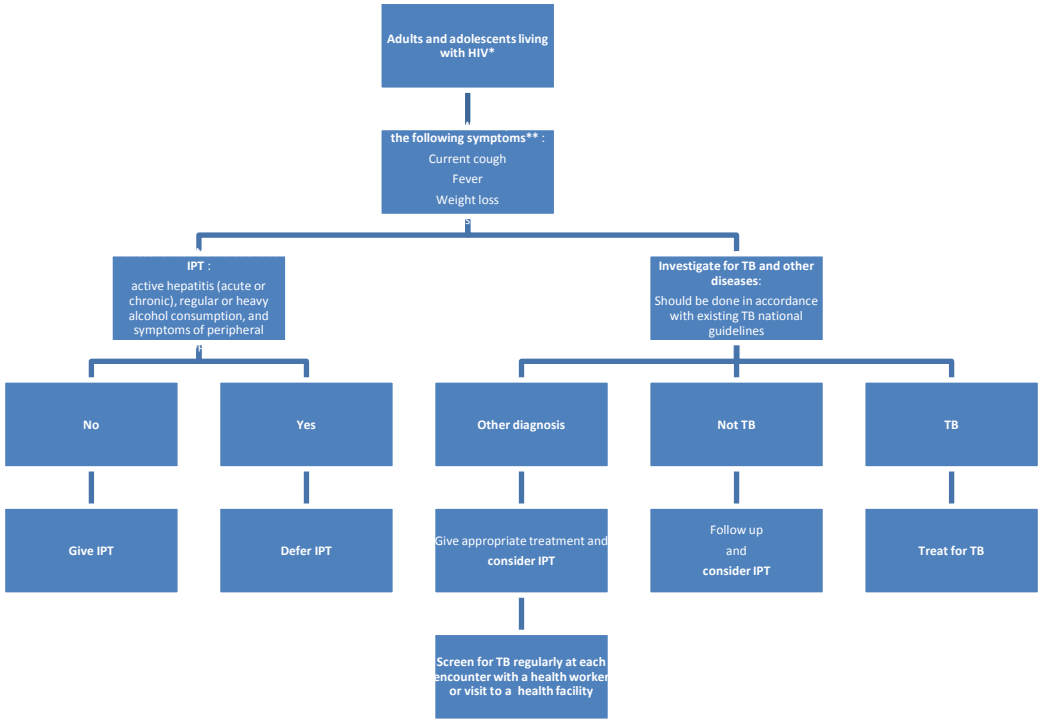
Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB and should be offered IPT regardless of their age:

- Primary Prophylaxis:
  - > 12 months and no active TB and **no contact** with TB case: IPT 10mg/kg/day for 6 months
  - < 12 months and no active TB and **in contact** with TB case: IPT 10mg/kg/day for 6 months;
  - Don't give IPT for HIV positive infant < 12 months who are not in contact with TB
- Secondary Prophylaxis:
  - All children who have successfully completed treatment for TB disease should receive INH for an additional six months

IPT course starting or completion should not delayed the start of ART.

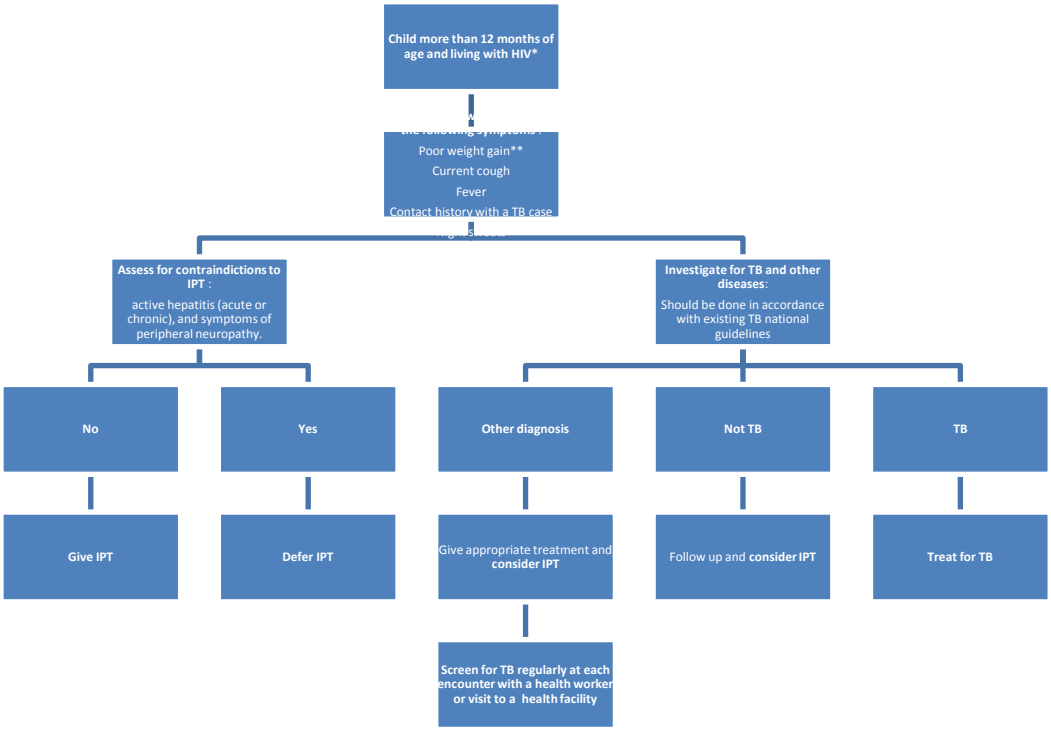
The following algorithms are supporting the TB screening in PLHIV adults and children[48]:

Algorithm 1: TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



[48] WHO 2010, Guidelines for intensified TB case finding and IPT for PLHIV in resource constrained settings

Algorithm 2: TB screening in children more than one year of age and living with HIV



13.3 When to start ART in Patients with Active TB

The first priority for TB patients living with HIV is to initiate TB treatment, followed by CPT and ART. Fatality rate is high during the first 2 months of TB treatment in co-infected patients, especially in patients with advanced AIDS.

Co-management of HIV and TB may be complicated by drugs interactions, immune reconstitution syndrome (IRIS), pill burden, overlapping toxicities and adherence issues.

Initiation of ART in a newly diagnosed TB co-infected patient should follow WHO recommendations[49].

- Start ART for all HIV positive patients with active tuberculosis, irrespective of CD4 count.
- Start TB treatment first followed by ART as soon as possible and within the first eight weeks

[49] WHO 2010 ART guidelines http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf

- Use Efavirenz preferably as NNRTI in patient starting ART while still on TB treatment.

13.4 Recommended ART Regimens for Patients With Active TB

	Adults	Children > 3y or > 10kg	Children < 3y or < 10kg
1st choice	TDF/3TC/EFV	AZT/3TC+EFV	AZT/3TC+ABC
Hb< 7g/dl		ABC+3TC+EFV	ABC+3TC+NVP
Intolerance to EFV	TDF/3TC+AZT AZT/3TC/NVP	AZT/3TC/NVP AZT/3TC+ABC AZT/3TC+LPV/r	
Alternative choices			AZT/3TC+LPV/r

- **In adults**: TDF/3TC/EFV is preferred as it comes as fixed dose combination (FDC) and is prescribed once daily, which reduces drastically the pill-burden and has a positive impact on adherence to treatment.
- EFZ at the standard dose of 600 mg, irrespective of the body weight in adult, should be preferred in all cases of co-administration of Rifampicin- containing TB treatment.
- EFV should not be used in women of child bearing potential without adequate contraception or in women who are in the first trimester of pregnancy.
- **Children > 3 years of age or > 10 kg** of body weight should be prescribed: AZT/3TC + EFV (follow dosage table according to body weight in annexes)
- **Children < 3 years of age or < 10 kg** of body weight should be prescribed: triple NRTIs (ABC+AZT/3TC) during the Rifampicine co-administration; when rifampicine is discontinued the child should switch to AZT/3TC/NVP.
- **Rifampicin** stimulates the activity of the cytochrome P450 liver enzyme system, which metabolizes Protease inhibitors (PI) and nevirapine (NVP). Co-administration of rifampicin with NVP and all PI's may result in ARV drug failure attributable to sub-therapeutic drug concentrations. NVP and PIs should therefore preferably not be used with rifampicin. However, if EFV is not tolerated, NVP can be used with Rifampicine, but no lead-in dose of NVP is required. LPV/r can also be used, but need doubling the standard LPV/r daily dose.
- **Rifampicin and fluconazole** interact on the blood concentration of each other. It is recommended that doses be separated by 12 hours: e.g. rifampicin in the morning, fluconazole in the evening.

13.5 TB Episodes in Patients on ART

ART decreases the incidence of TB by up to 90%. Rates of TB among treated patients nevertheless remain higher than among HIV negative individuals.

Prior to Rifampicine	Switch for
TDF/3TC/EFV	Keep the same
AZT/3TC/NVP	AZT/3TC + EFV AZT/3TC + ABC AZT + TDF/3TC
2 NRTIs + LPV/r	2 NRTIs + LPV/r (double dosage of LPV/r)

- In patients on 2 NRTI + NVP : substitute EFV for NVP. Substituting back to the original regimen once the rifampicin containing regimen is completed can be considered. When switching back from EFV to NVP, no lead-in dose is required.
- In patients on 2 NRTI + LPV-r (400/100 mg bid), due to rifampicin, increase the dose of ritonavir to 400 mg bid; ensure close clinical and laboratory monitoring to detect hepatic toxicity as the risk for this is increased.
- A TB episode in patients on ART may or may not herald ART failure. See section of management of treatment failure and second line treatment.
- If EFV is absolutely contra-indicated, use the following alternative regimens:
  - AZT + 3TC + ABC
  - AZT + 3TC + TDF
  - if alternative regimens are not available, then NVP 200 mg bid can be continued under close clinical supervision.

13.6 IRIS and TB

See section on Immune reconstitution syndrome in chapter 9.

IRIS may occur in up to a third of persons with TB who initiate ART.

Patients commencing ART who are receiving TB treatment or who have sub-clinical TB disease, may experience an exacerbation of TB symptoms. This usually occurs within the first two months of starting ART but usually in the first 2-3 weeks. TB treatment must be started if patients not on treatment yet.
For those on ART this follows an initial improvement in symptoms. Symptoms include high fever, lymphadenopathy, expanding CNS lesions and worsening of chest X-ray findings. Most cases resolve without any intervention and ART can be safely continued. Without immediate response, in the most serious cases, it can rapidly lead to a fatal outcome. Serious reactions such as tracheal compression caused by massive adenopathy, or respiratory difficulty, may occur; therapy may require the use of corticosteroids.

13.7 TB Detection in HIV+ Patients

The prevention and treatment of TB should be an integrated part of HIV care and the converse is also true. This implies an efficient strategy for screening and diagnosing TB in HIV patients and HIV in TB patients as well an integrated management of both diseases in co-infected patients.

The following tools should be available in health facilities dealing with TB diagnosis in HIV patients :

- **Clinical symptoms-based algorithm to screen TB**[50] **(cf algorithms in IPT section)**: Adults and adolescents living with HIV and screened with a clinical algorithm and who report any one of current cough, fever, weight loss or night sweats may have active tuberculosis and should be evaluated for TB and other diseases.
- **Diagnostic tools**:
    - **Ziehl-Neelsen** stain on sputum smear;
    - **GeneXpert** (PCR method) when available will be implemented in TL
    - **CSF** chemistry and hematology
    - **Ascitis/pleural** liquid: Rivalta & Pandy tests (tests for protein estimation)
    - X-Ray
    - **Cultures and DST** : currently not available at national level; culture of sputum/samples for MDR suspected cases are referred to Australia. HIV positive patients are part of the MDR suspected cases and sputum/samples of HIV positive patients with TB coinfection are being integrated in the referral system of TB samples for culture and DST.
    - **FNAC**[51] : fine needle aspiration cytology : at district level; requires specific skills for reading; implies specific training of staff.
    - **Ultrasound** : at district hospital level; can help in diagnosing abdominal and thoracic TB nodes, and peritoneal TB.

13.8 HIV detection in TB patients

TB clinics are a crucial entry point into HIV prevention and care services. HIV counselling and testing for all patients with known or suspected TB is recommended as a basic component of the TB care package.

In Timor-Leste, diagnostic HIV testing (PITC) is part of the standard of care of the National TB Program for all patients with known TB[10] [52]

Note that PITC is also recommended in TL for adults and children who present to health facilities with signs and symptoms or medical conditions that could indicate HIV infection, including suspicion of TB (see chapter 2).

13.9 Organization of TB & HIV Care

ONE STOP PATIENT-FRIENDLY SERVICES should be foreseen for the future in Timor-Leste health services.

[50] WHO 2010, Guidelines for intensified TB case finding and IPT for PLHIV in resource constrained settings

[51] WHO 2007 smear negative or EPTB guidelines: http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf The technique is described page 19

[52] WHO 2009 TB treatment guidelines http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

Principles

- It is the aim to manage the one patient with two diseases at the same time and place as much as possible, rather than the converse. To do this efficiently and effectively requires close integration of HIV/TB services.
- Services are organized in an user-friendly manner for TB/HIV co-infected patients : health services are provided in places close to where patients live and organized in such a way that limit to a minimum the number of appointments; etc
- Services are organized in a staff-friendly way for health personnel providing TB and/or HIV care : information on individual patient treatment for both diseases is easily available from files; patient flow inside services is clearly defined; staff can benefit from training on both diseases; etc

In Timor-Leste

The current context does not allow the country to go for "one stop services" for HIV & TB co-infected patients. Indeed HIV services are concentrated at district level while TB services are decentralized at sub-district level. The referral system is developed as follow:

- **TB patients** will be screened for HIV infection at CHC level where VCCT services are available (the number of VCCT at sub-district level will progressively increase, improving the coverage of the country)
- **TB patients found to be HIV co-infected**
    - Will start Cotrimoxazole prophylaxis (960mg daily) at HIV centre level
    - Will be managed for HIV at the nearest HIV treatment centre within 15 days after beginning of TB treatment; the patient will be encourage to come with his/her TB treatment card updated
    - Will continue to receive TB medicines at TB services at the sub-district level until completion of TB treatment
    - Will receive intensive adherence and support counselling all along the course of TB treatment by the counsellor AND by the peer support group.
- **HIV patients** will be screened for TB in accordance with the WHO clinical tool (annex 6)
- **HIV patients found to be TB co-infected**
    - Will continue the HIV medical management at the Referral Hospital level
    - Will be referred to the most geographically appropriate TB center for TB treatment initiation
- **All TB-HIV co-infected patients**:
    - Will have sputum or other fluid sample collected and sent abroad for culture and DST as part of the suspected group of MDRTB.
    - This is part of the TB national program responsibility.

Adapted adherence strategy[53]

HIV program puts in place adherence counseling based on patient education and empowerment. Therapeutic education is covering adherence for HIV medical care and TB treatment. In co-infected patients, adherence counselling should be the rule to promote adherence to both TB and ART.

Both programs may rely on outreach/community workers to ensure active tracing of patients lost to follow-up. As an integrated program, all workers should be in charge of promoting adherence to both diseases.

Prevention of TB nosocomial transmission

Prevention of TB nosocomial transmission is essential as pulmonary smear+ TB patients are highly infectious during the first 2 weeks of anti-TB treatment and HIV positive individuals are highly susceptible to infections.

Preventive measures should be taken:

- Well ventilated, light-painted waiting area which is ideally organised in two spaces for patients with and without TB.
- Patients with cough for more than 2 weeks should wait in a different zone and be investigated for TB.
- TB smear + patients are isolated during the hospitalization; this being part of the basic infection control in health facility.

Monitoring

- Duplicated TB treatment card and medical data record forms should be in the same patient folder
- TB register with HIV related information (HIV testing) should be used
- Standard case and outcome definitions should be used. Definitions used by national TB program for "treatment failures" and relapses (or recurrence) are often limited to smear positive pulmonary TB. They should include all forms of the disease (including smear negative PTB and EPTB)
- Monitor TB screening among HIV + patients
- Monitor uptake of cotrimoxazole prophylaxis and ART in HIV positive TB patients
- TB data collection forms should be properly recorded and TB related data entered in the HIV data monitoring system.

[53] This issue is part of the "towards one stop service" section but is worth being considered specifically.

Chapter 14: Nutritional Rehabilitation in HIV Infected Patient

14.1 Introduction

HIV infected people may suffer from malnutrition for several reasons :
- reduced intake because of poor appetite or discomfort while eating;
- poor absorption directly linked to the HIV infection (e.g. chronic diarrhoea);
- nutritional needs increased by HIV infection and AIDS[54];
- severe poverty, decreased work capacity, social isolation/stigmatization.

Malnutrition in turn has a significant detrimental effect on immunity and hastens progression of HIV disease. To avoid this spiral, all HIV-infected patients require specific nutritional attention. All cases of malnutrition should be treated even where there is no nutritional program as such.

In Timor-Leste, nutritional support will be given in the following ways:

- **Empowering PLWHA**: provision of information to PLHA to help them improve their nutritional status. Nutritional education should be part of the treatment education of HIV infected patients. Especially advice adapted to the individual circumstances that can help them increase their intake of protein and micronutrients as well as information on measures that help prevent OI such as diarrhoea, are important.
The nutritional session will be part of the package of health education sessions that will be provide at adherence group meeting or individual counselling through peer educators or by the counsellor.

- **Treatment of severe malnutrition**: The diagnosis of malnutrition should be ruled out at each contact with HIV services; physical examination should systematically include measurement of weight and height as well as calculation of BMI [55], measurement of the Mid Upper Arm Circumference (MUAC) and a check for nutritional oedema. Severe malnutrition should be managed at hospital level.

- **Support for moderate malnutrition**: Food supplement can be provided and managed at home level;

[54] basal metabolic rate is around 10 % higher in AIDS patients and their requirements of protein up to 50% higher

[55] **Calculation of Body Mass Index** : Formula: weight (kg) / [height (m)]$^{2;}$

- **Support to groups at risk**: A supplement in food and/or a multi-micronutrient supplement should be provided to vulnerable groups: first 6 months of ART, orphans, single mother, elders…

14.2 Management of Severe Malnutrition of PLWHAs

Admission and discharge criteria for nutritional program

	Admission criteria	Discharge criteria
Malnourished adults (> 18 years)	BMI < 16 (or MUAC < 160) irrespective of clinical signs Or BMI < 17 (or MUAC < 185) and poor clinical conditions (inability to stand, severe medical conditions, severe anorexia, …) And/or Presence of bilateral oedema grade 3 or above	Weight gain on 2 consecutive measurements one week apart And Total weight gain > 10-15% And Oedema less than grade 2 And Good clinical condition
Malnourished pregnant and lactating women	MUAC < 170 Or Presence of bilateral oedema grade 3 or above	Weight gain on 2 consecutive measurements one week apart And Oedema less than grade 2 And Good clinical condition

The presence of oedema should be looked for systematically
-by using firm pressure applied over a bony pro-eminence for three seconds
-assessing whether an indentation remains after the pressure is removed
-if any pitting oedema, confirming bilaterally.
Note: as far as possible other causes should be investigated as oedema in HIV infected adults may also be due to cardiac, renal or hepatic failure.

Grading of oedema in adults, based on the Beattie classification

Grade	Extent of oedema
0	Absent
1	minimal oedema on the foot or ankle, demonstrable but not obvious
2	obvious oedema on foot or ankle

3	oedema demonstrable up to knee (tibias)
4	oedema demonstrable up to groin (inguinal ligament)
5	total body oedema (anasarca)

Nutritional treatment for severe malnutrition

Please refer to the National Nutrition Program and Guidelines. HIV patients presenting severe malnutrition, adults and children, should be hospitalized and managed as non HIV positive patients for the nutrition therapy.

14.3 Management of Moderate Malnutrition in PLWHA

Admission and discharge criteria for nutritional program

	Admission	**Discharge**
Malnourished adults (> 18 years)	BMI between 16 and 17 (or MUAC between 160 and 185) and patient can stand and walk Or Has completed initial (and transition) phase of treatment	For at least 2 weeks, BMI >= 18 (or MUAC > 185 mm)
Malnourished pregnant and lactating women	MUAC between 170 and 210 Or Has completed initial (and transition) phase of treatment	Discharge 6 months after delivery

Nutritional treatment

	Adults	**Children (6-59 months)**
Reference	HIV+ adults will have their own nutritional supply chain, in order to avoid stigma and respect confidentiality	Refer to the national program for malnutrition.
BP5 (RUTF)[56]	4 bars daily	2 bars daily
Daily Kcal	1016 Kcal	508 Kcal

- The patient is followed up weekly or bi-weekly.
- Other food should be taken but RUTF should always be eaten first
- As the treatment may be long, different RUTF's can be used alternatively; this should promote acceptability.

[56] RUTF: Ready to Use Therapeutic Food

- It should be explained that RUTF is not a food item to be shared within the household
- It should be explained to patients and caretakers that RUTF has to be taken with plenty of clean water

14.4 Support to vulnerable groups

Criteria of Admission	Possible reference	Criteria of Exit
All newly enrolled HIV positive patients, regardless of BMI	If severe malnutrition, refer to national program for malnutrition	After 6 months on ART And/Or BMI > 18
All HIV positive hospitalized patients, regardless of BMI	If severe malnutrition, refer to national program for malnutrition	Discharge from hospital And/Or BMI > 18
BMI 16 < 17	If severe malnutrition, refer to national program for malnutrition	BMI > 18
Pregnant and lactating women, regardless of BMI	MCH	After end of breastfeeding And/Or BMI > 18
Infants (6-24 mths), regardless of nutritional status	MCH	At 24 months If no sign of severe or moderate malnutrition
Elders, isolated, single mothers and their children	If severe malnutrition, refer to national program for malnutrition	Ongoing

Hospitalized patients need nutrient dense food because of the severity of the pathology (low food intake must provide all nutrients needed). HIV infected patients usually stay long periods in hospital where in most resource limited settings, families are left in charge of feeding the patient. It is therefore recommended that the HIV program also provides nutritional support to non-malnourished HIV infected hospitalized patients.

	Adults	Children (6-59 months)
Reference		Refer to the national program for malnutrition
BP5 (RUTF)[57]	4 bars daily	2 bars daily
Daily Kcal	1016 Kcal	508 Kcal

These patients will also be screened for their food security situation and when needed will be referred to an appropriate agency for social support and food distribution.

[57] RUTF: Ready to Use Therapeutic Food

Chapter 15: MANAGEMENT of MALARIA in HIV POSITIVE PATIENTS

15.1 In Non Pregnant Adults

Risks

- HIV impairs the acquired immunity to malaria seen in older children and adults in endemic areas.
- In areas of stable transmission of P. Falicparum, like for Timor-Leste, there is evidence of increased frequency of both parasitaemia and clinical malaria, with increased risk and higher parasitemia associated with more advanced immune suppression.
- HIV infected individuals have a poorer response to anti-malarial treatment with failures due to both new infections and recrudescence.

Diagnosis

Fever can have a wide variety of causes in HIV infected patients. Therefore any suspect malaria patient should get a biological confirmation either by

- Thin-thick blood smear examined by microscopy or
- Rapid diagnostic test (RDT)

On and off fever in HIV positive patients: the disappearance of symptoms with cotrimoxazole prophylaxis should not lead to a diagnosis of malaria without confirmation.

Prevention

Bednet

Insecticide treated bednets reduce the incidence of malaria among adults with HIV infection. All HIV infected patients must be distributed Long Lasting Insecticidal Nets (LLIN) . LLINs should be given to the patient at the first opportunity and it would be advisable to give two nets per family to protect other members who may be exposed to malaria also and to encourage good usage in the family and benefit from the extra protection afforded by the knock down effect of the insecticide. This will protect against other vectors as well.

Distribution of LLIN for HIV positive patients: the District Malaria Office of Dili will supply the HIV centres of Dili (HNGV and Bairo Pite) on a 3 monthly basis. The counselors will supply each HIV positive patient with 2 LLINs for a period of 3 years (Insecticide Impregnation last for 3 years). After 3 years the LLINs will be replace by

new ones. The patients will have to sign a format when they receive the LLIN. The report to malaria will remain confidential and will only mention the ID code of the patients. The purpose of this report to Malaria program is for monitoring and it is important to respect it.

Counseling about LLIN: Patients will be inform about malaria and its symptoms; patients will be explained how to use the LLIN and how to maintain it in the best manner; the LLIN needs to be washed every 3-6 months to remove the dust; if it is not done, the dust will recover the insecticide on the net and it will not be active on the mosquitos when they land on the net.

Cotrimoxazole prophylaxis[58] for opportunistic infections and malaria
Daily cotrimoxazole (CTX) prophylaxis reduces malaria incidence in HIV infected patients and other bacterial/protozoal infections.

- ***HIV infected adults with CD4 <350*** cells/mm3 irrespective of WHO stage or
- WHO stage 2, 3 and 4 when CD4 count is not available

Antiretroviral treatment
ART also reduces the risk of malaria in HIV infected patients[59].

Recommended Treatment for Malaria in HIV infected adults and adolescents

- Artemisinin-based combination therapy (ACT) should be used to treat malaria patients whether HIV infected or not. (According to National Malaria Treatement protocol Artemether 20 mg/Lumefanthrin 120 mg combination is used to treat uncomplicated P. falciparum Malaria. Chloroquine (150 mg base) 10 mg/kg on the first two days and 5mg/kg on day 3 + Primaquine 0.5mg/kg/day for 14 days is given for the treatment of P. vivax.

In Timor-Leste, it is highly recommended to treat[60]:

1. **uncomplicated malaria in HIV positive patient with:**
    - P. Falciparum: Artemether 20mg / Lumefanthrin 120mg combination:

[58] See Chapter 6: Prophylaxis
[59] Mermin J, Lancet 2006 : this study in Uganda found a reduction in febrile parasitaemia of 76% associated with cotrimoxazole; of 92% associated with cotrimoxazole and ART; and of 95% when LLIN were associated with cotrimoxazole and ART.
[60] Malaria Treatment Protocol, June 2007, Ministry of Health, Timor-Leste

Age group	Weight group	Blister color	(Day 1)	(Day 2)	(Day 3)
4 months to 5y	5 to 14 kg	Yellow	1 tb ☼, 1 tb ☾	1 tb ☼, 1 tb ☾	1 tb ☼, 1 tb ☾
6 to 11y	15 to 24 kg	Blue	2 tb ☼, 2 tb ☾	2 tb ☼, 2 tb ☾	2 tb ☼, 2 tb ☾
12 to 14y	25 to 34 kg	Orange	3 tb ☼, 3 tb ☾	3 tb ☼, 3 tb ☾	3 tb ☼, 3 tb ☾
> 14y	> 34	Green	4 tb ☼, 4 tb ☾	4 tb ☼, 4 tb ☾	4 tb ☼, 4 tb ☾

Source: Guideline for the treatment of malaria, WHO; 2006.

Note that the Blister color may change according to the supplier. Please always control what you are providing to the patient, if it corresponds to the right dosage.

In case of resistance[61], Quinine and Doxycycline should be prescribed for 7 days.

- P. Vivax: Chloroquine and 14 days of Primaquine

Age Group	*Weight group (Kg)	CHLOROQUINE (150 mg base) 10 mg/kg on the first two days. 5 mg/kg on day 3			PRIMAQUINE (15 mg base) 0.5 mg/kg bw
		Give for 3 days			Start concurrently with CQ and give daily for 14 days
		Day 1	Day 2	Day 3	
4 months up to 12 months	4 - <10	½	½	¼	–
13 months up to 5 years	10 - <19	1	1	½	¼
6 - 7 years	19 - <24	1½	1½	1	½
8 - 11 years	24 - <35	2½	2½	1	¾
12 - 14 years	35 - <50	3	3	2	1½
15 +	50 or more	4	4	2	2

2. Severe or Complicated malaria in HIV positive patient:

Pre-referral treatment for severe malaria the administration of Artesunate by the rectal route is recommended for all except pregnant women during the first trimester.

[61] Refer to Malaria Treatment Protocol of TL, table 5, page 8, 2007

	Age	Weight group (kg)	Artesunate dose (mg)	Regimen (single dose)
Children	0 – 12 months	5 – 8.9	50	One 50 mg suppository
	13 – 42 months	9 – 19	100	One 100 mg suppository
	43 – 60 months	20 – 29	200	Two 100 mg suppositories
	6 – 13 years	30 – 39	300	Three 100 mg suppositories
	> 14 years	> 40	400	One 400 mg suppository
Adult		< 40	10 mg/ kg bw	Use appropriate number of 100 mg rectal suppositories
		40 – 59	400	One 400 mg suppository
		60 – 80	800	Two 400 mg suppositories
		> 80	1200	Three 400 mg suppositories

Source: Guidelines for the treatment of malaria, WHO; 2006.

In case Artesunate is not available, IM quinine[62] injection 20mg/kg should be given. Note that Quinine should be avoided in patients on ritonavir boosted PIs (risk of cardio-toxicity due to increased quinine plasma level).

Drug-drug interaction:
Plasma level of some antimalarial drugs may be decreased when used with ARVs:

- quinine with NNRTI,
- This may also be the case for artemisinin derivatives when used with PIs and to a lesser extent with NNRTI.

According to the available information, ARV blood levels are usually not affected by concomitant use of anti-malarial drugs[63]

[62] Malaria Treatment Protocol, table 8, page 18&19, edition 2007
[63] except for AZT with atovaquone (increased by 30%), indinavir with atovaquone (decreased) and ritonavir with mefloquine).

Recommended treatment for uncomplicated malaria in non-pregnant adults on ART

ARV regimens	Anti-malaria drugs	Comments
2 NRTI + NVP	Artemether /Lumefantrine	
2 NRTI + EFV	Artemether/Lumefantrine	
Ritonavir boosted PI containing regimen	Arthemeter/lumefantrine	Arthemeter/lumefantrine should be used with caution[64] **Avoid quinine**

15.2 In HIV Infected Pregnant Women

Risk

- The loss of partial immunity against malaria during the first and second pregnancies in women living in high transmission area is extended into later pregnancies in women who are HIV positive.
- HIV/malaria co-infected pregnant women are more likely to develop clinical and placental malaria, more often have detectable malaria parasitaemia and have higher malaria parasite densities in peripheral blood than HIV negative pregnant women.
- Compared to women with either malaria or HIV infection, women that are co-infected have a higher risk of abortion, preterm birth and intrauterine growth retardation and are therefore more likely to have low birth weight infants.
- Studies on the impact of malaria infection on the risk of mother to child transmission (MTCT) of HIV have reported conflicting results. Therefore, it is not known whether malaria infection increases the risk of MTCT.

Diagnosis

- All HIV + pregnant women should be screened for malaria at each antenatal visit. RDTs are preferable to microscopy in this screening process. Malaria treatment should be given on the result of the test whether or not the woman is symptomatic,
- Pregnant women with suspicion of malaria should get a biological confirmation either by microscopy or RDT.

Prevention

Use of Long Lasting Insecticided Nets

[64] according to manufacturer and WHO 2004 recommendations because of a potential risk of cardio-toxicity; however no study has showed the effect of lumefantrine on cardiac conduction.

All pregnant women regardless of HIV status must be given a free LLIN. Their use is effective for the prevention of pregnancy-related anaemia in women with unknown HIV status. In Timor-Leste, the malaria program distributes LLIN bednets for pregnant women and children < 5 years old.

Cotrimoxazole Prophylaxis

HIV pregnant women who fulfil the HIV recommended criteria for cotrimoxazole prophylaxis should receive it.

- HIV infected adults with CD4 <350 cells/mm3 irrespective of WHO stage or
- WHO stage 2, 3 and 4 when CD4 count is not available
- Pregnant women with the criteria for CTX prophylaxis should be administered CTX prophylaxis regardless of the stage of the pregnancy
- Breastfeeding mother should continue cotrimoxazole prophylaxis following the usual recommendations of CTX prophylaxis

If CTX is introduced during pregnancy it should be started as early as possible (if CTX is not begun until the third trimester, malaria-related anaemia and foetal growth retardation may already have developed).

Treatment

HIV pregnant women not on ART

- ACT combinations (Artemether/Lumefanthrin) should be used during the 2nd and 3rd trimester.

- **Quinine 300 mg base (10mg/kg, TID, 7 days) and Clindamycin 300 mg base (3 mg/kg, OD, 7 days)** are safe and efficacious during the first trimester (safety of ACT using during the first trimester is not yet fully demonstrated).

HIV pregnant women on ART

- ACT combinations (Artemether/Lumefanthrin) should be used during the 2nd and 3rd trimester.

- For interactions between ART and antimalarial treatment, see text above (non pregnant adults) and table below.

- Quinine 300 mg base (10mg/kg, TID, 7 days) and Clindamycin 300 mg base (3 mg/kg, OD, 7 days) should be used during the first trimester and lactating period. However quinine should NOT be used in patients on RTV boosted PIs (risk of cardiotoxicity due to increased blood level of quinine); these women should receive 7 days of artesunate (2 mg/kg/day).

All HIV pregnant women

- As in non pregnant HIV infected adults, pregnant HIV infected women may have a poorer response to antimalarials but there is no published data on this issue.
- Pregnant women with malaria should be considered as severe malaria and treatment monitored in hospital if possible until parasites are cleared

Recommended treatment for uncomplicated malaria in pregnant women on ART

ARV regimens	FIRST TRIMESTER	2nd & 3rd TRIMESTER	COMMENTS
2 NRTI + NVP	QUININE[65] and Clindamycine 7 days	Arthemeter /lumefantrine	
2 NRTI + EFV (EFV is contra-indicated during 1st trimester)	QUININE and Clindamycine 7 days	Arthemeter /lumefantrine	
Ritonavir boosted PI containing regimen	Artesunate[66] IM 7 days	Arthemeter/lumefantrine	Quinine should be used with caution[67] Artemether /Lumefanthrin should be used with caution[68]

NB : Artesunate IV is the treatment of choice in case of severe malaria in pregnant women in the three trimesters of pregnancy.

[65] In areas where quinine efficacy is reduced, particularly in Asia, Clindamycine 7 days may be added to quinine

[66] Malaria Treatment Protocol, table 7, page 18, edition 2007

[67] PI may increase plasma level of quinine; on the other hand plasma levels are lower in pregnant women than in non pregnant adults. Usual doses of quinine should be used.

[68] according to manufacturer and WHO 2004 recommendations because of a potential risk of cardiotoxicity; however no study has found any effect of lumefantrine on cardiac conduction.

15.3 In children and infants

Risks:
In areas of stable transmission, there is a higher risk of parasitaemia and more severe malaria in HIV infected compared to non HIV infected children.
In infants, there is no such increase in frequency or density of parasitaemia, but anaemia and hospitalization are common in HIV infected infants with malaria.

Contrary to adults, it has not been demonstrated that HIV infected children have a poorer response to anti-malarial treatment.

Diagnosis:
Fever have a wide variety of causes in HIV infected children. Therefore any suspect malaria patient should get a biological confirmation by microscopy or RDT

Prevention:

Distribution of LLIN is recommended to all HIV infected / exposed children

Daily CTX (cotrimoxazole) prophylaxis reduces malaria incidence in HIV infected children.

- ***All HIV exposed infants and children*** starting at 4-6 weeks after birth and maintained until cessation of risk of transmission and exclusion of HIV infection
- ***HIV confirmed infants < 1 year***: regardless of CD4 percentage or clinical status
- ***HIV confirmed children 1 - 4 years***: WHO stage 2, 3 and 4, regardless of CD4 percentage or any WHO stage and CD4 < 25%
- ***HIV confirmed children > 5 years***: follow adult recommendations

ART also reduces the risk of malaria in HIV infected patients.

Recommended treatment for simple malaria in children on ART:

ARV regimens	Anti-Malaria drugs	Anti-Malaria drugs	Comments
	0-4 months	> 4 months – 5 years	
2 NRTI + NVP	Artesunate[69]	Artemether - lumefantrine	Preferably used in severely immune-compressed
2 NRTI + NVP	Artesunate	Artemether - lumefantrine	
Ritonavir boosted	Artesunate	Artemether -	Use with caution,

[69] Way of administration in Malaria Treatment Protocol for Timor-Leste, table 8, edition 2007

PI containing regimen		lumefantrine	cardio-toxicity

In case of severe malaria in children, use Quinine injectable:

Age or Weight	Intramuscular Quinine	
	150 mg/ml* (in 2 ml ampoules)	300 mg/ml* (in 2 ml ampoules)
2 months up to 4 months (4 < 6 kg)	0.4 ml	0.2 ml
4 months up to 12 months (6 < 10kg)	0.6 ml	0.3 ml
12 months up to 2 years (10 < 12 kg)	0.8 ml	0.4 ml
2 years up to 3 years (12 < 14 kg)	1.0 ml	0.5 ml
3 years up to 5 years (14 < 19 kg)	1.2 ml	0.6ml

Source: Chart Book of Integrated Management of Childhood Illness, WHO.
* Quinine salt

15.4 Overlapping Syndromes & Toxicities

Syndrome	Possible causative factors
Fever	Malaria, opportunistic infections, HIV itself, drug hypersensitivity (ABC, NVP)
Anaemia	Infection related: malaria, HIV, OI Drug related: AZT, dapsone, CTX
Agranulocytosis or pancyptopenia	Drug related: Amodiaquine, dapsone, CTX, AZT Infection related: HIV, OI
Rash	Most ARV and anti-malarial drugs can cause rash; HIV
Stevens-Johnson syndrome	NVP, ABC, SP, CTX
Lactic acidosis	NRTI, severe malaria
Hepatitis	Amodiaquine, NNRTI, PI, NRTI, chronic HBV/HCV infection, malaria
Renal failure	Malaria nephritis, HIV nephropathy, TDF, IDV

Annexes

Annex 1 : Patient admission form

KARTAUN PASIENTES

ID code:	Date of Admission	Date of Discharge	Outcome
			☐ Lost to FU ☐ Transferred ☐ Dead

First Name	Middle Name	Family Name

Address Phone number Contact for tracing	Electoral card: Home: Landline: Mobile: Name: Patient's link: Phone: (use only in case of patient's failing to call, confidentiality should not be breached)

Date of birth:	☐ Male ☐ Female

Marital Status:	☐ Single ☐ Married	☐ Widow ☐ Divorced

Profession	

Spouse Children	……Years HIV test : yes / no ID code: …… 1: …… Years HIV test: yes / no ID code: …… 2: …… Years HIV test: yes / no ID code: …… 3: …… Years HIV test: yes / no ID code: …… 4: …… Years HIV test: yes / no ID code: …… 5: …… Years HIV test: yes / no ID code: …… 6: …… Years HIV test: yes / no ID code: …… 7: …… Years HIV test: yes / no ID code: ……

Mode of entry	VCT	PITC: TB	PITC: STI	PMTCT	From other ART center	Other:

Date of first HIV pos. test	Weight and enrolment	BMI	Past TB dates

ARV drugs past exposure: yes / no	Date of ARV previous exposition:	Names of ARV drugs taken previously:

Drug Allergy: yes / no	Name of ARV drugs allergy:	Non ARV drugs allergy:

Annex 2: Patient monitoring form

DEPARTAMENTO DOENÇAS CONTAGIOZAS - PROGRAM HIV/AIDS

ID code:…… Naran:…… Visit: ☐ on time ☐ late ☐ unplanned

Date of consultation/hospitalization: ……/……/…….
Next appointment: ……/……/…….
If hospitalization, date of discharge: ……/……/……

Main complaint:……

Anamnesis:……
……
……
……

Physical examination:
Anemia:……
Lymph nodes……
Cardiovascular……
Lung auscultation……
Neurological symptoms:……
Abdomen……
Urinary-genital symptoms:……
Skin……

Diagnostic:……
……
……

Pulse:……/mn
Temp:……...
BP:……...
Weight:……Kg
Height:……....m
BMI or W/H%…….
Lab tests:
Date:……/……/…...
CD4:……../ml
CD4%:……
Hb :…..……g/dl
Creat:……..
ALAT:…….
VL:…..……

WHO clinical stage:

Comments and prescription (other than ARV):……
……
……
……
……

Main Drugs	*Dose*	*Code*	*Intolerance*
TDF-3TC-EFV……			AZT-
3TC-NVP or EFV ……			
ABC-3TC-NVP or AZT or EFV……			
TDF-3TC-LPV/r ……			
AZT-3TC-LPV/r ……			
Other regimen: ……			
CTX PRO / RX ……			
FLUCO PRO (1 / 2) or Rx (400 or 800 mg/d)……			

(Codes B: Begin. C: Continue, CI Continue with Intolerance, R: Restart, SF: Stop for Failure. SI: Stop for Intolerance. SC: Stop non-compliance. SP: Stop for Patient request, S: Stop other)

Annex 3: Monthly data reporting form

VCT/PITC	
Nber of patients tested during the period	
Nber of new HIV positive during the period	
Cumulative number of HIV positive patients	
HIV cohort report (on ART and not on ART all together)	
number of HIV positive patients in the active cohort at the end of the previous period	
number of new HIV positive patients < 15 years enrolled during the period	
number of new HIV positive patients > or = 15 years enrolled during the period	
number of patients trnasferred in during the period	
total number of new HIV positive patients enrolled during the period	
total nber of death during the period	
nber of HIV positive patients transferred out during the period	
nber of HIV positive patients lost to follow up during the period	
total number of HIV positive patients in the active cohort at the end of the period	
ART program	
number of ARV patients at the end of the previous period	
number of patients < 15 years initiated on ART during the period	
number of patients > or = 15 years initiated on ART during the period	
number of patients ARV transferred in during the period	
total number of patients initiated on ART during the period	
total nber of ART patients dead during the period	
nber of ART patients transferred out during the period	
nber of ART patients lost to follow up during the period	
total number of ART patients in the active cohort at the end of the period	
cumulative number of ARV patients initiated since the beginning of the program	
number of ART patients < 15 years switched to 2nd line treatment during the period	
number of ART patients > or = 15 years switched to 2nd line treatment during the period	
total number of ART patients switched to 2nd line treatment during the period	
cumulative number of ART patients on 2nd line treatment since the beginning of the program	
PMTCT	
See PMTCT data reporting form	

Annex 4: Appointment and Tracing Registers

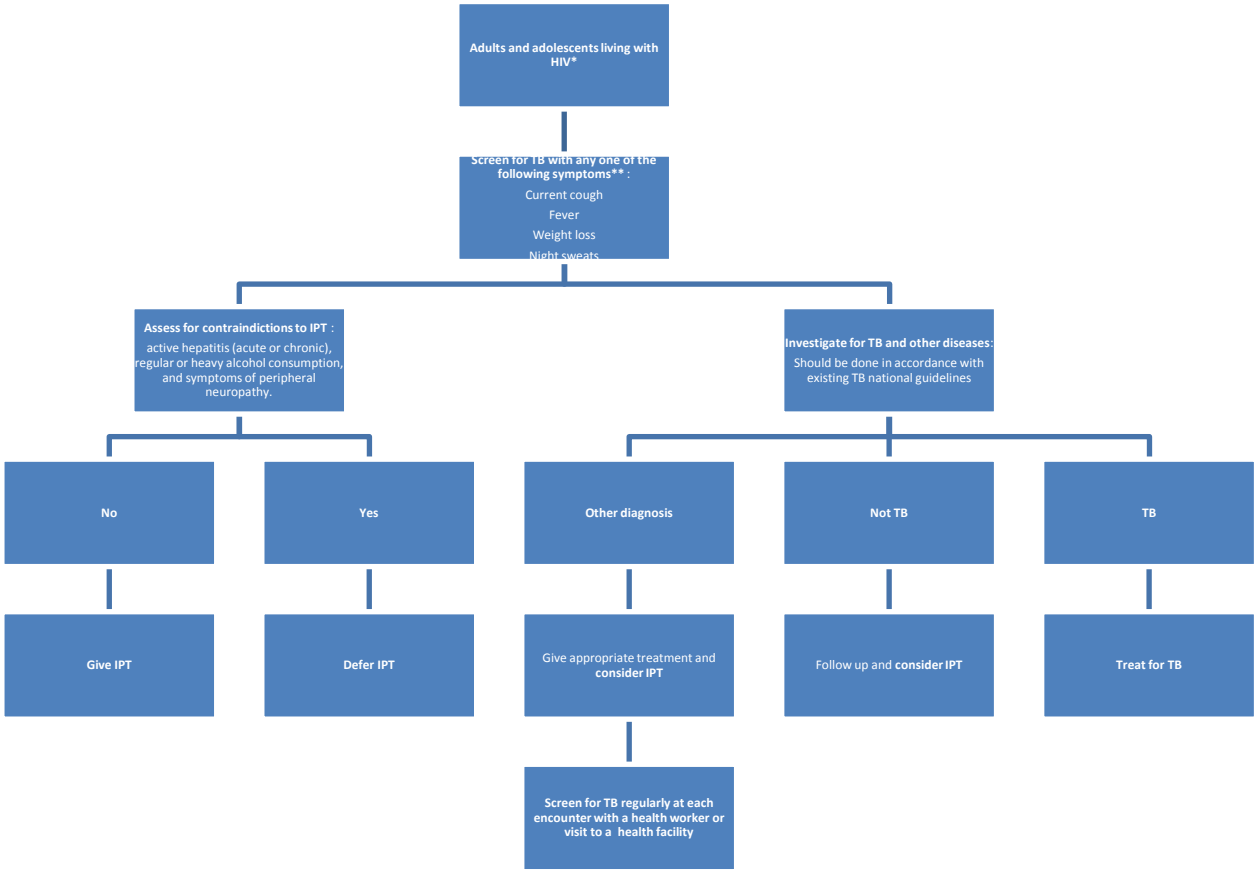
Exemple of « appointment agenda »

Week 9/05 to 13/05/11	**ID code**	**Counselor**	**Doctor**	**Lab**
Monday 2-5 pm	ID 0011JF ID 0687ML ID 0541HT	X X X	X X	- CD4 Hb, CD4
Tuesday	*Off*	*Off*	*Off*	*Off*
Wednesday 8-10 am	**ID 0225JK**			Hb, LFT
Thursday	*Off*	*Off*	*Off*	*Off*
Friday 8 am – 12 pm	**ID 0225JK**	X	X	

Exemple of "tracing register"

ID code	**Date of defaulting**	**Tracing activities**	**Outcome**
ID 0154DE	15 dec 2010	Phone call : 15 Dec 2010 (no reply) Home visit: 22 Dec 2010	Died on 11 Dec 2010
ID 0314TR	10 Jan 2011	Phone call: 10 Jan 2011 (will come on 15 Jan 2011) Phone call: 15 Jan 2011 (no reply) Home visit: 22 Jan 2011 (family stigma: provide information to family to encourage medical follow-up)	Came back to consultation on 24 Jan 2011
ID 0114AZ	02 Feb 2011	Phone call: 02 Feb 2011 (no reply) Home visit: 10 Feb 2011 (wrong address) Peer group mobilization: no success	Declared lost to follow-up on 02 April 2011

Annex 5.1: Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings[70]

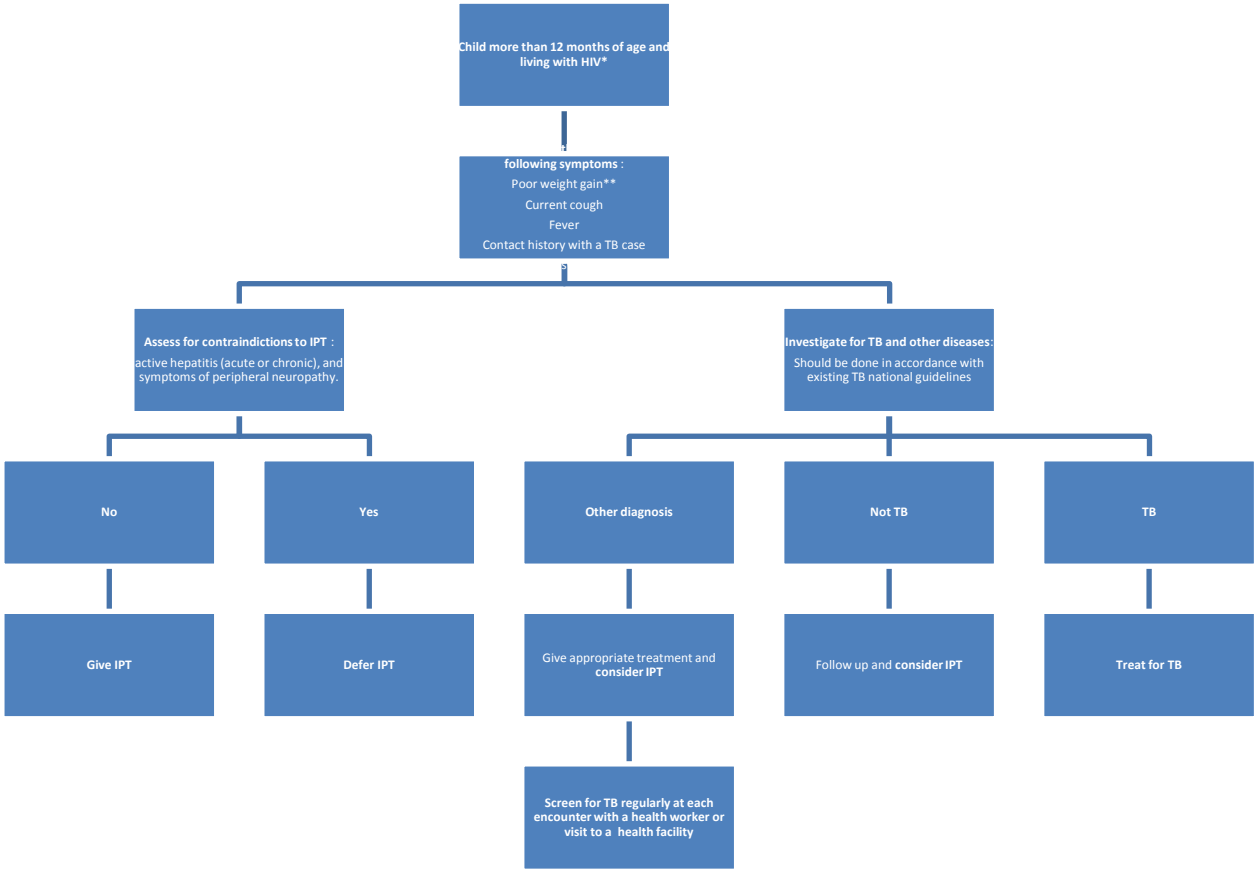


*Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce M;tuberculosis transmission in all settings that provide care.

** Chest radiography can be done if available, but is not required to classify patients into TB and non-TB groups.

[70] Guideline for intensified TB case finding and IPT for PLWHA in resources constrained settings, WHO 2010

Annex 5.2: Algorithm for TB screening in children more than one year of age living with HIV[71]



* All children and infants less than one year of age should be provided with IPT if they have a history of household contact with a TB case

**Poor weight gain is defined as reported weigh loss, or very low weight (weight for age less than -3Zscore), or underweight (weight for age less than -2Zscore), or confirmed weight loss (>5%) since the last visit, or growth curve flattening.

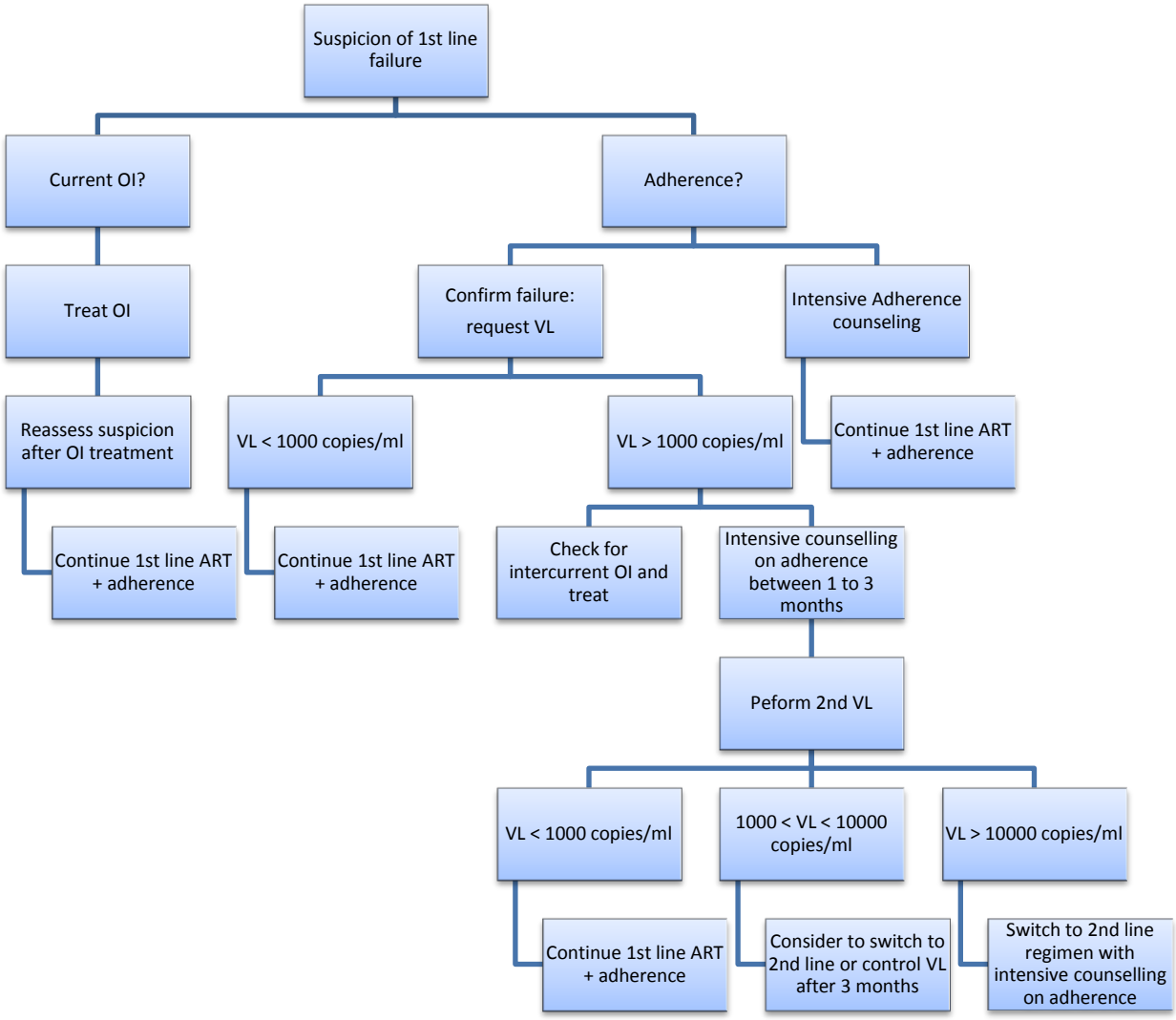
[71] Guideline for intensified TB case finding and IPT for PLWHA in resources constrained settings, WHO 2010

Annex 6: Check list of symptoms to follow-up after ART initiation

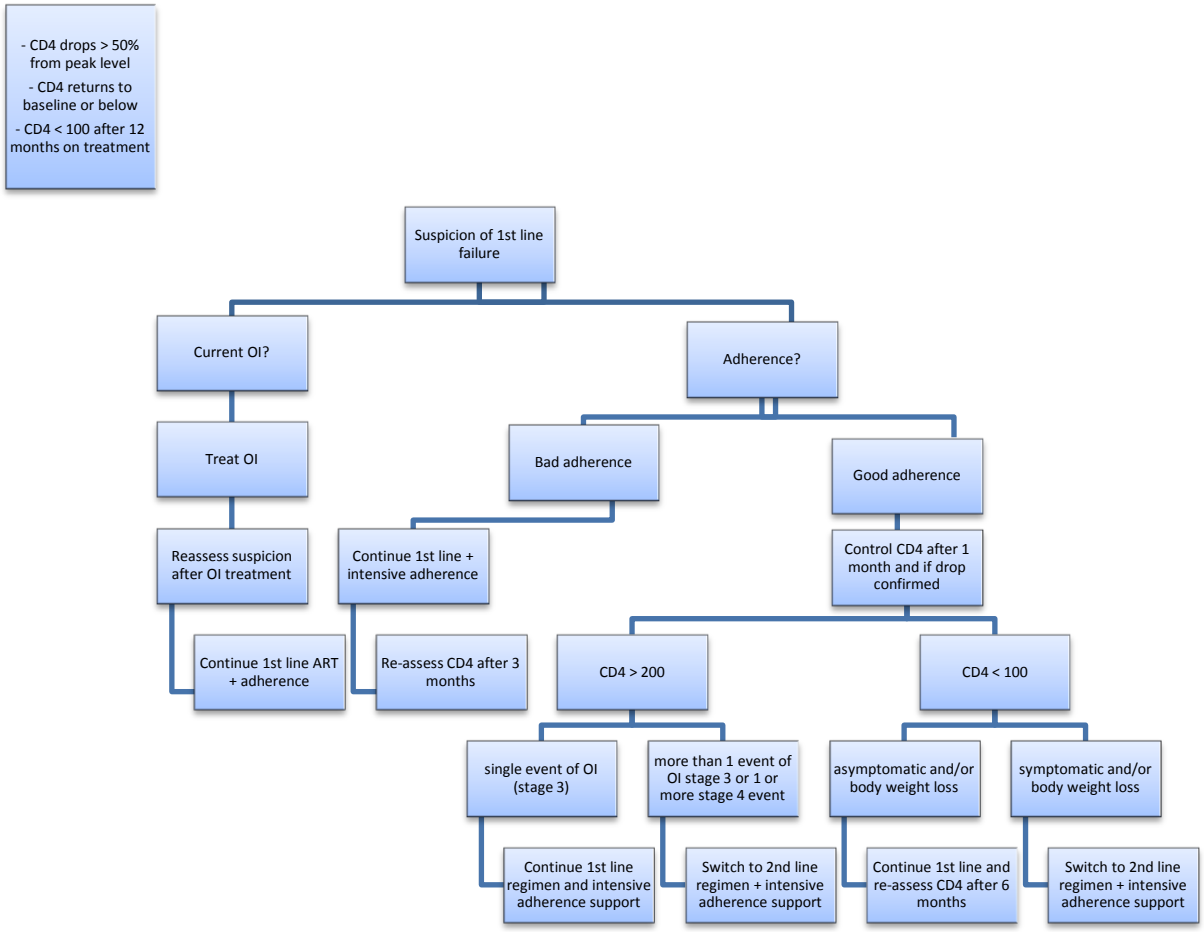
Support for the identification of side effects	Yes	No	Happens to you	It disturbs you
Tired or loss of energy, pallor, dyspnoea.	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Fever, chills	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Pain tingling in the hands or feet	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Vomiting or nausea	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Jaundice or upper abdominal pain or abnormally dark urine	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Diarrhoea or cramps in the stomach.	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Feeling sad, depressed and wanting to cry	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Problems to sleep, insomnia	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Skin problems	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Headache	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot

Loss of appetite	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot
Other symptoms or difficulties	□	□	□ Rarely □ Frequently □ very often □ In permanence	□ Not at all □ A bit □ Moderately □ A lot

Annex 7.1.1: Flowchart for diagnosis of 1st line regimen failure and management



Annex 7.1.2: Flowchart for diagnosis of 1st line regimen failure without viral load



Annex 7.2: 6 monthly failure assessment and checklist for viral load request

ID Code:……. **Treatment failure check up**

Check nr …… (……. months ARV) **Suspicion of failure** ❑ **yes** ❑ **no**

Date: …… / …… / ……

❑ new episode of a stage III or IV disease, after the first 6 months on ART

and/or one of the following immunological criteria :

❑ > 30% fall from on therapy CD4 peak level
❑ CD4 drops back to a level at or below the pre-therapy CD4 baseline after at least 6 months of ART.
❑ CD4 fails to increase by 25-50 above the baseline count after the first six to twelve months of therapy
❑ If CD4 remains < 100 at 12 months of therapy

Refer for VL on …….. / …… / ……

Check nr …… (……. months ARV) **Suspicion of failure** ❑ **yes** ❑ **no**

Date: …… / …… / ……

❑ new episode of a stage III or IV disease, after the first 6 months on ART

and/or one of the following immunological criteria :

❑ > 30% fall from on therapy CD4 peak level
❑ CD4 drops back to a level at or below the pre-therapy CD4 baseline after at least 6 months of ART.
❑ CD4 fails to increase by 25-50 above the baseline count after the first six to twelve months of therapy
❑ If CD4 remains < 100 at 12 months of therapy

Refer for VL on …….. / …… / ……

Notes:

(1) OI occurring during the first 6 months of ART is considered to be due to IRIS or to a still insufficient immune reconstitution
(2) TB may occur at any CD4 count level
(3) Perform CD4 count one month after the first one to confirm the CD4 drop, before asking VL
(4) Very sensitive in case of very low baseline CD4

Annex 8.1: Children dosages of antiretroviral drugs[72]

Harmonized dosing schedules

Simplified table giving number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above								Strength of adult tab (mg)	Number of tablets by weight-band		
		Number of tablets by weight-band morning and evening									25 – 34.9kg		
		3 – 5.9kg		6 – 9.9kg		10 – 13.9kg		14 – 19.9kg		20 – 24.9kg			
		am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
SINGLE DRUGS													
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
ddI	25	2[a]	2[a]	3	2	3	3	4	3	4	4	5	5
CO MBINATIONS													
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	[b]	
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
d4T/3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	1	1
LPV/r[c]	100/25	NR	NR	2	1	2	2	2	2	2	2	3	3

[a] This dose should only be appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

[b] See ABC/3TC FDC dosing table.

[c] Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, tipranavir (TPV), rifampicin.

[72] WHO 2010, Antiretroviral therapy for HIV infections in infants and children

Simplified table giving ml of liquid formulation and number of tablets or capsules of adult solid formulation for morning and evening dosing

Drug	Strength of paediatric liquid (mg/ml) and adult tab/cap (mg)	Children 6 weeks of age and above									
		Number of tablets/capsules or ml by weight-band morning and evening									
		3 – 5.9kg		6 – 9.9kg		10 – 13.9kg		14 – 19.9kg		20 – 24.9kg	
		am	pm	am	pm	am	pm	am	pm	am	pm
AZT	10 mg/ml; 300 mg	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	0.5	0.5	1	0.5
ABC	20 mg/ml; 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
3TC	10 mg/ml; 150 mg	3ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
d4T	1 mg/ml; 15 mg or 20 mg	6 ml	6 ml	9 ml	9 ml	1 (15 mg)	1 (15 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)
NVP	10 mg/ml; 200 mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	0.5	1	0.5
ddI	10 mg/ml; 25 mg	3 ml [a]	3 ml [a]	5 ml	5ml	6 ml	6 ml	4	3	4	4
LPV/r	80/20mg/ml	1or 1.5 ml[b]	1 or 1.5ml[b]	1.5 ml	1.5 ml	2 ml	2 ml	2.5ml	2.5 ml	3 ml	3ml

[a] This dose of ddI is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

[b] LPV/r liquid: for 3 – 3.9 kg, use 1 ml a.m. and 1 ml p.m.; for 4 – 5.9 kg use 1.5 ml a.m. and 1.5 ml p.m. In addition, higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV or rifampicin.

Simplified table giving number of tablets of child-friendly solid formulations for once-daily dosing

Drug	Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily					Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily
		3 – 5.9 kg	6 – 9.9 kg	10 – 13.9 kg	14 – 19.9 kg	20 – 24.9 kg		25 – 34.9 kg
		Once daily	Once daily	Once daily	Once daily	Once daily		Once daily
SINGLE DRUGS								
EFV[a]	200 mg	NR	NR	1	1.5	1.5	200	2
ddI [b]	125 mg or 200 mg EC	NR	NR	1 (125 mg)	1 (200 mg)	2 (125 mg)	125 mg EC	2

[a] EFV is not recommended for children below 3 years and weighing less than 10 kg.

[b] ddI EC is not recommended for children weighing less than 10 kg; this dose is recommended only for those 10 kg and above.

NR = not recommended; EC = enteric coated

Annex 9.1: Treatment Chart for 1st line regimen TDF/3TC/EFV initiation in adults and adolescents

Week 1														
														
TDF/3TC/EFV		1		1		1		1		1		1		1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														
Week 2														
														
TDF/3TC/EFV		1		1		1		1		1		1		1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														
Week 3														
														
TDF/3TC/EFV		1		1		1		1		1		1		1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														
Week 4														
TDF/3TC/EFV		1		1		1		1		1		1		1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														

Annex 9.2: Treatment Chart for 1st line regimen AZT/3TC/NVP initiation in adults and adolescents

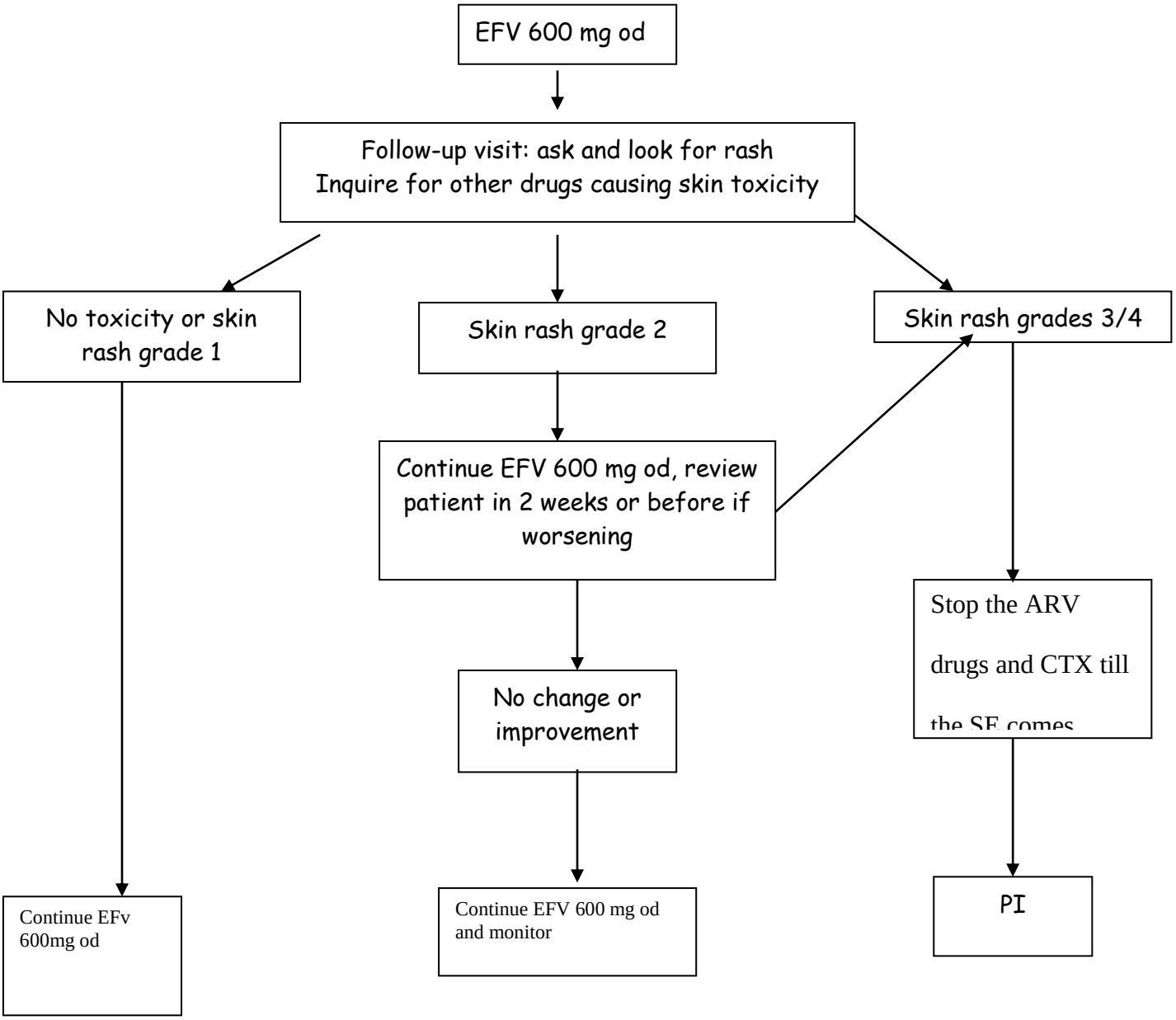
Week 1														
														
AZT/3TC	1		1		1		1		1		1		1	
AZT/3TC/NVP		1		1		1		1		1		1		1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														
Week 2														
														
AZT/3TC	1		1		1		1		1		1		1	
AZT/3TC/NVP		1		1		1		1		1		1		1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														
Week 3														
														
AZT/3TC/NVP	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														
Week 4														
AZT/3TC/NVP	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cotrimoxazole ……. mg														
Fluconazole 200 mg														

Annex 9.3: Treatment Chart for ART adherence support

Dates:														
Names of drugs:														
Dates:														
Names of drugs:														
Dates:														
Names of drugs:														
Dates:														
Names of drugs:														

Annex 10.1: EFV and skin toxicity

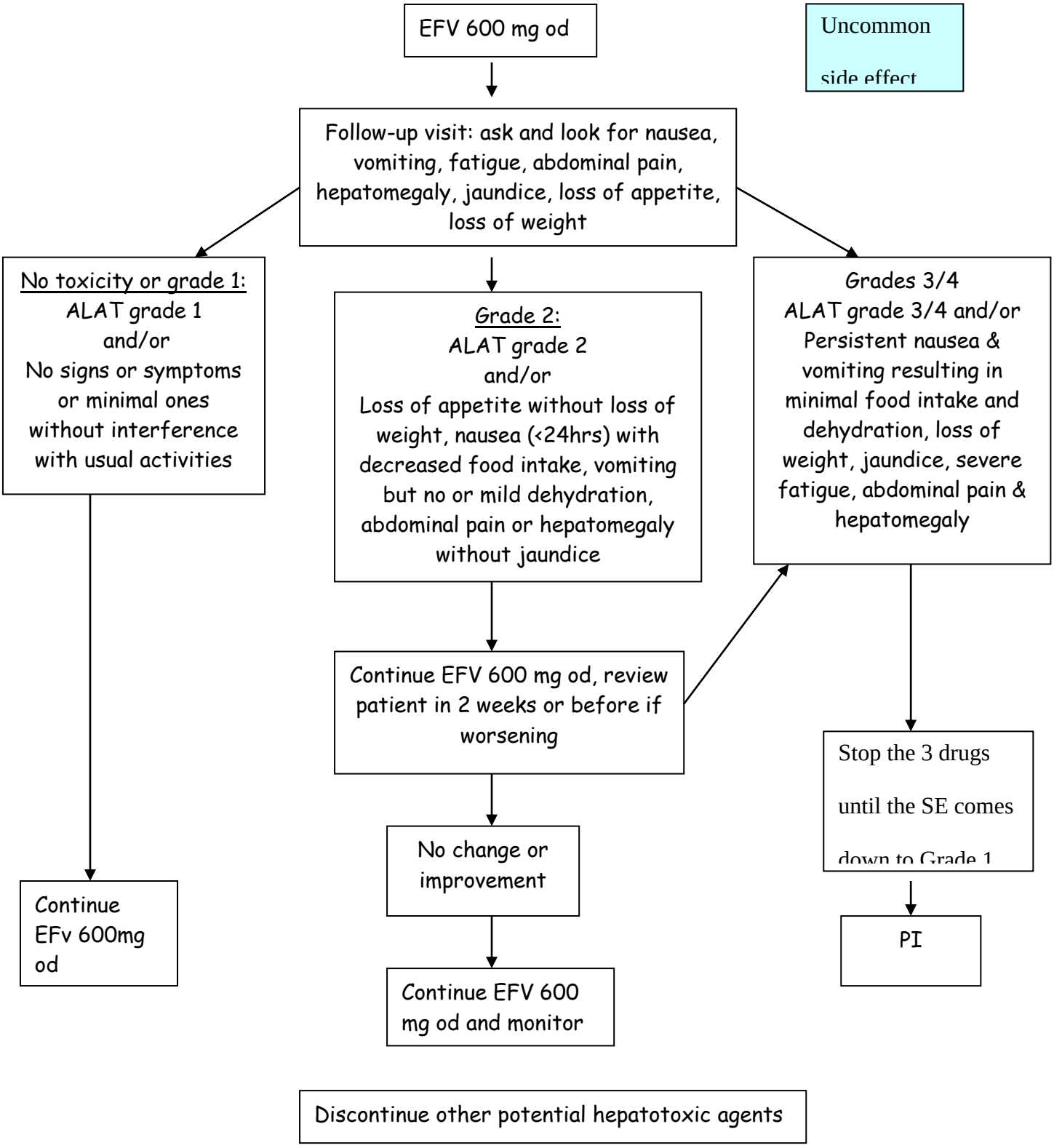
In 10% of patients but rarely severe (<1%)



	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous reaction – rash	Localized macular rash	Diffuse maculopapular or morbilliform rash OR Target lesions	Diffuse maculopapular or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis

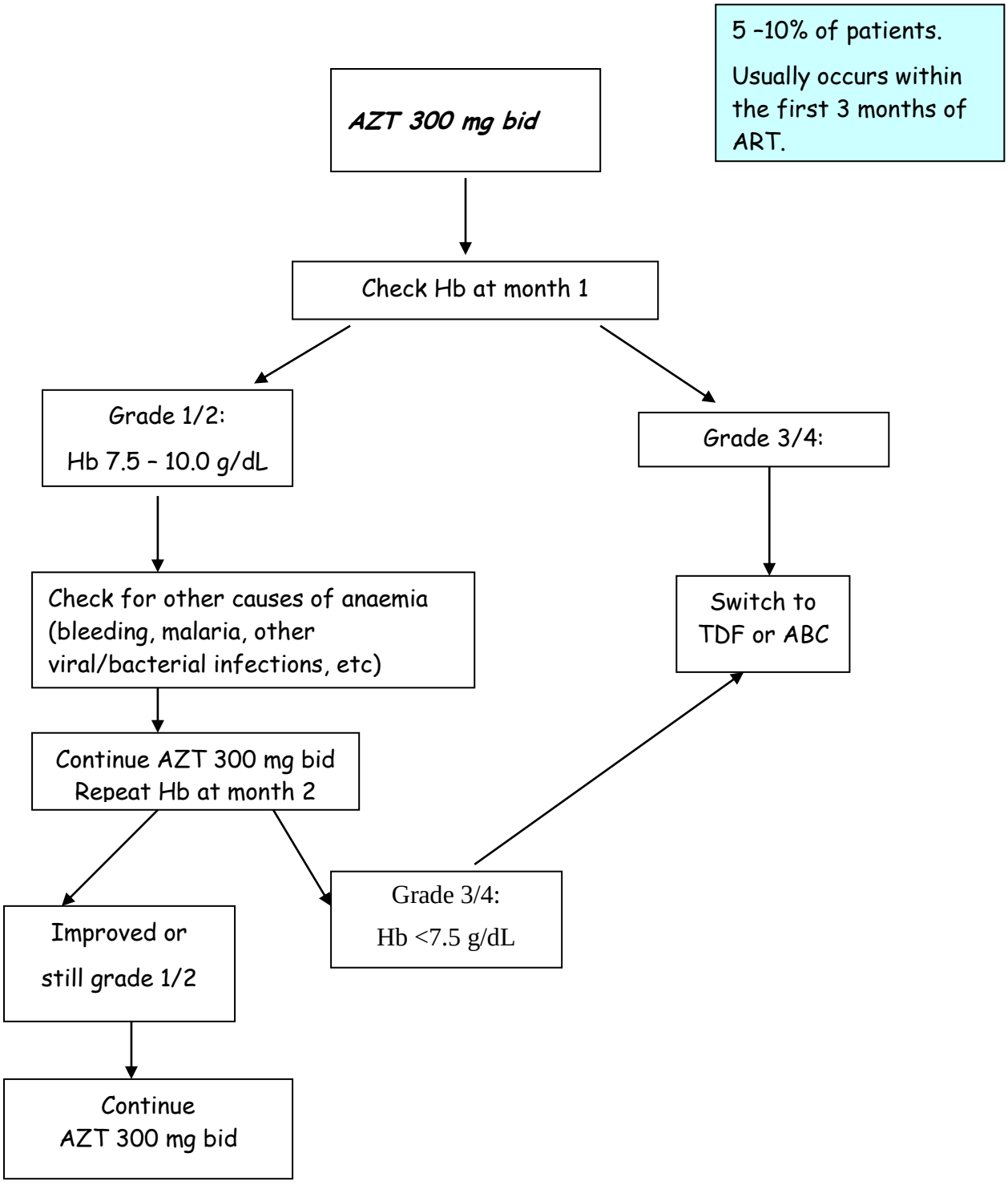
Annex 10.2: EFV and hepatotoxicity

Routine ALAT are not done for patient on EFZ as liver toxicity is uncommon; (if done at baseline, ART should not be started if ALAT > 3 x ULN). The algorithm is based on clinical signs and symptoms. Ask for ALAT (if possible) in case of clinical suspicion. ALAT toxicity values are the same than for NVP. I n case of ALAT toxicity grade 3/4, EFZ will be discontinued and switched for a PI.



Annex 10.3: AZT and anaemia

Check base-line haemoglobin. If at M0, Hb is <7.5 g/dL, do not start AZT.



Annex 10.4: NRTI and Lactic Acidosis when lactate dosage available

Routine lactic acid monitoring is not recommended as it is not predictive of lactic acidosis in asymptomatic patients.

Adherent patient with good response to ART, usually more than 6 months after treatment initiation, with suggestive symptoms: fatigue, dyspnea without respiratory cause, tachycardia, GI symptoms (nausea, vomiting, diarrhoea, abdominal pain, sudden unexplained weight loss, abdominal cramps, hepatomegaly), cramps in legs, rapid ascending neuro-motor weakness. NB: liver function tests can be normal.

↓

Assess risk factors: female, high BMI, prolonged NRTI use

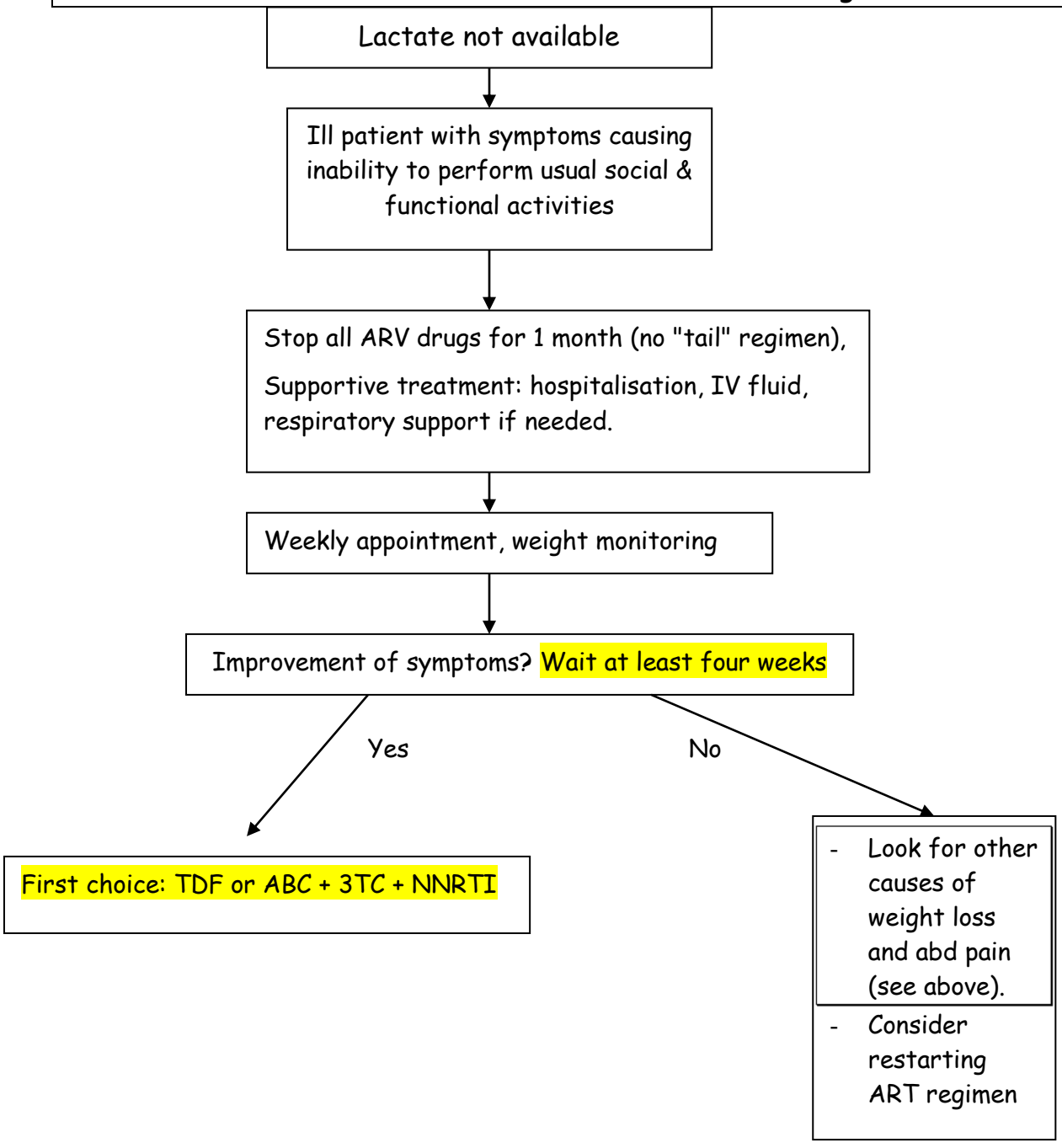
2-8/1000 patients/year.

Usually occurs after 10 to

- **If Lactate available**:
- Assess respiratory rate (RR)

<2 mmol/mL	2 - 5 mmol/mL RR <20	>5 mmol/mL **or** 2 – 5 mmol/mL and RR >20
Look for other causes of weight loss & abd pain: - OI or IRIS (check for TB) - Chronic diarrhoae with malabsorption - Treatment failure - Depression - Malignancy - Diabetes - Pancreatitis - Hepatitis/steatohepatitis - GI intolerance of drugs - Unrelated causes (e.g. appendicitis) Recheck in one week. If still < 2 mmol/l, continue ART	- Check ALAT and amylase/lipase if available - Continue ART but replace AZT by TDF or ABC - recheck lactate after 3 days. If lactate continues to increase or symptoms worsen, stop all ARV	- Stop all ARV drugs (no "tail" regimen), - Supportive treatment: hospitalisation, IV fluid, respiratory support if needed. Normalization of lactate level First choice: TDF or ABC + 3TC + NNRTI

Annex 10.5: NRTI and Lactic Acidosis when lactate dosage NOT available



If ABC or TDF not available, re-challenging with AZT is an option to be considered but only under very close monitoring.

Annex 10.6: NVP and hepatotoxicity

If ALAT done at baseline, do not start ART if > 3 ULN

8 –15% of patients.

Usually occurs during the first 3 months of ART.

NVP 200 mg od

2 weeks visit: ask and look for nausea, vomiting, fatigue, abdominal pain, hepatomegaly, jaundice, loss of appetite, loss of weight. ALAT if available

No toxicity or grade 1:
No signs or symptoms or minimal ones without interference with usual activities and/or
ALAT grade1

Grade 2:
Loss of appetite without loss of weight, nausea (<24hrs) with decreased food intake, vomiting but no or mild dehydration, abdominal pain or hepatomegaly without jaundice
and/or
ALAT grade 2

Grades 3/4:
Persistent nausea & vomiting resulting in minimal food intake and dehydration, loss of weight, jaundice, severe fatigue, abdominal pain & hepatomegaly
and/or
ALAT grades 3/4

Continue NVP 200 mg od, for not more than 2 more weeks and under medical supervision. Discontinue other potential hepatotoxic agents

Improvement

No change or worsening

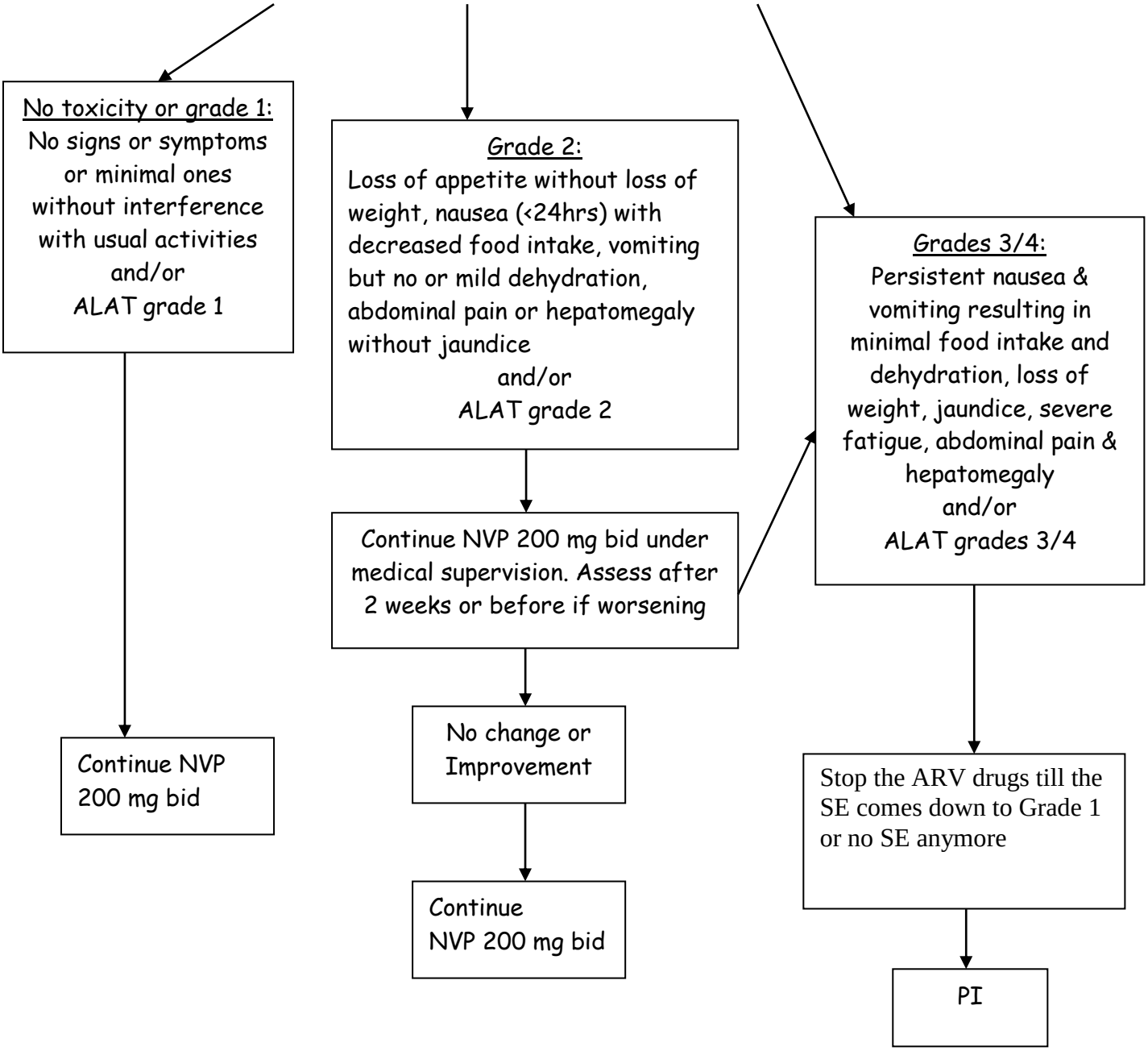
Stop the 3 drugs until the SE comes down to Grade 1

Increase to NVP 200 mg bid

Increase to NVP 200 mg bid

If grade 3 on NVP, EFV may be tried under close monitoring; alternative : PI
If grade 4 on NVP, switch to PI

NVP 200mg bid: at each visit, ask and look for nausea, vomiting, fatigue, abdominal pain, hepatomegaly, jaundice, loss of appetite, loss of weight. Check ALAT if patient is symptomatic and if available.



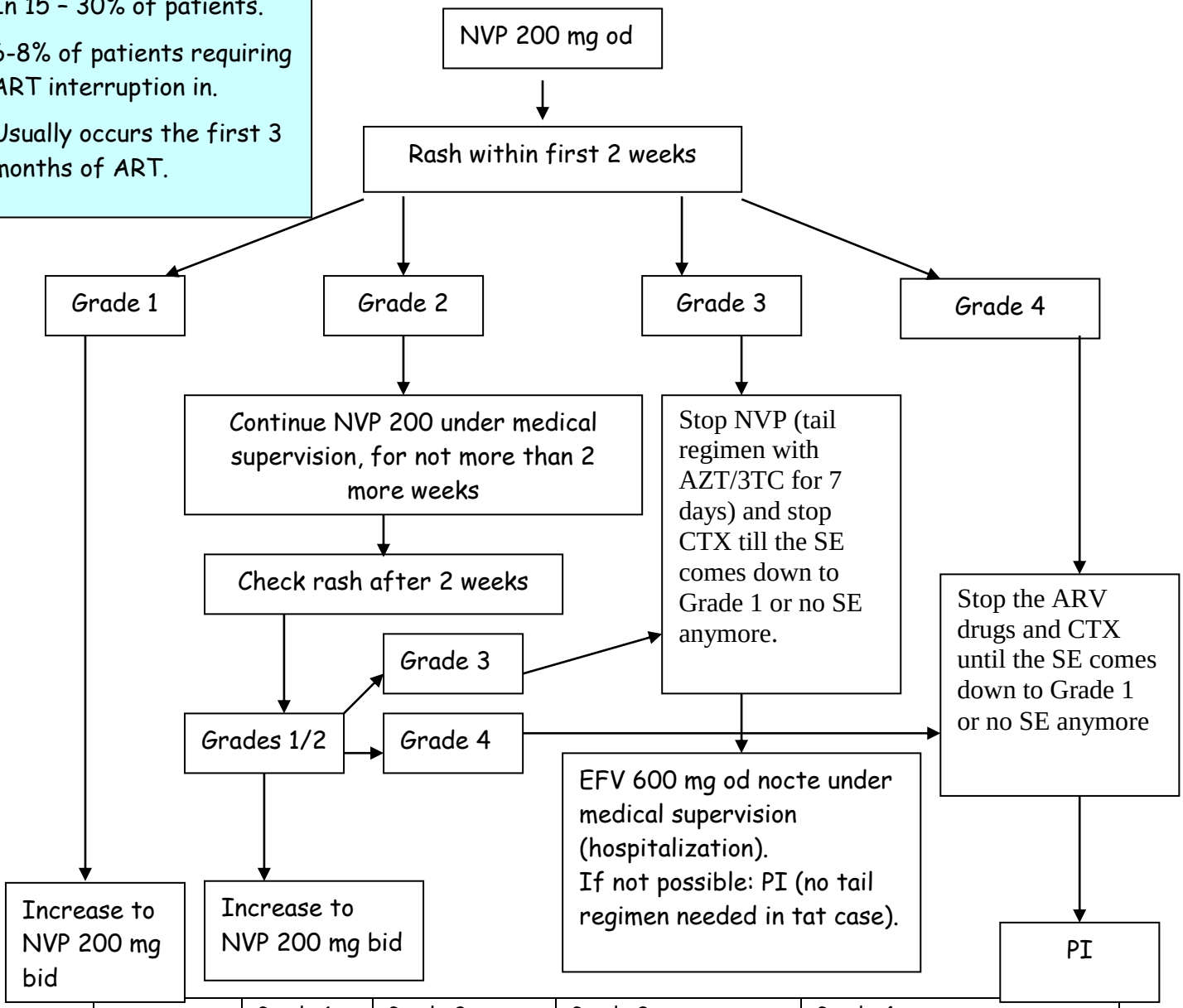
	Grade 1	Grade 2	Grade 3	Grade 4
ALAT	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN

Annex 10.7: NVP and skin toxicity

In 15 – 30% of patients.

6-8% of patients requiring ART interruption in.

Usually occurs the first 3 months of ART.



	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous reaction - rash	Localized macular rash	Diffuse maculopapular or morbilliform rash OR Target lesions	Diffuse maculopapular or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis