

Guidelines for Antiretroviral Therapy & Management of Opportunistic Infections for Children, Adolescents & Adults Living with HIV

July2022

National HIV/AIDS Programme
Department of Communicable Diseases
Ministry of Health
Democratic Republic of Timor-Leste

Ministério da Saúde

World Health Organization
Timor-Leste

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Message from Hon'ble Minister of Health



dr. Odete Maria Freitas Belo, MPH
Minister of Health
Democratic Republic of Timor-Leste
Dili
July 2022

Timor-Leste is considered as "HIV Low Endemic Country". The estimated adult prevalence of HIV was 0.2 % in 2021 with estimated 1400 People Living with HIV (PLHIVs) at the end of December 2021. HIV/AIDS continues to be driven primarily by transmission of infections among Key Population.

I am very pleased to note that National AIDS Programme has revised the national guidelines on HIV treatment, and Elimination to Mother to Child Transmission (EMTCT) based on updated WHO recommendations.

The updated guidelines for antiretroviral therapy and management of opportunistic infections (OI) for children, adolescents, and adults Living with HIV, aims to provide guidance and support to health care workers involved in the HIV/AIDS clinical management, including ART and OI, in Timor-Leste.

HIV treatment and services, including ARV and OI treatment, are provided free of charge for all Timorese citizens through the government-run health facilities and select private centres namely, Bairo Pite Clinic and Maluk Timor Clinic at CHC Vera Cruz.

The key audiences for these guidelines are policy makers in the MoH and the managers of the NAP who formulate country specific HIV treatment guidelines. In addition, health professionals- including doctors, nurses, and educators working both in Govt. and Non- Govt. Organizations (NGOs) involved in management and care of HIV patients and organizing treatment services – are expected to use this updated and consolidated guideline.

I look forward to the successful implementation of and adherence to the revised ART guidelines (2021 Edition) by all PLHIV care providers.



Dr. Odete Maria Freitas Belo, MPH
Minister of Health

Message from WHO Representative



Dr. Arvind Mathur
WHO Representative to Timor-Leste
World Health Organization
Dili
July 2022

I am proud to present the national guidelines on HIV treatment. The guideline development was completed by the Ministry of Health (MoH) with technical assistance from WHO. I congratulate and thank everyone who contributed to this revision.

This guideline aims to provide guidance and support to health care workers involved in the HIV/AIDS clinical management, including ART and OI, in Timor-Leste. Recently, WHO has come out with many new updates based on the evidence from other clinical trials. The latest guideline brought out in July 2019 provides an evidence-based recommendation for use of dolutegravir-based triple ART.

The national guideline development has been developed in close consultation with the Technical Working Group for ART in Timor-Leste and supported by WHO. The guideline aims at:

1. Revising and consolidating existing ART and OI guidelines and incorporate WHO recommendations for all age groups, gender and populations

2. Providing a standard approach for the use of ART with uniform recording and reporting formats

3. Providing a transition plan for shifting to dolutegravir-based regimen.

WHO is committed to continue its support to the national program to End Inequities and End AIDS and to ensure that the country can meet the target of elimination of AIDS as a public health problem by 2030.

Dr. Arvind Mathur
WHO Representative

Acknowledgements

Timor-Leste brought out its first ART and OI guidelines in 2011 and were revised in 2014 and 2017. This is the 2021 revision necessitated by the updates provided by WHO in the past two years.

The Ministry of Health, Democratic Republic of Timor-Leste gratefully acknowledges the contributions from the National AIDS Programme, WHO, The Global Fund, and National HIV, Hepatitis and STI Technical Advisory Group (TAG) for their valuable support and contributions in revising the national guidelines on HIV treatment and EMTCT.

The final guidelines were reviewed by the TAG, WHO SEARO HIV Unit, WHO Country Office and NAP Team lead by Mr Bernardino da Cruz.

The Ministry of Health gratefully acknowledges the financial support provided from The Global Fund for TB, AIDS and Malaria (GFATM) and the continued technical support from the World Health Organization (WHO).

Acronyms and abbreviations

ABC	Abacavir
ACT	artemisinin based combination therapy
AFB	acid fast bacilli
ART/ARV	antiretroviral therapy/antiretrovirals
AZT	azidothymidine or zidovudine
AZV	Atazanavir
BID or b.i.d or bid	'Bis in die' in Latin means twice in a day
BMI	body mass index
CDC	department of communicable disease control
CHC	community health centre
CLHIV	children living with HIV/AIDS
CM	cryptococcal meningitis
CMV	cytomegalovirus
CTX	co-trimoxazole
3TC	Lamivudine
DDI	Didanosine
DST	drug sensitivity test
DTG	Dolutegravir
EMTCT	elimination of mother to child transmission of HIV/AIDS, syphilis,and hepatitis B
EFV	Efavirenz
EPTB	extra pulmonary tuberculosis
FDC	fixed dose combination
Hb	Haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HNGV	Hospital National GuidoValadarès
IM	intra-muscular
INH	Isoniazid
INSTI	integrase strand transfer inhibitors
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
IV	Intravenous
LFT	liver function tests
LPV/r	lopinavir boosted with 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
NNT	number need to treat
NRTI	nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OD	once daily
OI	opportunistic infections

PCP	*Pneumocyctiscarinii* (*jirovici*) pneumonia
PI	protease inhibitor
PLHIV	people living with HIV and AIDS
PMTCT	prevention mother to child transmission
RAL	Raltegravir
SPC	standard package of care
STI	sexually transmitted infections
TB	Tuberculosis
TDF	Tenofovir
VL	viral load
ZDV	zidovudine

Chapter 1

Introduction

International HIV/AIDS situation

By the end of 2019, there were an estimated 38.0 million (31.6–44.5 million) people living with HIV (PLHIV) worldwide. With 1.7 million new infections (1.2–2.2 million) and 690 000(500 000–970 000) deaths, the disease is far from gone. The number of people with access to antiretro viral therapy (ART) was 25.4 million (20.5–24.3 million). While new HIV infections fell by 39% and HIV-related deaths fell by 39% amid 2010 and 2019,an estimated 12.1 million lives were saved due to ART. It is heartening to note that 68% of adults and 53% of children living with HIV/AIDS (CLHIV) are on lifelong ART and 85% of all pregnant and breastfeeding women are also accessing ART.[1]

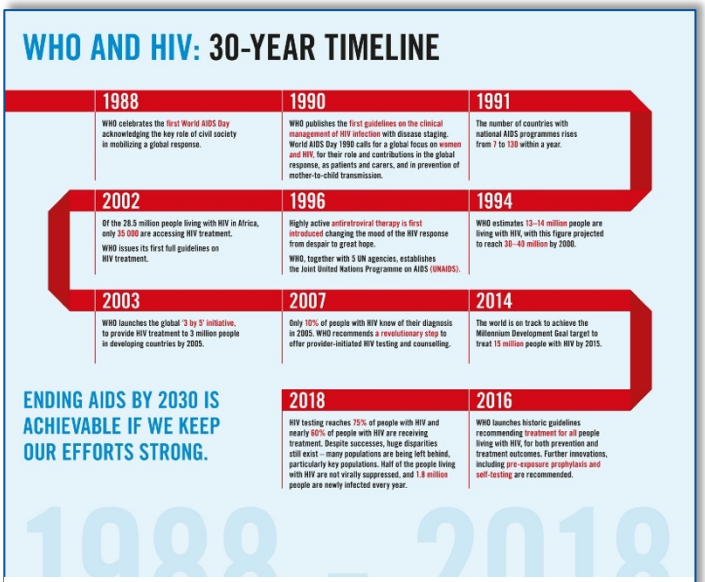

Fig. 1. The 30 years of HIV/AIDS control effort, 1988--2018

Sexual transmission accounts for more than 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 sero discordant couples by 96%.[2] However, this must be used in combination with other HIV prevention options such as consistent condom use, voluntary male circumcision and a few partners.

[1] Global HIV and AIDS statistics- 2020 fact sheet. Geneva: UNAIDS (https://www.unaids.org/en/resources/fact-sheet, accessed 28 November 2020).
[2] https://www.hptn.org/research/studies/hptn052.

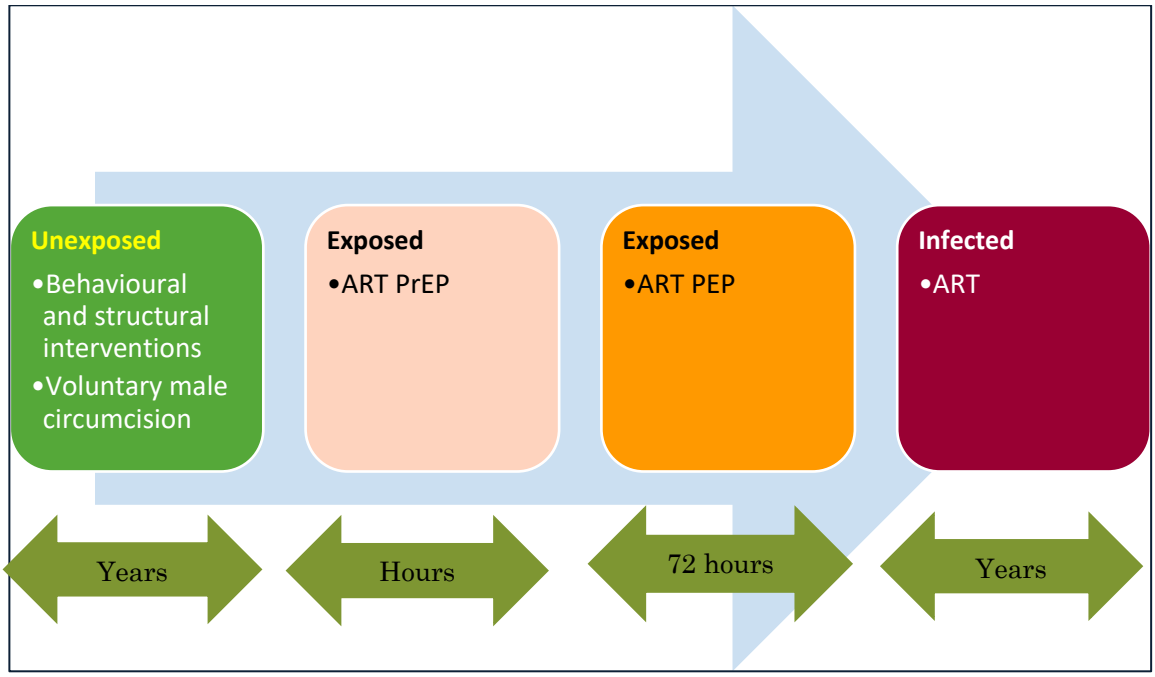

Fig. 2. Four opportunities for HIV prevention

Source: Cohen, Myron S et al. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? Lancet. 2013; 382: 1515--24 doi:10.1016/S0140-6736(13)61998-4.

Improvement in the quality of life for those who are HIV positive includes universal access to ART and opportunistic infections (OI) treatment. This is possible with availability of free antiretrovirals (ARVs), a sustainable resource flow, planning and coordination in procurement among health workers, a strong and effective participation of civil society and PLHIVs, 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.

HIV/AIDS in Timor-Leste

The first case of HIV infection in Timor-Leste was reported in 2001. The country has diagnosed cumulatively 716 cases since 2003.[3] The mode of transmission is overwhelmingly sexual. There are only three cases, though doubtful, of transmission through infected blood and sevencases of mother to child transmission recorded in the programme database.

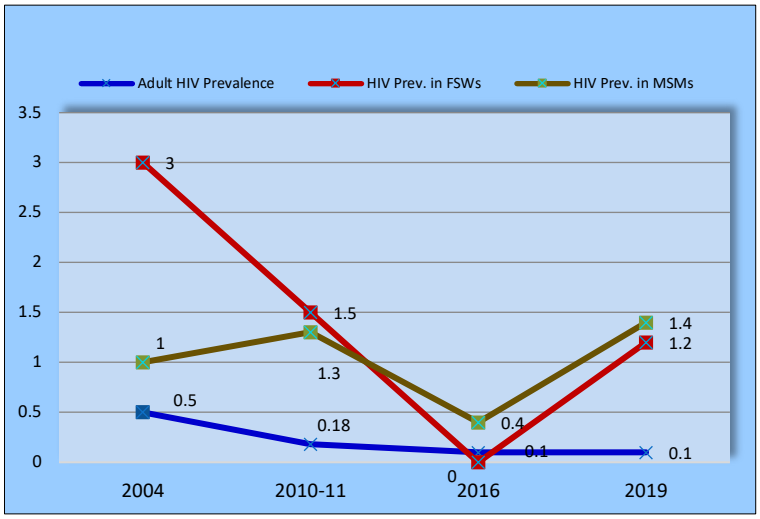

Fig. 3. HIV prevalence (%) in Timor-Leste, 2004–-2019

The estimated adult prevalence of HIV was 0.1% (2019). Thus, there were

[3]Program report. National HIV/AIDS program, updated October 2019. Ministry of Health, Democratic Republic of Timor-Leste.

approximately, 909 PLHIVs at the end of December 2019. The prevalence among the female sex workers (FSW) has reduced from a high of 2.76 (3%) in 2004 to no new cases detected in integrated biological and behavioural surveillance (IBBS), 2016. Similarly, the prevalence among men having sex with men (MSM) has reduced from a high of 1.0% (2004) to 0.4% (IBBS, 2016). The estimated adult prevalence has come down from 0.5% (2004) to 0.1% (2019).

The National HIV/AIDS Programme (NAP) is in its second decade of implementation. Things have gone well for this country because the HIV prevalence has not increased. The prevalence in the neighbouring country is many times higher than that of Timor-Leste, and it shares a large part of its borders with Nusa Tengara Timur (NTT) region of Indonesia.

ART was initiated in Timor-Leste through the private sector (Bairo Pite Clinic) in 2002, using donated ARV drugs. The public sector followed through with the Hospital Nacional Guido Valadares (HNGV) starting its first ART clinic in 2005 by a generous support from the Government of Brazil for first-line ARV drugs, technical assistance, and training of health workers. Since 2007, the country received its ARV through the Global Fund programme (Round 9).

In 2017, the Government of Timor-Leste resolved to provide all the PLHIVs with ART irrespective of their immune status or CD4 count, and also introduced HIV viral load (VL)monitoring for follow up of PLHIVs on ART (The 'Test and Treat' policy is provided in Annex 1. 'Test and Treat' protocol for Timor-Leste).

Timor-Leste is a signatory to the Sustainable Development Goals (SDGs). Goal 3, Target 3.3 is about bringing an end to epidemics of AIDS, TB, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases. Moreover, the UN 90-90-90 strategy of ending AIDS by 2030 has some interim milestones of:

- 90% of estimated PLHIVs know their status, of which
- 90% are accessing sustained lifesaving ART, of which
- 90% have sustained viral suppression.

The current achievements are presented in Fig. 4.

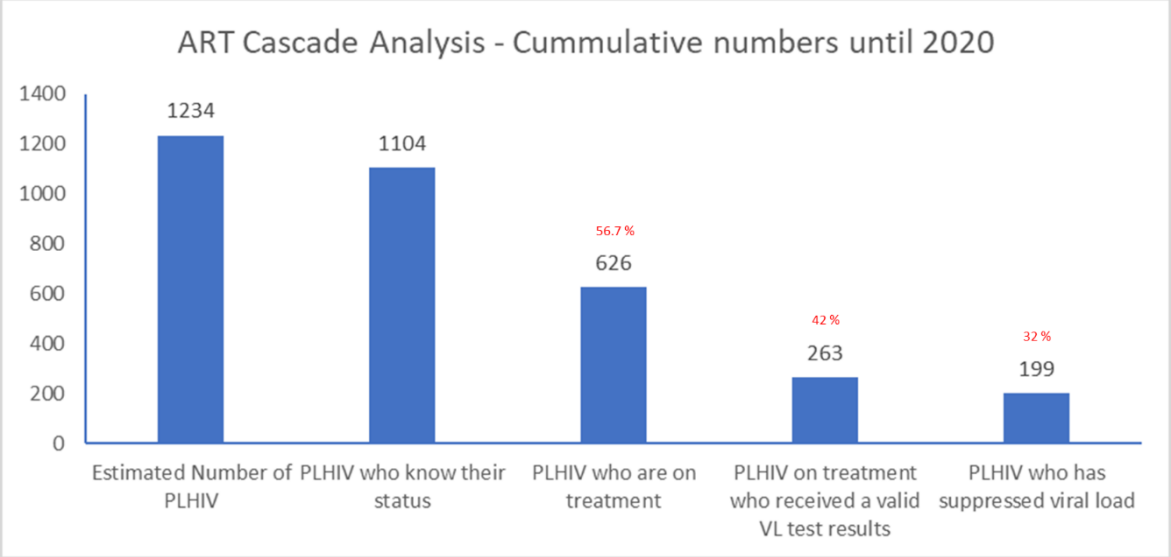

Fig. 4. HIV treatment cascade, 2020 (Cumulative data until December 2020)

HIV treatment and services, including ARV and OI treatment, are provided free of charge for all Timorese citizens through the government-run health facilities and select private centres namely, Bairo Pite Clinic and Maluk Timor Clinic at CHC Vera Cruz. The Constitution of the Democratic Republic of Timor-Leste, approved on the 22 March 2002, states that the citizens of Timor-Leste have the following as a fundamental right, duty, freedom and guarantee regarding health:

- Everyone has the right to health and medical care, and the duty to protect and promote them
- 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
- The national health service shall have, as much as possible, a decentralised participatory management.

Objectives of the guideline

This guideline aims to provide guidance and support to health care workers involved in the HIV/AIDS clinical management, including ART and OI, in Timor-Leste. Recently, WHO has come out with many new updates based on the evidence from other clinical trials. The latest guideline brought out in July 2019 provides an evidence-based recommendation for use of dolutegravir-based triple ART.

The guideline has been developed in close consultation with the Technical Working Group for ART in Timor-Leste and supported by WHO. It considered in detail the present epidemiological situation of HIV infection in Timor-Leste, demand and sustainability for ART in the country.

The guideline aims at:

- Revising and consolidating existing ART and OI guidelines and incorporate WHO recommendations for all age groups, gender and populations
- Providing a standard approach for the use of ART with uniform recording and reporting formats
- Providing a transition plan for shifting to dolutegravir-based regimen.

Chapter 2

HIV testing

HIV testing service for OPD and IPD

The model followed in Timor-Leste includes a pre-test information followed by testing and a post-test counselling. Essentially build on the model of 'opt out' approach, i.e., the HIV test is offered unless the patient actively opts out of the procedure. It is also known as provider-initiated testing and counselling (PITC).

Pre-test information

Pre-test information may be provided in group, where resources do not permit individual sessions, but preferably on a one-to-one basis.

Pre-test information should include at the minimum:

- The reasons why HIV testing and counselling are recommended
- The benefits of testing, as well as the potential adverse outcomes (violence, stigma, abandonment, etc.)
- 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 (opt out approach)
- 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 healthcare 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 ARV 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.

HIV testing services

Three tests algorithms are currently used for diagnosis of HIV in any adult, adolescent or children (above 18 months of age). The diagnostic algorithm for HIV testing for adults, adolescents and children >18 months is given in Fig.5.

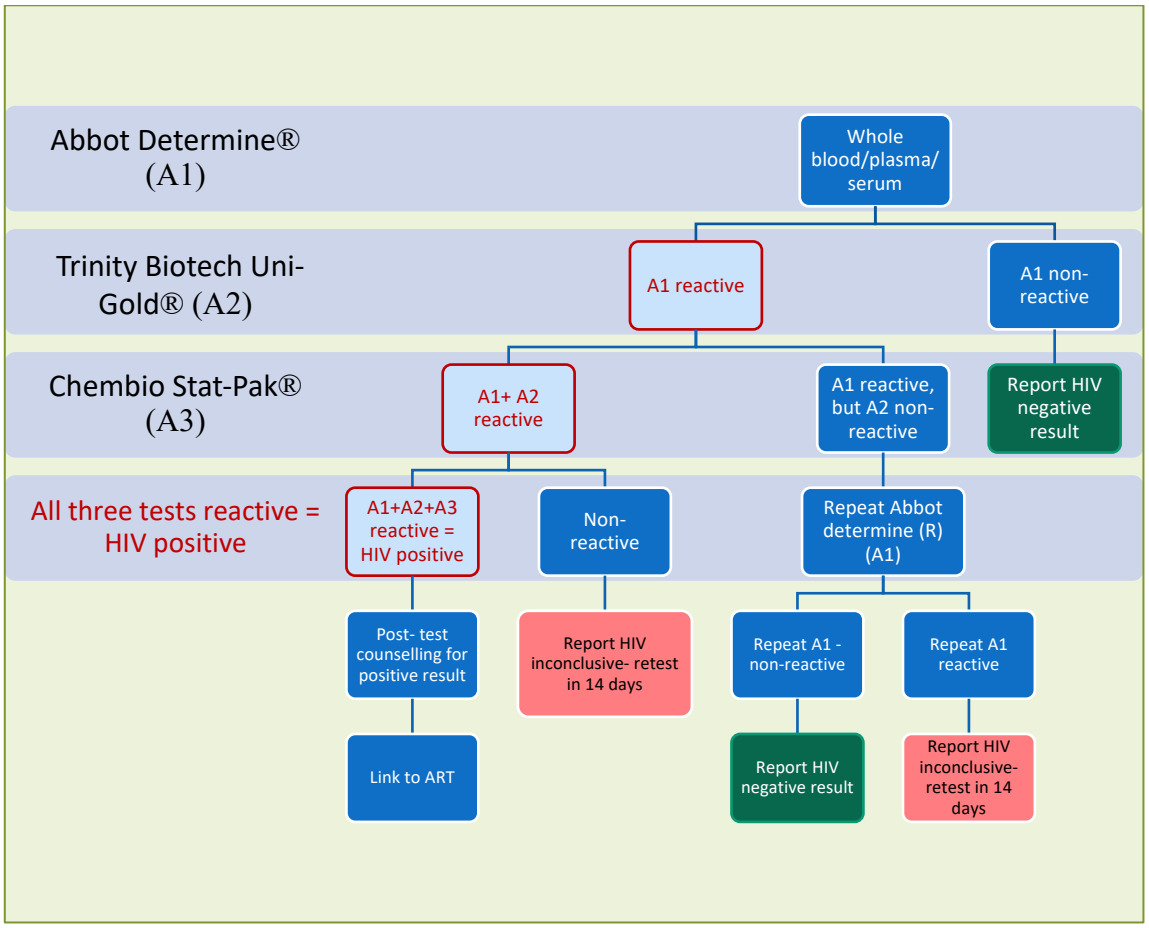

Fig. 5. Diagnostic algorithm for HIV testing

Post-test counselling

Post-test counselling should be provided for all people, whether they test HIV positive or negative. The test result should be provided 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, whether positive or negative
- To provide emotional support to help the person to cope with the result if positive
- To discuss the physical, emotional and social implications of a positive result
- To discuss prevention for HIV-positive and -negative individuals
- To refer the client for any care or treatment indicated
- To advocate for prevention of HIV so that the person remains HIV negative.

Table 1. Protocols to be followed for outcomes of an HIV test

Criteria	What to do?
Negative HIV test	• 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 three 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
Positive HIV test	• 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 (PLHIV) 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 postcounselling to the needs of each client and avoid "*one conversation fits all*" approach. 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 their emotional state. Therefore, the counsellor should first assist them psychologically and offer further session(s) to explain general facts.

Chapter 3

Technical guidance on ART

ART has been a game changer for HIV/AIDS globally. It has not only allowed PLHIVs to live a dignified life, but also improved their quality of life and life expectancy. Timor-Leste has been offering its citizens free ARTs since 2010. It also introduced 'Test and Treat' for all in 2017.

ART consists use of a combination of at least three ARV drugs from different classes to inhibit the replication of HIV and reduce viremia to undetectable levels. Continued suppression of viral replication leads to the restoration of immune response, reflected by an increase in the CD4 count.

There are two lines of ART available in the country, namely, first-line and second line. The first-line consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) backbone (e.g., tenofovir, zidovudine and abacavir) and one NNRTI (e.g., nevirapine and efavirenz) or integrase strand transfer inhibitors (INSTI) (e.g., dolutegravir and raltegravir) and second-line NRTIs/NtRTIs + Protease Inhibitors (e.g., lopinavir, ritonavir and atazanavir). ART was earlier known as highly active ART (HAART) and as combination ART (cART).

With the new guidance from WHO, a new drug dolutegravir (Class: Integrase Inhibitors) is now recommended as the first choice among the first-line. Dolutegravir has been introduced in Timor-Leste since April 2020, and it has been planned to scale up.

WHO also recommends a 'test and treat' or 'treat-all', which states:

- PLHIVs belonging to all populations and age groups, including pregnant women and children, irrespective of their CD4 count levels, are now eligible for treatment
- The once-per-day combination pill is now recommended for all adults living with HIV, including pregnant women, and those with TB, hepatitis and other coinfections.

The guidelines are ambitious in their expected impact, yet simplified in their approach, and firmly rooted in evidence. Starting ART early keeps PLHIV alive, healthier and reduces the risk of transmitting the virus to their sexual and drug-sharing partners. It also has the further advantage of simplifying the operational demands on programmes.

In Timor-Leste, the national programme follows the 'Test and Treat' policy.

> All individuals with confirmed HIV infection are eligible for ART irrespective of CD4 cell levels, WHO clinical stage, age, pregnancy or breastfeeding status, coinfection status, risk group, or any other criteria.

Table 2. Special consideration for initiation of ART

Population	Timing of ART initiation	Comments
Pregnant and breastfeeding women	Support ART initiation as early as possible after testing positive for HIV	Intensive adherence counselling and close follow-up required because of limited time for patient preparation
Infants (< 12 months old)	Support ART initiation on the same day as mother after testing positive for HIV	Intensive adherence counselling and close follow-up required because of limited time for caregiver preparation
Patients with strong motivation to start ART immediately	Support ART initiation as soon as they meet ART Readiness Assessment criteria after testing positive for HIV	Intensive adherence counselling and close follow-up required because of limited time for patient preparation
Patients with newly diagnosed TB	Start anti-TB treatment immediately and initiate ART as soon as anti-TB medications are well tolerated, preferably within 2–4 weeks. For TB meningitis and disseminated TB, consider delaying ART for up to 8weeks or more	Monitor closely for IRIS
Patients with cryptococcal meningitis (CM)	Defer ART until after completing 5weeks of CM treatment and symptoms have resolved	Monitor closely for IRIS
Patients for whom adherence will be particularly challenging	Start ART as soon as adequate support systems are in place for adherence (e.g., psychiatric treatment for a patient with mental illness; caregiver identified for an orphan, etc.)	A treatment supporter (preferably from PLHIV group) should be assigned to all patients with complex adherence challenges
All other patients	Start ART as soon as possible once they meet ART Readiness Assessment criteria	Adequate ART preparation, and continued adherence monitoring and support is recommended after ART initiation for all patients

Objectives of ART

HIV is not curable, but definitely treatable. Early in the course of the disease, a pool of latently infected CD4 cells was noted. This is the means by which HIV infection escapes the ART drugs. It persists within the organs/cells and fluids (e.g., brain, liver and lymphoid tissue), despite prolonged suppression of plasma viremia by ART to <50 copies/mL. The primary aim of ART is to prolong the viral suppression for the immune cells to carry out their normal functions. ART is provided with the following objectives in mind:

- Increase survival and improved quality of life of PLHIVs – clinical
- Enforce maximum VL suppression---virological
- Immune reconstitution that is beneficial to the patient–immunological
- Use of cART to achieve maximum benefit with minimal adverse effects–therapeutic
- Achieve secondary prevention of HIV transmission–preventive.

Due to the continued viral suppression, the destruction of CD4 lymphocyte cells is reduced and over time there is an increase in the CD4 count, which is accompanied by partial restoration of pathogen-specific immune function. This leads to a reduction in OIs, reduced morbidity and mortality.

Principles of ART

HIV life cycle and classification of ART drugs

HIV targets and terminates the CD4 cells of the immune system. CD4 cells are a type of white blood cells that play a major role in protecting the body from infection. In fact CD4 cells are like leaders who direct the other soldiers to fight the infection. HIV uses the machinery of the CD4 cells to multiply and spread throughout the body. This process, which is carried out in seven steps or stages, is called the HIV life cycle.

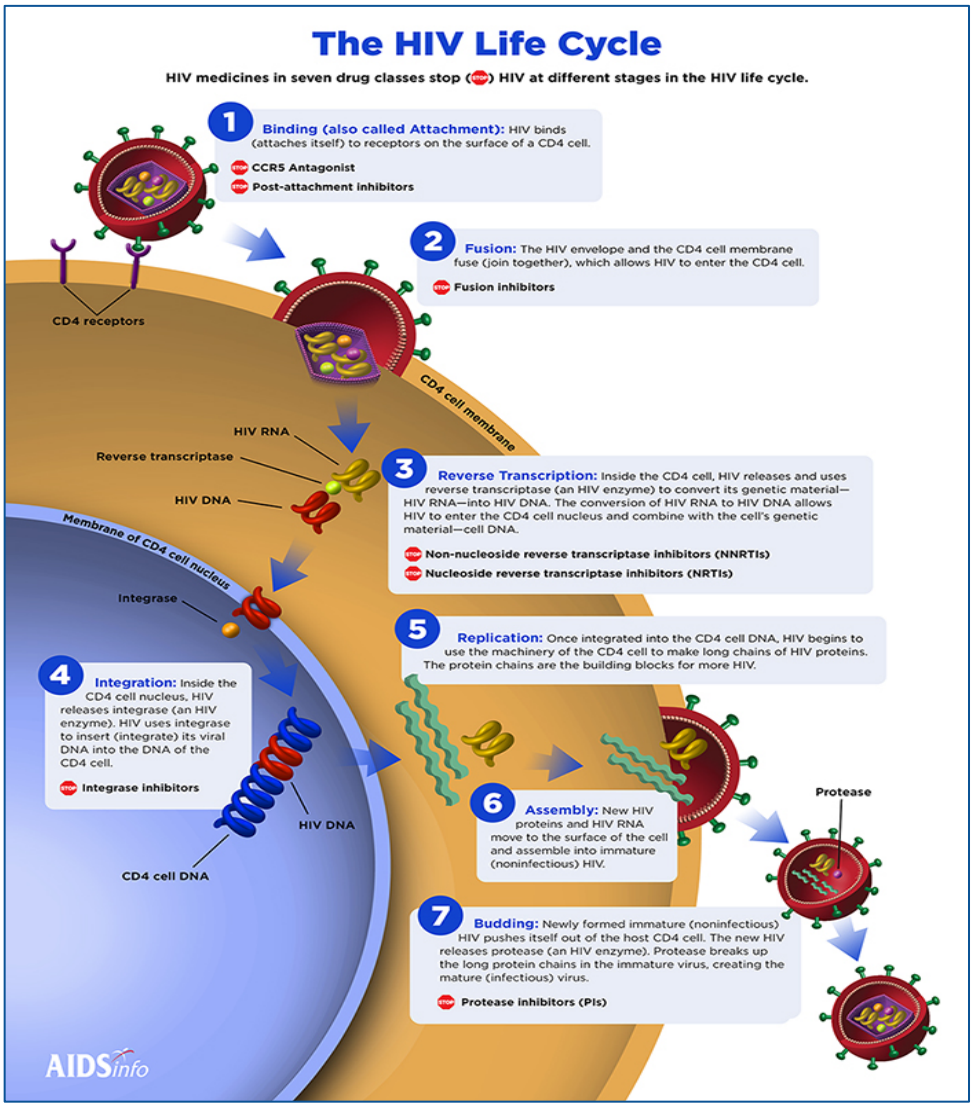

Fig. 6. HIV life cycle and classes of ART drugs

Source: AIDSinfo. US Department of Health and Human Services (https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/73/the-hiv-life-cycle,accessed 29 October 2019).

Based on the HIV replication or life cycle, the ARVs are classified into seven classes namely, the nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, post attachment inhibitors and Integrase strand transfer inhibitors (INSTIs):

- NRTIs block reverse transcriptase (an HIV enzyme Site 3 in Fig. 6). HIV uses reverse transcriptase to convert its RNA (single stranded) into DNA (double stranded) (reverse transcription), e.g., Zidovudine (ZDV), Lamivudine, Abacavir, Didanosine and Tenofovir (Nucleotide reverse transcriptase inhibitor)
- NNRTIs bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription), e.g., Nevirapine and Efavirenz
- PIs block protease (an HIV enzyme). By blocking protease, PIs prevent new (immature) HIV from becoming a mature virus that can infect other CD4 cells, e.g., Lopinavir, Ritonavir, Atazanavir, etc.
- INSTIs block integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the host CD4 cell. Blocking integrase prevents HIV from replicating, e.g., Dolutegravir, Raltegravir, etc.
- A FI blocks the HIV envelope from merging with the host CD4 cell membrane (fusion). This prevents HIV from entering the CD4 cell, e.g., Enfuvirtide, etc.
- CCR5 antagonists block the CCR5 coreceptor on the surface of certain immune cells, such as CD4 T lymphocytes (CD4 cells). This prevents HIV from entering the cell, e.g., Maraviroc, Aplaviroc, etc.
- Post-attachment inhibitors are a class of drugs that bind to the CD4 receptor on a host CD4 cell. This blocks HIV from attaching to the CCR5 and CXCR4 coreceptors and entering the cell. Post-attachment inhibitors are part of a larger group of HIV drugs called entry inhibitors, e.g., Ibalizumab.

The classes of ARTs available in Timor-Leste are given in Table 3.

Table 3. Characteristics of ART drugs available (and proposed) in Timor-Leste

Class	Drug name	Dose	Food interactions	Adverse effects
Nucleotide reverse transcriptase inhibitors (NtRTIs)	Tenofovir (TDF)	300 mg once daily	None	Renal toxicity, bone demineralization
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine (AZT)	300 mg twice daily Infants and children: Weight band-based dosing	No food related issues noted	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis, skin and nail hyperpigmentation
	Lamivudine (3TC)	150 mg twice daily or 300 mg once daily Infants and children: Weight band-based dosing	No food-related issues noted	Minimal toxicity, rash (though very rare)
	Abacavir (ABC)	300 mg twice daily or 600 mg once daily Infants and children: Weight	No food related issues noted	Hypersensitivity reaction in 3–5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia,

		band-based dosing		respiratory symptoms (sore throat, cough, shortness of breath); Rechallenging after reaction can be fatal.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (EFV)	600 mg once daily (bedtime administration is suggested to decrease CNS side-effects)	Avoid taking after high fat meals	CNS symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation) and personality change. Rash occurs, but less common than NVP.
	Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily Infants and children: weight band-based dosing	None	Hepatitis (usually within 12 weeks);sometime life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes should not be rechallenged
Protease inhibitors (PIs)	Lopinavir/ritonavir(LPV/r) heat stable tablets	200 mg Lopinavir/50 mg ritonavir fixed dose tablet 2 tablets twice daily Infants and children: weight band-based dosing	None	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance
	Darunavir (DRV)*	600 mg twice a day(when used with Ritonavir 100 mg twice daily) Infants and children: weight band-based dosing	None	Hepatotoxicity, skin rash, diarrhoea, nausea, headache, hyperlipidaemia, serum transaminase elevation, hyperglycaemia
Integrase strand transfer inhibitors (INSTI)	Dolutegravir (DTG)	50mg once daily Infants and children: weight band-based dosing	None	Insomnia and headache. Dolutegravir can cause serious, life-threatening side-effects. These include hypersensitivity (allergic) reactions and liver problems. People with a history of HBV or HCV infection or who have elevated results on liver function tests may

				have an increased risk of developing new or worsening liver problems while taking dolutegravir
	Raltegravir (RAL)*	400mg twice daily Infants and children: weight band-based dosing	None	Rhabdomyolysis, myopathy, myalgia, diarrhoea, fever, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis and hepatic failure

**Darunavir and Raltegravir are currently not available in Timor-Leste*

ART regimens in Timor-Leste

The first-line regimens are presented in **Table *4***.

Table 4. Proposed first-line regimens for adults, adolescents, children and infants

A. **Adults and adolescents**		
First-line	**Alternative first-line**	**Special considerations**
TDF+3TC+DTG	• TDF+3TC+EFV_{400}	• TDF + 3TC+ EFV_{600} • AZT + 3TC + EFV_{600} • TDF+3TC+LPV/r

B. Children and neonates

First-line **Children**	**Alternative first-line**	**Special considerations**
ABC+3TC +DTG	• ABC+3TC+LPV/r • ABC+3TC+RAL	• ABC + 3TC + EFV (or NVP) • AZT +3TC + EFV (or NVP) • AZT + 3TC + LPV/r (or RAL)
Neonates		
AZT +3TC + RAL*	• AZT+3TC+NVP	• AZT+3TC+LPV/r • ABC + 3TC + LPV/r (ATV/r or DRV/r)

*Raltegravir (RAL) is currently not available in Timor-Leste and not used. The alternative first line AZT+3TC+NVP will be the first line choice in neonates till RAL is available.

Table 5. Dosing of solid and liquid formulations for infants and children of four weeks of age and older

Drug	Strength of tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 /150 mg	1	1
AZT/3TC/NVP[2]	Tablet (dispersible) 60/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 /150 /200 mg	1	1
ABC/3TC	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 /300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 /300 mg	0.5	0.5
ABC/3TC/LPV/r	30/15/40/10 mg	2	2	3	3	4	4	5	5	6	6			
Solid single formulations														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
NVP[2]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
	Tablet 200 mg	–	–	–	–	0.5	0.5	1	0.5	1	0.5	200 mg	1	1
LPV/r[3]	Tablet 100/25 mg	–	–	–	–	2	1	2	2	2	2	100/25 mg	3	3
	Tablet 200/50 mg	–	–	–	–	–	–	1	1	1	1	200/50 mg	2	1
	Pellets[4] 40/10 mg	2	2	3	3	4	4	5	5	6	6			
DRV[5]	Tablet 75 mg	–	–	–	–	3	3	5	5	5	5			
RAL[6]	Chewable tablets 25 mg	–	–	–	–	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5	400 mg	1	1
	Granules (100 mg/sachet)	0.25	0.25	0.5	0.5	–	–	–	–	–	–		–	–
Liquid single formulations														
AZT	10 mg/mL	6 mL	6 mL	9 mL	9 mL	12 mL	12 mL	–	–	–	–	–	–	–
ABC	20 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
3TC	10 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
NVP[2]	10 mg/mL	5 mL	5 mL	8 mL	8 mL	10 mL	10 mL	–	–	–	–	–	–	–
LPV/r[3]	80/20 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.5mL	2.5 mL	3 mL	3mL	–	–	–
DRV[5]	100 mg/mL	–	–	–	–	2.5 mL	2.5 mL	3.5mL	3.5 mL	–	–			

Notes:

1. The dosage of infants less than 4 weeks is presented in Table 6.
2. NVP dose escalation with half dose for 2 weeks as in adults. The infants who are on NVP prophylaxis can initiate the full dose when detected HIV positive.
3. LPV/r requires cold chain for storage and transportation. Heat stable tablet formulations are available and should be used instead. They should not be chewed, crushed or dissolved. Adult 200/50 mg tablets could be used for children with weight band 14.0–24.9 kg.
4. LPV/r pellets are also available, but should not be used in infants below 3 months of age.
5. DRV if administered must be done along with 0.5 mL of RTV 80 mg/mL oral suspension if less than 15 kg and with RTV 50 mg solid formulation in children weighing 15 – 30 kg.
6. WHO recommends use of RAL granules for children as young as 4 weeks, but availability remains a challenge. Also, this formulation has not been investigated for wider use and adverse effects. Currently RAL is not available in Timor-Leste.

The dosage of ART in infants less than four weeks is presented in **Table *6***.

Table 6. Dosage of ART in infants below four weeks

ART drug	Formulation	Weight band		
		2–3 kg	3--4 kg	4–5 kg
AZT	10 mg/mL	1 mL	1.5 mL	1.0 mL
NVP	10 mg/mL	1.5 mL	2.0 mL	1.0 mL
3TC	10 mg/mL	0.5 mL	0.8 mL	1.0 mL
LPV/r	80/20 mg/mL	0.6 mL	0.8 mL	1.0 mL
RAL	100 mg/sachet	¼ sachet	¼ sachet	¼ sachet

Notes:

1. NVP for treatment can be initiated with twice daily dosing for infants < 2 weeks of age (they do not require once-daily lead-in dosing).
2. Do not use LPV/r solution in infants aged <2 weeks of age. LPV/r pellets should not be used in infants younger than 3 months.

It may be confusing to provide the proper ART schedule in children as there are many challenges including the measurement of proper weight. Table 7provides a simplified version for use by the clinician.

Table 7. Simplified regimen for ART in infants, children, adolescents and adults

Age	Preferred regimen	Dosing (based on weight band)
Neonates	AZT+3TC+NVP (RAL**)	Refer to Table 6. Dosage of ART in infants below four weeks
4 weeks to less than 3 years	ABC + 3TC + LPV/r	3–5.9 kg: ABC/3TC (120/60 mg): 0.5 tab b.i.d plus LPV/r (80/20 mg/mL): 1.5 mL b.i.d
		6–9.9 kg: ABC/3TC (120/60 mg): ½ tab am and 1 tab pm plus LPV/r (80/20 mg/mL): 1.5 mL b.i.d
		10–13.9 kg: ABC/3TC (120/60 mg): 1 tab b.i.d, plus LPV/r (80/20 mg/mL): 2 mLb.i.d, or LPV/r (100/25 mg): 2 tabs am and 1 tab pm
		14–9.9 kg: ABC/3TC (120/60 mg): 1 tab am and 1.5 tabs pm, plus LPV/r (80/20 mg/mL): 2.5 mL b.i.d, or LPV/r (100/25mg): 2 tab b.i.d
3–10 years (and < 35 kg body weight)	ABC + 3TC + LPV/r	20–24.9 kg: ABC/3TC (120/60 mg): 3 tabs once daily, plus LPV/r (200/50 mg): 1 tab b.i.d
		25–34.9 kg: ABC/3TC (600/300 mg): 1 tab once daily, plus LPV/r (200/50 mg): 2 tab am and 1 tab pm
> 10 years or body weight > 35 kg	TDF + 3TC + EFV_{600} to be transitioned to TDF + 3TC + DTG* or TDF +3TC + EFV^{*}_{400}	TDF/3TC/EFV (300/300/600 mg): 1 tab once daily or TDF/3TC/DTG (300/300/50 mg): 1 tab once daily or TDF/3TC/EFV (300/300/400 mg): 1 tab once daily

Note: * Currently introduced and available across Timor-Leste.

** RAL is not available in Timor-Leste and thus alternate first line is the preferred regimen till RAL is available in Timor-Leste.

Introducing Dolutegravir

Class of drug: Anti-retroviral-integrase inhibitor

Used in treatment of HIV infection in any adults, adolescents and children weighing more than 30 kg (USFDA guidance).

Efficacy

The efficacy of DTG has been demonstrated in several randomized control trials conducted among ART naïve (SINGLE, SPRING, FLAMINGO) and experienced patients (STRIIVING).[4,5,6,7] Among the treatment naïve patients, DTG is superior to both efavirenz (EFV) and ritonavir-boosted darunavir, and noninferior to raltegravir– a twice-daily dosed integrase inhibitor.

Recent systematic reviews and meta-analysis conducted by WHO have showed that DTG-based regimens are better tolerated and tend to be protective against treatment discontinuation due to adverse events (AEs), when compared with EFV 600.[8]

Dosage forms and strengths

Tablets: 10 mg, 25 mg and 50 mg as single or combined fixed dose combinations (FDCs).

Known AEs

- **Side-effects:** Common side-effects include insomnia, headache, tiredness, redistribution of body fat, depression, etc.
- **Hypersensitivity reactions:** They have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury (less than 1%)
- **Hepatotoxicity**: Hepatic AEs have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations
- **Embryo-fetal toxicity**: Initial results from Tspeamo study showed risk of neural tube defect among women who became pregnant while on DTG. As more evidences have become available, the risk of neural tube defects with DTG is only marginally higher than other ARVs. DTG has major benefits of health of mother and prevention of MTCT of HIV, and hence women of child-bearing age need to be counselled on benefits and risks of DTG to make an informed choice
- **Risk of AEs or loss of virologic response due to drug interactions**: This can happen with calcium-containing agents such as antacids, calcium supplements, carbamazepine, iron supplementation, etc.

Drug interactions

1. Rifampicin

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[4]Walmsley S, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013; 369: 1807–18.

[5]Stellbrink H, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F et al. Dolutegravir in antiretroviral-naïve adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS. 2013; 27: 1771–78.

[6]Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I et al. Once daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO):48-week results from the randomised open-label phase 3b study. Lancet. 2014; 383(9936):2222—31.

[7]Trottier B, Lake JE, Logue K, Brinson C, Santiago L, Brennan C et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study. AntivirTher. 2017; 22(4):295–305.

[8]Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest J et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: asystematic review and network meta-analysis. Lancet HIV. 2016;3:e510–20.

- Rifampicin lowers DTG levels: increase DTG to 50 mg twice daily for patients on rifampicin
- There are no significant drug interactions between DTG and other currently used anti-TB medications (including for MDR-TB).

2. Mineral supplements, including antacids containing calcium, zinc, magnesium or aluminium; iron supplements; prenatal vitamins (which contain iron and calcium)
    - These supplements decrease the absorption of DTG: administer DTG at least 2 hours before or 6 hours after taking any of these supplements
    - Dose separation is not required for calcium and iron supplements (including prenatal vitamins), if DTG is taken with a meal
    - It is critical to educate patients about this important drug interaction because many of them get these supplements and antacids over the counter without informing their health care provider.
3. Carbamazepine, phenobarbital and phenytoin
    - These anticonvulsants decrease DTG levels: use a different anticonvulsant if available.
    - If DTG must be co-administered with these drugs, then increase to DTG 50 mg twice daily, although there is little data to guide this.
4. Metformin
    - DTG increases levels of metformin; the levels of DTG are not affected: use a lower dose of metformin (often 50% of usual dose) and monitor glycemic control. Use a maximum daily dose of metformin 1 g
5. Other drug–drug interactions with DTG and RAL (Table 8).

Table 8. Drug--drug interactions--INSTIs

Drugs	Dolutegravir	Raltegravir
Efavirenz	Co-administration not recommended because EFV decreases levels of DTG	Efavirenz decreases RAL plasma levels, but it is unlikely to be clinically significant
Rifampicin	Increase DTG to 50 mg b.i.d when co-administered with rifampicin (for children, use double the standard weight based DTG dose) There is no known drug interaction between DTG and rifabutin	Increase RAL to 800 mg b.i.d when co-administered with rifampicin (for children, use double the standard weight-based RAL dose; there is no data to guide dose adjustment for children below 2 years of age) Rifabutin may alter RAL plasma levels, but it is unlikely to be clinically significant
Bedaquiline (BDQ)	No interactions expected	No interactions expected
Delamanid (DLM)	No interactions expected	No interactions expected
Metformin	DTG may increase metformin plasma levels. Hence, metformin dose may need to be decreased. Limit daily metformin dose to 1000 mg DTG does NOT require a dose adjustment when used with metformin	No interactions expected
Anticonvulsants -Carbamazepine -Phenobarbital -Phenytoin	Avoid use of DTG with carbamazepine, phenobarbital, or phenytoin because they decrease DTG plasma levels If the DTG must be used in combination with any of these anticonvulsants then increase DTG dose to 50mg BD and monitor VL	No interactions expected

Mineral supplements and antacids containing cations (e.g., calcium, iron, zinc, magnesium, aluminium), including prenatal vitamins	Administer DTG at least 2 hours before or 6 hours after taking any of these supplements (note: if taking DTG with a meal, then it is safe to take at the same time as prenatal vitamins, calcium, or iron) There are no drug–drug interactions between DTG and proton pump inhibitors or H_2 blockers used for gastritis	Do not use calcium, magnesium and aluminium containing antacids with RAL

Known contraindications

- Effective contraception needs to be offered to adult women, adolescent girls of the child bearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception, if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy
- DTG is contraindicated for any patient with a history of hypersensitivity reaction to DTG
- DTG is not currently recommended for patients with end-stage renal disease or end-stage liver disease, because it has not been evaluated in these populations.

Monitoring and changing the regimen of ART

Clinical and laboratory monitoring during ART is done to identify and treat CIs, assess and manage adverse drug reactions (ADRs),evaluate response to treatment and change the ART drugs, if an active intervention is required. The purpose of monitoring is to ensure that the patient gets the optimized regimen and has minimal side-effect while the objectives of ART are met.

Indications for changing ART regimens include optimizing therapy for patients who have undetectable VL, managing ADRs or toxicity, drug–drug interactions, comorbidity and treatment failure (virological, immunological and clinical) and responding to pregnancy intention.

Patients who are virally suppressed on first-line ART may benefit from regimen modification, even if they are currently tolerating their regimen well and have no drug–drug interactions requiring a change. Regimen modifications may be done for age/weight transitions among children and adolescents and to simplify a regimen, prevent long-term toxicity and improve cost-effectiveness.

WHO's current recommendations suggest transition of patients on first-line treatment from TDF+3TC+EFV to TDF+3TC+DTG. There is enough evidence to suggest that this change in regimen is not only beneficial to the patient, but also has improved tolerability and lesser side-effects. Studies too suggest that this optimized regimen with INSTI inhibitor and the tail and two NRTIs as the backbone may have a better VL suppression and a longer duration, as compared to NNRTI tail with two NRTI backbones.

The possibility of new side-effects when changing to a new ARV, particularly side-effects common to all ARVs (headache, nausea and diarrhoea) and any side-effect specific to the new ARV should always be kept in mind. It is commonly noted that most side-effects resolve with continued use after 1–2 weeks.

Table 9 recommends the substitution for various ART drugs for a stable adolescent or adults on ART.

Table 9. Optimized regimen for ART in a stable adult or adolescent patient

Existing ART	Switch to	Alternatives
EFV	DTG(if currently on rifampicin-containing TB treatment, then continue EFV until TB treatment is completed before switching to DTG) or else shift to DTG with double dose of DTG (50 mgBD)	Continue EFV
NVP	DTG	EFV, if tolerated, or LPV/r combination
LPV/r	DTG	Continue the same regimen or switch to ATV/r, which is currently not available in Timor-Leste
AZT	TDF	ABC if indications of renal complications are noted

Usual reason for changing ART is the ADRs to one or more ART drugs that are used in the cART. Patients starting ART should be educated on its potential side-effects and all other prescribed medication. ADRs can have a significant impact on patient adherence and must be identified early and managed aggressively.

DTG has been introduced in a phased manner in Timor-Leste from September 2020. This country has limited experience with this ARV drug, and thus an intense pharmacovigilance needs to be in place to detect the initial signs of DTG AEs.

Details on changing the ARV drugs for any serious ADRs are provided in Table 10.

Table 10. Common ADRs due to ARVs

ARV drug	ADR	Comments
NRTIs (and NtRTIs)		
TDF	Renal dysfunction	*Risk factors*: Underlying renal disease; age > 40 years; BMI < 18.5 (or body weight < 50 kg); diabetes; hypertension; concomitant PI use or nephrotoxic drug
AZT	Anaemia, neutropenia	*Risk factors*: CD4 count < 200 cells/mm^3; BMI < 18.5 (or body weight < 50 kg); anaemia at baseline; concurrent use of other drugs with similar ADR (cotrimoxazole, ganciclovir, ribavirin)
	Lactic acidosis	*Risk factors*: obesity and pregnancy
	Lipoatrophy	*Risk factors*: low CD4 count
ABC	ABC hypersensitivity reaction	Do not re-challenge
NNRTIs		
EFV	CNS side-effects	*Risk factors*: Pre-existing psychiatric disorder
	Gynaecomastia	Switch from EFV to an alternative, and consult if gynecomastia does not improve
All NNRTIs	Rash/hypersensitivity (NVP>>EFV>ETR)	*Risk factors*: for NVP hypersensitivity, women with CD4 count > 250 cells/mm^3, men with CD4 count > 400 cells/mm^3
PIs		
LPV/r	GI intolerance (LPV/r>DRV/r>ATV/r)	Refer to physician/internist or gastroenterologist

	Dyslipidaemia (LPV/r>DRV/r>ATV/r)	*Risk factors*: Obesity; sedentary lifestyle; diet high in saturated fats and cholesterol
INSTI		
DTG	Insomnia	Give in the morning, if no improvement then try giving with low fat meal or on empty stomach
	Rash/hypersensitivity	Refer to dermatologist/physician or internist

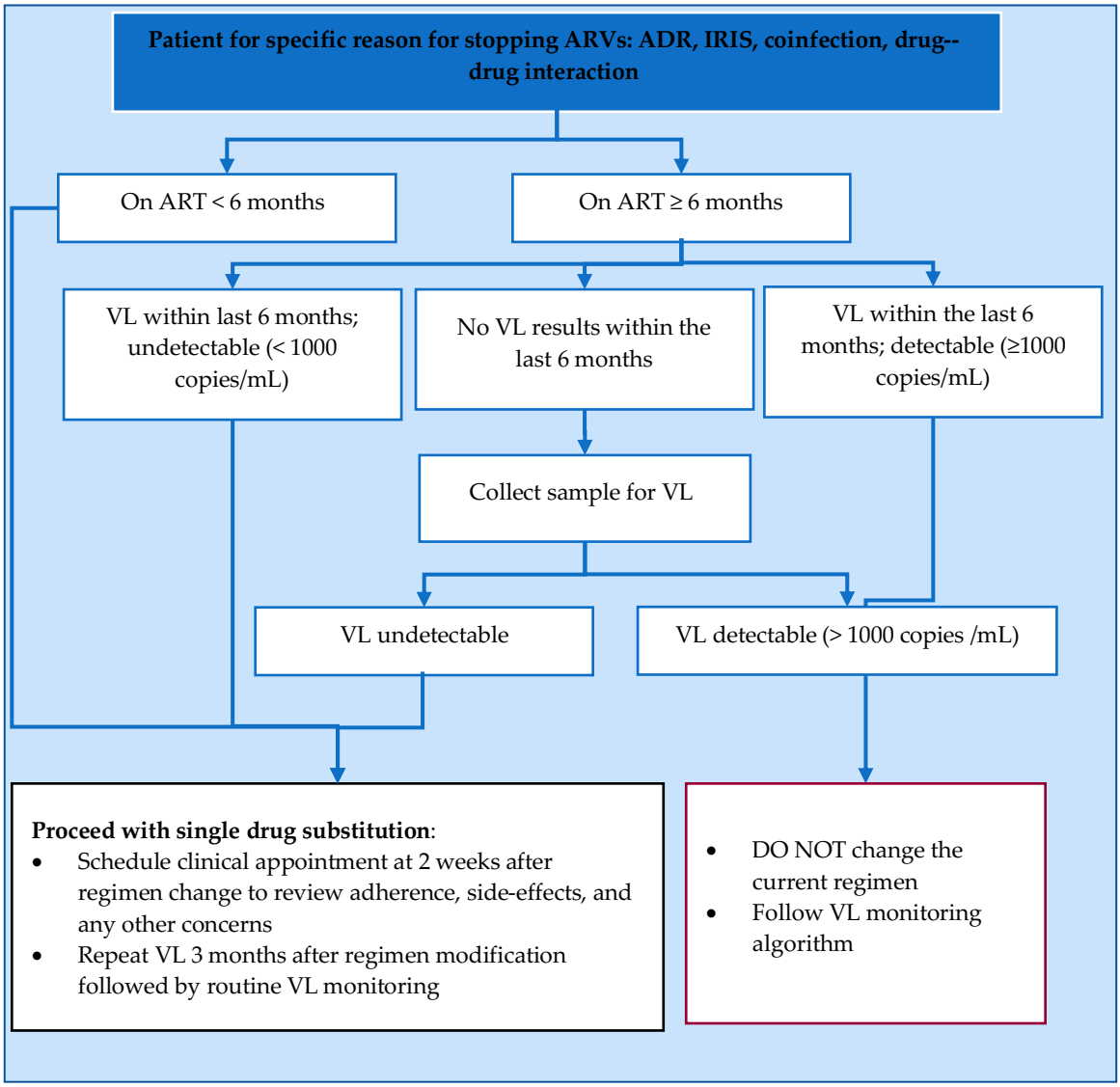


Fig. 7. Algorithm for managing single drug substitution

Changing of ARVs due to treatment failure

VL is the test of choice for monitoring response to ART and identifying treatment failure. Frequency of routine VL monitoring for specific populations is given below:

- Age 0–24 years old: every 6 months
- Age ≥ 25 years old: at 6 months after ART initiation, then at 12 months and then annually
- Pregnant or breastfeeding: at confirmation of pregnancy (if already on ART) or 3 months after ART initiation (if ART initiated during pregnancy/ breastfeeding), and then every 6 months until cessation of breastfeeding before making any drug substitution (if no VL results from the prior 6 months)

- 3 months after any regimen modification (including single-drug substitutions), and then as per population group
- For any patient with a detectable VL, follow the VL monitoring algorithm.

Treatment failure is suspected when a patient has a high VL ≥ 1000 copies/mL after at least 6 months of using ART. It is only confirmed when VL is ≥ 1000 copies/mL after assessing for and addressing poor adherence or other reasons for high VL, and then repeating VL after at least three months of excellent adherence to allow for viral resuppression.

Note: Diagnosing treatment failure based on clinical and immunological criteria has poor sensitivity and specificity. Every attempt should be done to diagnose treatment failure based on VL. Nonadherence is the most frequent cause of treatment failure. As per the VL monitoring algorithm, adherence issues must be addressed before confirming treatment failure.

Second-line regimens

The proposed second-line regimens for ART for adults and adolescents, children and infants are given in Table 11.

Table 11. Proposed second-line regimens for adults and adolescents, children and infants

A. **Adults and adolescents**

Failing first-line	Current options	Alternative options
TDF + 3TC + EFVor NVP	• AZT + 3TC + DTG	• AZT + 3TC + LPV/r • TDF + 3TC + LPV/r
AZT + 3TC + EFV or NVP	• TDF + 3TC + DTG	• TDF + 3TC + LPV/r
TDF + 3TC + DTG	• AZT + 3TC + LPV/r (or ATV/r)	• AZT + 3TC + DRV/r

B. Children and neonates

Failing first-line	Current options	Alternative options
ABC + 3TC + LPV/r	• AZT+ 3TC + DTG	• AZT + 3TC + RAL*
AZT + 3TC + LPV/r	• ABC+ 3TC + DTG	• ABC + 3TC + RAL*
ABC + 3TC + NVP or EFV	• AZT+ 3TC + DTG	• AZT + 3TC + LPV/r (orATV/r orDRV/r)*
AZT + 3TC + NVP or EFV	• ABC+ 3TC + DTG	• ABC + 3TC + LPV/r (or ATV/r or DRV/r)

*Note:*Raltegravir,* Atazanavir (ATV) and Darunavir (DRV) is not available in Timor-Leste as of now.

Important considerations for first-line treatment failure in children

Second-line ART in infants and children is more challenging to manage. It is important that these children and their caregivers undergo thorough clinical and psychosocial assessment to rule out other coinfections or **nonadherence** as the reason for a sustained high VL.

All children failing first-line should be discussed in the technical working group(TWG) and preferably with an experienced paediatric ART provider prior to change of ART to second line. However, this should not cause undue delay in switching a failing regimen.

The choices for infants and children failing an alternative first-line regimen are limited and need to be discussed with the TWG. Some of these children will require HIV drug resistant testing (HIV DR) to determine the most suitable second-line regimen. As of now, HIV DR is not available in Timor-Leste.

Starting of ART regimen

An ART regimen for the patient needs to be started as early as possible preferably within 2 weeks of detection. Table 12 provides a quick reference to starting ART in all, namely, infants, children, adolescents and adults.

Table 12. Starting ART in infants, children, adolescents and adults

Condition	Recommended steps
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
TB	• Start TB treatment first; start ART as soon as possible after 2 weeks and before 2 months • For those with CD4 less than 50/cmm, start ART within 2 weeks • Caution is needed for PLHIV with TB meningitis, since immediate ART is associated with more severe adverse events than initiating ART 2 months after the start of TB treatment
PCP	• Treat PCP first; start ART when PCP treatment is completed
Invasive fungal diseases: Oesophageal candidiasis, penicilliosis, histoplasmosis, etc.	• Start treatment for oesophageal candidiasis first; start ART as soon as the patient can swallow comfortably • Treat penicilliosis and histoplasmosis first; start ART when patient is stabilized or OI treatment is completed
CM	Treat Cryptococcal Meningitis. ART initiation should be deferred until there is evidence of sustained clinical response to antifungal therapy and after 4weeks of induction and consolidation treatment with Amphotericin B containing regimen
Bacterial pneumonia	Treat pneumonia first; start ART when treatment is completed
Malaria	Treat malaria first; start ART when treatment is completed
Acute diarrhoea which may reduce absorption of ART	Diagnose the cause and treat diarrhoea first; start ART when diarrhoea is stabilized or controlled
Nonsevere anaemia (Hb< 9 g/dL)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia)
Skin conditions such as PPE and seborrhoeic dermatitis, psoriasis, HIV-related exfoliative dermatitis	Start ART (ART is therapeutic)
Suspected MAC, cryptosporidiosis and microsporidiosis	Start ART (ART is therapeutic)
Cytomegalovirus retinitis	Start treatment for cytomegalovirus (CMV) urgently and start ART after 2weeks of CMV treatment
Toxoplasmosis	Treat toxoplasmosis; start ART after 6 weeks of treatment and when patient is stabilized

Management of common side-effects to ART

In a vast majority of cases, there is minimal side-effect to starting ART. It can be managed easily either through counselling and/or symptom-based treatment. **Table *13*** provides the steps to be taken for common side-effects.

Table 13. Steps to manage the common side-effects of ART

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 2weeks, 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 4–6 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 and insomnia	These 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
Nausea	Take the drugs with food. If on AZT, reassure that itis common, usually self-limited. Treat symptomatically. If vomiting, hospitalization 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 2weeks. Meanwhile, look for other causes of diarrhoea
Jaundice or abdominal pain	Stop drugs. See appropriate hepatotoxicity flowchart. Refer to HNGV
Tingling, numbness, pain in the feet/legs	If new or worse on treatment, sign of mitochondrial toxicity. Refer to HNGV
Cough or difficulty inbreathing	Look for respiratory infections: TB, PCP, bacterial pneumonia, cryptococcosis, cytomegalovirus infection and manage accordingly. Refer to HNGV

ART education and 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 underestimate the importance of emotional support given to the patient and his/her family (Table 14).

"*Extent to which a person's behaviour--- the taking of medication and the following of a healthy lifestyle including a healthy diet and other activities – corresponds with the agreed recommendations of the health care providers*" (*sic.*) (WHO, 2003).

Table 14. Measures to optimize adherence to ART

Measures	Details
Ensure free and simplified treatment with uninterrupted supply of ARV	• Provide free ARV drugs: see section on access to HIV/AIDS care • Ensure no stockout of ARV drugs • Simplify treatment minimizing pill burden with FDC
Prepare health facilities and set up PLHIV 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 PLHIV 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 • Encourage participation of PLHIV 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 one box of 30 days and ask the patient to come back after 28 days) • Assess adherence to treatment in a supportive manner

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, though some patients will need more time.

Table 15provides guidance to preparing the patient for better compliance and adherence.

Table 15. Guidance for preparing the patient for better compliance and adherence

Criteria	Steps
ART	• Lifesaving, 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 three 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 4hours of usual time; beyond 4hours wait until the next usual dose; in both cases report event to counsellor at next visit • Drugs must not be 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 PLHIV, or peer support by joining PLHIV support group

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 them (Table 16).

Table 16. Assessment of adherence and its remedial measures

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 pills on time. How many have you missed in the last 4 days and in the last month?	• 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 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

Ask about the common important factors that may interfere with adherence Ask about stigma related to taking the pills	• Address all the common challenging factors, myths and misconceptions and stigma
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 For example, (28⊠5)/28 x100= 89% adherence	• Reiterate the need for adherence, if less than 95% • Explain and discuss the measures that could be adopted to improve adherence

Also note the 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 his/her treatment properly 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.

The factors that influence adherence are given in Table 17.

Table 17. Factors that may influence adherence

Factors	Promote adherence	Reduce adherence
Patient	• 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 stigmatization • Non-disclosure of HIV status to family member or friend • Poor social support, living alone
Disease	Late or symptomatic HIV/AIDS disease	• Early, asymptomatic disease • No change in health status
Therapy	• Small number of tablets to swallow • Few adverse events • Empathic health staff	• Large and frequent (more than twice a day) number of tablets • Severe or ongoing minor side-effects • Food requirement • Treatment at cost

	• Friendly environment in the health facility	• Follow-up visits too frequent and transportation problems • Too long time to spend in the clinic

Practical orientation

Treatment education and adherence sessions are usually conducted by counsellors or nurses trained in counselling. PLHIVs 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 timesaving (particularly in setting with high work load) 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.

Calculating adherence

There are number of ways of measuring adherence like self-reporting by patient, pill count, home visit, patient diary, etc. Pill count is the most used method to assess adherence. In each follow-up visit, patient should be asked to bring the pill box with the unconsumed remaining pills. For more than one type of pill, adherence needs to be calculated for all drug combinations separately, and reasons for different adherence patterns to different drugs should be explored.

Following formula is used to calculate the adherence:

$$\text{Adherence (in \%)} = \frac{\text{Total number of pills the patient has actually taken}}{\text{Total number of pills should have taken in that time period}} \times 100$$

This is equal to

$$\frac{\text{Number of pills given to the client} - \text{Number of pills balance in the bottle}}{\text{Number of pills the client should have taken}} \times 100$$

Examples:

1. Tab TLD (Single pill daily) = No. of pill balance- 9, patient returns on 28th day.

Adherence calculation:

(30 – 9)/28 × 100 = 75%.

2. Tab ZLN (One pill twice daily dose) = No. of pill balance- 23, patient returns on 25th day.

Adherence calculation:

(60 – 23)/(25 × 2) × 100 = 37/50 × 100 = 74%

3. Tab TL +LPV/r (TL and ATV/r two pills once daily dose) = No. of pill balance- 9 TL and11 ATV/r, patient returns on 25th day.

Adherence calculation: Individual drug combination adherence needs to be calculated and whichever is lower, can be considered for reporting purpose.

TL adherence = (30 – 9)/25 × 100 = 21/25 × 100 = 84%

LPV/r adherence = (30 – 11)/25 × 100 = 19/25 × 100 = 76%

Hence overall adherence = 76%.

4. Tab ZL +LPV/r (ZL--one pill twice daily and LPV/r two pills twice daily dose) = No. of pill balance- 11 ZL and 25 LPV/r, patient returns on 25th day. Adherence calculation: Individual drug combination adherence needs to be calculated, and whichever is lower can be considered for reporting purpose.

ZL Adherence = (60 – 11)/(25 × 2) x 100 = 49 / 50 × 100 = 98%

LPV/r adherence = (120– 25)/(25×4) × 100 = 95/100 × 100 = 95%

Adherence calculation: Individual drug combination adherence needs to be calculated, and whichever is lower can be considered for reporting purpose.

Hence, overall adherence = 95%.

Chapter 4

ART operational guidance: assessment of adolescents and adults with HIV infection

Timor-Leste has a 'Test and Treat' policy in HIV. ART is available free of cost for all PLHIVs among Timorese citizens. The programme should be linking all HIV positives to lifelong ART at any ART clinic. The sections below follow the patient and provide the required guidance for each step.

Initial HIV consultation

When the patient comes to the ART centre, s/he could be still in a state of shock and denial. Therefore, the counsellor/nurse/doctor or public health professional should be aware of this situation. The initial or first visit is important from this point of view. The major steps that should be taken are:

- Create a relationship of trust with the patient
- Evaluate the patient--take proper history, conduct detailed clinical examination and then request for specific laboratory investigation as part of ART work up
- Fill the ART card and register
- If the patient is having a coinfection or any OI, treat it first and then go for the other work up
- Assess if the patient has ever been exposed to any ARVs
- Conduct a detailed nutritional assessment
- Conduct a detailed mental health assessment and need for psycho-social support.

It is a good practice to use WHO clinical staging (Annex 7)for the patient to correlate the findings with the laboratory investigations. The tasks required for initiation of ART are given in Table 18.

Table 18. Overview of tasks to be completed before ART initiation

Tasks	Details
History	• Social and demographic history, household history, i.e., date of first HIV test, partner informed, partner tested, partner on treatment, number of children, EMTCT 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 Papsmear 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) • Symptoms of active TB, i.e., four symptoms screening namely, 1) cough; 2) fever; 3) weight loss; and 4) night sweats • Symptoms suggestive of latent TB infection (LTBI): **No symptoms of active TB infection**, but history of exposure to TB patients may be present
Clinical examination	• Complete physical examination, even in the absence of symptoms, including temperature • Weight, height, oedema and BMI or W/H% or mid-upper arm circumference (MUAC) • Signs of active TB, e.g., lymph node, chest signs
WHO clinical staging	• Stage patients according to WHO clinical classification (see Annex 5) • Start co-trimoxazole prophylaxis

Diagnosis and treatment of intercurrent infections	• Treat any OI diagnosed in line with national protocols 6 • Refer for AFB smear, GeneXpert® testing and/or X-ray if suspicion of TB disease • Start nutrition supplement, if needed
Laboratory investigations	• Take blood samples for CD4 count and HIV VL (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, KFT and urine routine examination)

For more details on each task please refer to **Annex 8. Assessment of patient during the first visit to ART centre.**

Initial laboratory investigation of PLHIVs

The laboratory investigations of PLHIVs should be based on the status during the present assessment. It should be directed towards confirming the clinical suspicion and uniform for all PLHIVs who are to be put on ART (Table 19).

Table 19. Initial laboratory investigations for PLHIVs

Test	Comment
HIV specific test	
Confirm and document positive HIV test result	Follow HIV testing algorithm
CD4 cell count	• Recommended at baseline for all patients (CD4% for children ≤ 5 years old) for differentiated care and prophylaxis • If CD4 ≤ 200 cells/mm^3 (for adults and adolescents), then laboratory may perform a serum cryptococcal antigen (sCrAg) on the same sample to screen for cryptococcal infection (If available)
HIV VL (HIV-1 RNA)	• Currently recommended for all patients who are starting ART • Subject to availability of adequate cartridges of HIV load, the guidelines for HIV VL testing may be revised to move from targeted testing to routine testing later (However, current WHO guidelines do not recommend HIV VL as a baseline)
Serum cryptococcal antigen (sCrAg)	• No cryptococcal antigen testing is recommended at the baseline
HIV DR	• Not currently recommended as a baseline investigation
Other laboratory tests	
Hb (preferably fullblood count, if available)	• Recommended for all • If Hb is < 9.0 g/dL, AZT should be avoided
Pregnancy status	• Pregnancy status should be determined for all women of reproductive age (based on history of last menstrual period, and if uncertain, irregular, or delayed, then a urine pregnancy test should be performed)
Urine routine examination	• Recommended for all patients
Creatinine	Recommended for all patients • Serum Creatinine as baseline, if above the normal limits, then proceed for creating clearance test. • Calculate Creatinine Clearance (CrCl), Annex 15 • If HBV negative and CrCl≤ 50 mL/min then TDF should be avoided • If HBV positive and CrCl ≤ 50 mL/min then TDF should still be used • CrCl is also used for dose adjustment of NRTIs, CTX and fluconazole
Syphilis serology (VDRL, TPHA, or RPR)	Recommended for all PLHIVs who are sexually active
Glucose, lipid profile	Recommended for all PLHIVs
HBsAg	• Recommended for all adolescent and adult PLHIV (plus children who did not complete routine childhood immunizations)

	• If negative, patients should be immunized for HBV as soon as they achieve confirmed viral suppression • If positive, refer to Section 9 for management of HIV/HBV coinfection
HCV antibody	• Recommended for any PLHIVs with history of drug use
ALT (SGOT)	• Not recommended as baseline investigation unless there is a specific clinical reason (e.g., patient with history of hepatitis, signs or symptoms of liver disease, or risk of liver disease -- alcoholics, HBV or HCV infection, hepatotoxic drugs such as fluconazole, etc.)

Note: It is likely that all ART centres may not be having facilities to do all the tests mentioned above. It is recommended that they do the tests that are available, but collect the samples for referring to nearest referral centres where these are possible and start the ART.

ART should not be delayed for want of baseline investigations and physician on site should take a decision on this based on history and clinical examination (WHO staging)

Tailored approach to care

It is likely that many PLHIVs who present to the programme may have advanced disease. In that case, the level of care may have to be enhanced to address the challenges.

Table 20 provides a concise direction on tailored approach based on stage of the disease.

Table 20. Care of PLHIVs based on stage of disease

Patients who present with advanced HIV disease: WHO stage 3 or 4, or CD4 count ≤ 200 cell/mm³ (or CD4% ≤ 25% for children ≤ 5 years old)	
Package of care	• Standard package of care (• • • Chapter 5 ART operational guidance: standard package of care **(SPC) for PLHIVs**) • Intensive management of presenting illnesses and malnutrition • Priority for identification, management and prevention of OIs, including GeneXpert™ (Xpert® MTB/RIF) for TB diagnosis for all PLHIVs with presumptive TB • Cryptococcal antigen screening for adolescents and adults with CD4 ≤ 200 cells/mm³ or clinical suspicion of meningitis (any age) • Cotrimoxazole preventive therapy (CPT) • Isoniazid preventive therapy (IPT) • Priority for ART initiation (caution, if suspected or confirmed TB, TB meningitis, or cryptococcal meningitis • Close monitoring for development of immune reconstitution inflammatory syndrome (IRIS)
Location of services	• Management at any ART service delivery point; all facility levels; home visits may be required if unable to come to facility • Initial management and ART initiation by trained and experienced health care worker • Consultation with TWG, mentors, and senior clinicians as needed (connect with NAP)

	• Referral to a higher-level facility when feasible, if consultation is not adequate to stabilize the patient
Treatment preparation and adherence counselling	• ART is required to prevent further damage to the immune system • Starting ART soon will decrease risk of disease progression, including wasting and other infections • ART is the most important treatment to restore health • ART will reduce the risk of transmitting HIV to others
Frequency of follow-up	• Weekly follow-up until ART initiation, and then at week 2 and 4 after ART initiation, and then monthly until confirmed viral suppression • More frequent visits or hospitalization may be required to stabilize acute medical conditions and address psychosocial and other concerns
Patients who present well: WHO stage 1 or 2, and CD4 count > 200 cell/mm³ (or CD4% > 25% for children ≤ 5 years old)	
Package of care	• Standard package of care (• • • Chapter 5 ART operational guidance: standard package of care **(SPC) for PLHIVs**) • Same-day or rapid ART initiation (as soon as patient is ready, preferably within 2weeks)
Location of services	• Management at any ART service delivery point; all facility levels • Initial management and ART initiation by trained and experienced healthcare worker and physician
Treatment preparation and adherence counselling	• ART is the most important treatment to maintain good health and an active life • Starting ART soon will decrease risk of developing wasting and other infections • ART will reduce the risk of transmitting HIV to others
Frequency of follow-up	• Weekly follow-up until ART initiation, and then at week 2 and 4 after ART initiation, and then monthly until confirmed viral suppression • Additional visits as required to address any medical or psychosocial concerns

Monitoring ART during the first year

ART is a lifelong effort. Preparing the patient during the initial visits is beneficial for reducing the dropouts in the programme. A sustained treatment literacy effort is beneficial. However, it needs to be understood that majority of side-effects of ART occur within the first couple of months after initiation.

Monitoring of patients on ART is also determined by the duration the patient has been on treatment as well as how well they understand the treatment and response to ART. Follow-up includes scheduled clinical appointments, unscheduled clinical assessments for patients with concerns/complaints, routine and as-needed laboratory monitoring. The details of such follow-up schedule are presented in Table 21.

After ART initiation, patients need to be followed up closely for development of adverse drug events (ADEs), identify and address barriers to adherence, and development of IRIS (particularly for those who initiate ART with advanced HIV disease). A reasonable follow-up schedule for most patients is 2 weeks and 4 weeks after ART initiation, then monthly until viral suppression is confirmed. If HIV VL is detectable at 6 months, they will need additional assessments for and management of the reason/s for detectable VL, with close follow-up until

viral suppression is achieved. Patients with confirmed viral suppression should be followed-up every 1–3 months based on patient preference and clinician judgment, with additional unscheduled visits any time the patient has a concern. Clinical follow-up can be spaced further once the patient has been on ART for a year or more and meets the criteria as "*stable*". Children and adolescents should be followed-up at least every 1–3 months.

Table 21. Follow-up schedule for ART patients

<table>
<tr><th></th><th>Initial visit</th><th>ART Prep.</th><th colspan="2">Weeks after ART</th><th colspan="5">Months after ART</th><th>≥ 1 year</th></tr>
<tr><td>Appointment</td><td></td><td>Every week</td><td>2</td><td>4</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>Stable – 3
Unstable- 1</td><td>Every 3--6 months depending on stability</td></tr>
<tr><td>History and physical examination</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>At each visit</td><td>At each clinical visit</td></tr>
<tr><td>Treatment adherence and literacy</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>At each visit</td><td>At each visit</td></tr>
<tr><td>TB screening</td><td>✓</td><td colspan="10">At every visit using ICF screening tool (4 symptoms screening) and document the result</td></tr>
<tr><td>CD4 count</td><td>✓</td><td colspan="10">• Baseline, and then only if develops treatment failure (to assess for risk of OIs), or if defaults from care (off ART) for at least 6 months (confirmed LFU cases)
• For patients on secondary prophylaxis for CM, repeat CD4 every 6 months until CD4 >100 cells/mm^3 for two consecutive measures 6 months apart and VL undetectable, after which CM prophylaxis and CD4 monitoring can be discontinued</td></tr>
<tr><td>HIV VL</td><td>✓</td><td colspan="10">• For PCR positive HEIs: baseline at the time of ART initiation
• Age 0–24 years: every 6 months
• Age ≥ 25 years: at month 6 after ART initiation and month 12 then annually thereafter
• All age groups: before any drug substitution for patients on ART for at least 6 months with no VL results from the last 6 months
• All age groups: after any regimen change (including single drug substitutions), perform VL at month 3 after regimen modification, and then as per population group
• All age groups: any patient with a detectable VL during routine monitoring, follow VL monitoring algorithm</td></tr>
<tr><td>Hb</td><td>✓</td><td colspan="10">Baseline then symptom directed; if on AZT, baseline then weeks 2, 4 and 12</td></tr>
<tr><td>Pregnancy status (for reproductive age group)</td><td>✓</td><td colspan="10">At every visit for reproductive age (by history +/- urine pregnancy test)</td></tr>
<tr><td>Urine analysis (Routine) and creatine</td><td>✓</td><td colspan="10">Baseline and then annually</td></tr>
<tr><td>Plasma glucose and lipid profile</td><td>✓</td><td colspan="10">Baseline and then annually</td></tr>
<tr><td>HBsAg</td><td>✓</td><td colspan="10">Baseline, followed by immunization for all patients who screen negative (after viral suppression is confirmed)</td></tr>
<tr><td>Syphilis serology</td><td>✓</td><td colspan="10">Baseline, then annually in those at-risk and as part of routine ANC profile</td></tr>
</table>

Drug resistance testing	Not recommended in Timor-Leste as facilities are not available
ALT (SGPT)	Not recommended as routine baseline or follow-up unless specific clinical indication
Cervical cancer	Should be done as per national guidelines. The recommended guidance is once every year
HCV	Not recommended as routine or follow up unless specifically indicated

Source: Ministry of Health, National AIDS & STI Control Program. Guidelines on use of antiretroviral drugs for treating and preventing HIV infection in Kenya. Nairobi: NASCOP. 2018 (Adapted for use in Timor-Leste with permission).

Follow-up of PLHIV beyond the first year of ART

The first year of ART is crucial. Experience from the National HIV/AIDS Programme, Timor-Leste, suggests that intensive monitoring during the first year allows for better adherence, but the dropouts increase after the first year. Hence, year two and three are equally crucial and challenging. After the first year of ART, most patients should have developed good adherence habits, have satisfactory coping mechanisms and support systems in place, and should have achieved full virological suppression. With their improved self-care, these "*stable patients*" are expected to require less follow-up and monitoring than other patients. This may allow resources to be concentrated on difficult and challenging patients.

The differentiated follow-up mechanism, suggested by WHO, allows for improved impact with limited resources (Table22).

Table 22. Differentiated follow-up mechanism for PLHIVs

Criteria	Details
Unstable patients	
Unstable patients (any of the following) • On their current ART regimen for < 12 months • Any active OIs (including TB) in the previous 6 months • Poor or questionable adherence to scheduled clinic visits in the previous 6 months • Most recent VL: detectable (including low-level viremia and VL ≥ 1,000 copies/mL) • Has not completed 6 months of IPT • Pregnant or breastfeeding • BMI < 18.5 • Age < 20 years • Healthcare team has concerns about providing longer follow-up intervals for the patient*	
Package of care	• Standard package of care (Section 5) • Case management to address reason/s for not meeting stable eligibility criteria
Location of services	• Management at any ART service delivery point; all facility levels • Consultation with MDT, CSC, mentors, and senior clinicians as needed • Referral to a higher-level facility, if consultation is not adequate to stabilize the patient
Counselling focus	• ART is the most important treatment to improve health and return to an active life • Targeted counselling to address reason/s they have not met stable eligibility criteria
Follow-up frequency	• Every 1--3 months, based on clinical judgment and the specific reason/s they have not met stable eligibility criteria • Additional visits as required to address any medical or psychosocial concerns
Stable patients	
Stable patients (all the following criteria) • On their current ART regimen for ≥ 12 months • No active OIs (including TB) in the previous 6 months • Adherent to scheduled clinic visits in the previous 6 months • Most recent VL: undetectable (VL < 1000 copies/mL)	

• Has completed 6 months of IPT • Nonpregnant or nonbreastfeeding • BMI ≥ 18.5 • Age ≥ 20 years • Healthcare team has no concerns about providing longer follow-up intervals for the patient	
Package of care	• Standard package of care (Section 5) • Monitoring of VL and other routine investigations timed to coincide with other patients' appointments and clinical follow-up visits • Re-assess the criteria for stable patient at every visit
Location of services	• Clinical review at any ART centre • If unstable or other criteria for referral, send to higher centre in Dili
Counselling focus	• Encourage patients to continue to do what they are doing. They are doing well • Remind them that any significant life event could change the current status
Follow-up frequency	• Clinical review should be done every 3 months • ART may be distributed for 3 months at a time • Patients on injectable contraceptives should also be closely monitored and must be provided condoms and other contraceptives as needed • Additional visits to address any social or psychosocial concerns

Source: Ministry of Health, National AIDS & STI Control Program. Guidelines on use of antiretroviral drugs for treating and preventing HIV infection in Kenya. Nairobi: NASCOP 2018 (Adapted for use in Timor-Leste with permission).

The tailored care approach for PLHIVs also include children, pregnant and breastfeeding women and adolescents. For caregivers/parents who are enrolled in ART as stable patients, their children or adolescents who also meet "stable" patient criteria (other than the age criteria) can be considered eligible for longer follow-up. This should follow a family-centred approach in which the family is given aligned appointments with longer prescription periods.

Children would require close monitoring of growth and developmental milestones, and weight-based dose adjustments of their ART and CPT till the age of two years.

Adolescents have unique challenges with adherence related to their psychological development and social support systems. For those enrolled as stable patients with less frequent appointments, psychosocial support and ongoing adherence assessments and counselling should be aligned with ART centre visits and outreach follow-up.

Pregnant/breastfeeding women may be clinically stable but should be followed-up with their HIV clinic appointments with focused ANC visits and with follow-up of the HIV-exposed infant (enhanced postnatal prophylaxis, ePNP).

Advanced disease management

Globally the burden of morbidity and mortality associated with HIV infection has decreased largely due to expansion of ART coverage, timely detection, and a trend of treating people earlier in the course of disease progression. However, the decline in AIDS-related deaths appears to have plateaued during the past three years due to a trend towards later detection of HIV.

Timor-Leste has a low prevalence of HIV and that poses additional challenges in timely detection of people with HIV and larger linkage losses. This in turn leads to higher mortality as patients tend to present late or often missed in HIV diagnosis. In 2019, there was almost 15% mortality of patients initiated on ART in the same year. The programme is committed to reduce mortality as well as morbidity among PLHIVs and improve quality of their life. In this

regard Timor-Leste will focus on the earlier detection of people with HIV and reducing mortality by adopting WHO guidelines on advanced disease management (ADM). WHO has defined ADM as CD4 cell count <200cells/mm^3 or WHO clinical stage 3 or 4 event for adults and adolescents. All children younger than five years old with HIV are considered as having advanced HIV disease. WHO recommends a package of interventions for those with advanced disease, which includes screening, treatment and/or prophylaxis for major OIs, rapid ART initiation, and intensified adherence support interventions to everyone presenting with advanced HIV disease.

In line with WHO package on ADM, Timor-Leste will roll out **four key interventions** for patients presenting with advanced disease:

A. Diagnostic

1. Urine for LAM for TB for those with CD less than 100 or at any CD 4 count for those with any other serious illness
2. Cryptococcal antigen (CrAg) test using later flow assay for those with CD less than 200

These are in addition to testing for TB by Xpert MTB/RIF for those with symptomatic illness.

B. Therapeutic

1. Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis with CD less than 100 (or 200).

This will be in addition to routine TPT and CPT as eligible.

C. Rapid ART initiation

This means initiation of ART on same day or as soon as patient has understood need for adherence to lifelong ART. By definition, rapid initiation means within seven days.

D. Intensified adherence support

Tailored adherence support during initial 3-6 months including home visits, for those presenting with advanced disease.

As per global data, it is presumed that TLS will also have around 30–35% of new patients presenting with advanced disease and some of existing patients while failing on ART may be defined as those with advanced disease. This translates to nearly 100–125 patients presenting with advanced disease who will need urine LAM test and CrAg test. In addition, around 75–80 patients are likely to present with CD less than 100 and will require daily fluconazole therapy 3–6 months. Around 5–7% of those with advanced disease will have cryptococcal meningitis who will need Amphotericin B and flucytosine therapy. These components will be met through the within allocation part for the funding grant as preventing mortality is key to success of ART programme.

Chapter 5

ART operational guidance: standard package of care (SPC) for PLHIVs

The SPC consists of the following elements:

- ART
- Positive health and prevention
- Identifying and supporting cases of gender-based violence (GBV) or intimate-partner violence (IPV)
- Screening and management for TB
- Screening and management of other coinfections and OIs
- Reproductive health services (in collaboration with RMNCHA programme)
- Screening for noncommunicable diseases (NCDs)
- Assessing and management of mental health
- Nutritional services
- Prevention of other infections.

The SPC should always be applied using a patient- and family-centred approach. Patient-centred care includes: 1) considering the individual patient's health needs; 2) eliciting and addressing the patient's concerns and expectations; 3) involving the patient's family (and/or friends as appropriate) in decision-making; and 4) respecting the patient's values and preferences. Family-centred care identifies, engages and provides care to all HIV-positive family members, prevents new infections among family members at-risk, and promotes family support and awareness. This is part of counselling and follow-up routine for PLHIVs on ART.

The SPC and its subcomponents are presented in Table 23.

Table 23. Standard package of care for adult and adolescent PLHIVs in Timor-Leste

Components of standard package of care	Sub-components
ART	• Patient preparation • ART • Monitoring (clinical and laboratory)

Positive health, dignity and prevention; GBV and IPV screening; and HIV education/counselling	• Positive health, dignity and prevention components
	  ○ Disclosure
	  ○ Partner/family testing
	  ○ Condom use
	  ○ Family planning
	  ○ STI screening, prevention and treatment
	  ○ Adherence counselling and support
	• GBV/IPV screening and support
	• HIV education/counselling

Specific OI screening and prevention	• Cotrimoxazole preventive therapy
	• TB
	  ○ Intensified case finding
	  ○ Isoniazid preventive therapy
	• ART for TB/HIV coinfected patients
	• Cryptococcal meningitis

Reproductive health services	• Sexually transmitted infections screening and management • Family planning and preconception services • Maternal healthcare • Cervical cancer screening
NCDs screening and management	• Hypertension • Diabetes mellitus • Dyslipidaemia • Chronic kidney disease • Other NCDs
Mental health screening and management	• Depression • Alcohol and drug use/addiction
Nutritional services	• Assessment • Counselling and education • Management and support
Prevention of other infections	• Immunizations • Malaria • Safe water, sanitation and hygiene

The HIV-exposed and HIV-infected infants would need a closer follow-up and intensive care for an improved survival. Table 24 provides a brief guidance on the different sub-components.

Table 24. Standard package of care for HIV-exposed and HIV-infected infants

Sub-components of SPC
• Determine HIV status at first contact through HTS/EID and link to HIV care
• Provide ARV prophylaxis (ePNP) for all HEIs and ART for all HIV-infected children; perform baseline clinical and laboratory assessment
• Provide nutritional assessment, counselling and support and monitor growth and development of the child
• Ensure that all immunizations are provided as per the national schedule
• Assess clinically at every visit, treat infections early, identify and manage ADRs aggressively and refer appropriately where specialized care is required
• Screen for OIs and provide prophylaxis (cotrimoxazole, isoniazid), deworm every 6 months (starting at 1 year of age) and provide supplemental Vitamin A every 6 months (starting at age 6 months)

• Educate the caregiver on all aspects of care for the child including infant feeding, immunizations, personal hygiene, adherence, child disclosure and follow-up requirements
• Provide age-appropriate psychosocial support for the family and child and refer to community-based support programmes as appropriate
• Ensure that the caregiver and family members are receiving appropriate care, support and treatment
• Provide intensive case management for mother/infant pair until 2 years postpartum; identify defaulters and prioritize this population for tracking

ART

The '*Test and Treat*' policy for PLHIVs in Timor-Leste allows to put on ART all PLHIVs irrespective of their CD4 count and condition. It is also recommended that once detected patient should be put on ART at the earliest opportunity, preferably within 2 weeks.

The choice of first-line ARVs have been revised by WHO in their interim guidelines in 2018. This was ratified in their subsequent version in December 2018.

The same was placed before the TWG meeting in June 2019. TWG came up with the following recommendations (June 2019 and September 2019):

- The preferred regimen for first-line ART to use DTG instead of EFV for all adults, adolescents, pregnant women and children above 10 years of age, i.e., the preferred first-line will be: 1) TDF+3TC+DTG instead of TDF+3TC+EFV
- Continue the same regimen for children below 10 years as before, i.e., ABC+3TC+LPV/r (ABC + 3TC + DTG and AZT + 3TC + NVP (RAL[9]) for neonates)

The deliberations and discussions around DTG are presented later in this guideline.

The proposed regimen is presented in Table 4.

The details of the ARV drugs, interactions and toxicities are presented in the chapter on ART.

Positive health and GBV prevention

Positive health and living with dignity are the rights of every PLHIV. The rights also include reducing risk of onward transmission of HIV and prevention of gender-based and intimate partner violence. They are covered under six core areas or domains (Table 25).

Table 25. Services to be provided for positive health and prevention for PLHIVs

Domain	Components
Disclosure of HIV status	• Assessment of disclosure status, particularly to sexual partners • Assisted disclosure *Note: for children and adolescents, it is also necessary to evaluate for and support age-appropriate HIV disclosure to the child/adolescent*
Partner testing	• HIV testing of sexual partners • HIV testing of other family members at risk • Enrolment of positive partners/family members into HIV care • Engagement of negative partners and family members in care and support for index patient
Condom use	• Risk minimization • 3Cs of condoms use – correct and consistent condom use • Provision of condoms

[9]Currently not available in Timor-Leste.

Family planning	• Intention to have a child (assessment) • Preconception counselling • Contraception until ready for pregnancy
STIs	• Screening of STIs as per protocol (please refer to enhanced syndromic management of STIs in Timor-Leste, 2017)
Treatment adherence	• Benefits and importance of adhering to ART

GBV is high in Timor-Leste. UN Women reports a lifetime physical and/or sexual IPV of 59%.[10] The same is true for women or key population (sex worker, MSM and transgender) accessing ART services. Given the magnitude of GBV or IPV, the success of ART would depend upon addressing this issue as best as possible.

Screening of ART patients who have experienced GBV or IPV would be the first step towards providing support services for GBV/IPV. Some basic questions that could be asked during the first/initial visit should be:

"*It is common to note that intimate partner violence or gender-based violence in Timor-Leste is high. Many of us have experienced these kinds of issues in the past and continue to experience it even today. Violence is common in a women's life, but there is help available. Please share your experience with us so that we could support you/direct you to appropriate places*". Now I would like to ask you some questions. Please be assured that a complete confidentiality will be maintained.

- Within the past year, has someone ever hit, kicked, slapped, or otherwise physically hurt you?
- Has someone ever threatened to hurt you?
- Has someone ever forced you to do something sexually that made you feel uncomfortable?

If the answer to any of the questions is yes, the patient must be counselled for GBV/IPV and referred to a specialized IPV centre that is available at HNGV.

Screening and management for TB

All PLHIVs must be screened at every visit for TB (intensive case finding, ICF). In Timor-Leste, PLHIVs are screened at every visit using a 4S screening tool (four symptom screening tool). If any of the symptoms are positive, the patient must be referred to a designated microscopy centre and tested for TB. GeneXpert™[11] is the preferred method for screening the sputum for TB bacilli in an HIV infected. For any extra pulmonary TB (EPTB) such as TB lymphadenitis, TB meningitis, etc., specific symptoms may have to be explored.

All PLHIVs older than 12 months of age who screen negative for TB should be provided with 6months of IPT, unless they have a specific contraindication.

For more details, please refer to Chapter on HIV-TB coinfection.

[10] http://evaw-global-database.unwomen.org/en/countries/asia/timor-leste.

[11] GeneXpert™ is a platform for cartridge based nucleic acid amplification test (CBNAAT) for TB with a sensitivity of 97% and specificity of 99% for detecting *Mycobacterium tuberculosis*.

Screening and management of other coinfections and OIs

There are many coinfections that can lead to challenging circumstances for the HIV infected. Hepatitis B and C coinfections can lead to higher side-effects with ART. It is important to screen for hepatitis B in Timor-Leste as the prevalence is high (~4–7% in blood bank screening).

HIV-hepatitis B and C

Prevalence of hepatitis B in Timor-Leste is estimated to be around 7% in blood donors.[12] It is higher among MSMs and sex workers (10.0% and 8.3%, respectively).[13]Hepatitis B is a very strong DNA virus. It uses a double replication mechanism to replicate and thus is highly infective. More importantly, the hepatitis B virus (HBV) can cause liver cirrhosis and cancer. Hence, a dual infection is highly damaging to the individual.

Chronic infection with hepatitis B is likely to have occurred during the infancy. It could be due to mother to child transmission or acquiring the infection in childhood. HBV is also transmitted through sexual route and blood transfusions, and use of infected syringes and needles.

Hepatitis C is less common in Timor-Leste. The prevalence estimated from blood bank is approximately, 3.5% (2015). The routes of transmission are the same as HIV or hepatitis B.

Details of this coinfection are presented in the chapter on HIV and hepatitis coinfection.

Co-trimoxazole prophylaxis

Co-trimoxazole is a FDC of two antimicrobial drugs (sulfamethoxazole and trimethoprim) that covers a variety of bacterial, fungal and protozoan infections. Co-trimoxazole preventive therapy is a feasible, well tolerated and inexpensive intervention for PLHIVs to reduce HIV-related morbidity and mortality.

Daily co-trimoxazole(CTX)prophylaxis reduces mortality and morbidity in HIV/AIDS patients by reducing the risk of development and recurrence of pneumocystis pneumonia 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.

In 2013, WHO issued a guideline of continuing lifelong CPT for all PLHIVs irrespective of their immune status or clinical condition. This was different from the guidelines issued earlier where immunological status was the mainstay of starting and stopping the treatment. In Timor-Leste, the current considerations are as follows:

- Malaria infection is rare and just five cases detected in 2019[14]
- Bacterial infection rates are moderate[15]
- Presence of pneumocystis pneumonia among PLHIVs is also low[16]
- Other bacterial infection rates are moderate.[17]

[12]http://www.searo.who.int/entity/hepatitis/tls-2018_ar.pdf?ua=1, accessed 14 October 2019.
[13]ibid
[14]Program data from National Malaria Program, updated 30 September 2019.
[15]Data from HNGV June 2019.
[16]Programme data from ART centres, September 2019.
[17]ibid

However, the presence of diarrhoeal diseases, bacterial pneumonia and other bacterial infections is high in Timor-Leste. Thus, the updated recommendations from WHO are applicable to the country (Table 26).

Table 26. Starting and stopping CPT prophylaxis

Population	Recommendations	
	When to start CPT	When to stop CPT
Adults and adolescent PLHIVs including pregnant women	*Primary prophylaxis* • Irrespective of WHO clinical stage: CD4 <350 cells/mm^3 or • WHO clinical stage II, III and IV: Irrespective of CD4 count *Secondary prophylaxis* • For all patients who have completed successful treatment for PCP until CD4 is >350 cells/mm^3 maintained over a period of 6 months	• If CD4 not available: do not discontinue CTX prophylaxis • If CD4 available: due to high prevalence of bacterial infection and malaria in Timor-Leste, itis recommended to discontinue CTX prophylaxis only after CD4 increased to 350 cells/mm^3 or above and after at least 6 months of ART
Children (above 5 years)	Follow same recommendations as adults	Follow same recommendations as adults
HIV exposed, but uninfected infants	Start at 6 weeks	Stop when confirmed to be HIV uninfected
HIV-TB coinfection	Initiate for everyone with active TB regardless of CD4 cell count	Follow adults or children's criteria for stopping
HIV-hepatitis B or C coinfection	Follow adults or children's recommendations for starting CPT	Follow adults or children's criteria for stopping
Newly detected HIV infection not started on ART	Follow adults or children's recommendations for starting CPT, but start CPT first and wait for 1–2 weeks to start ART	Follow adults or children's criteria for stopping

Note: In most cases, the PLHIV presents to the ART centre with low to moderate CD4 counts (<350 cells/mL). Thus, CPT is likely to be provided together with ART.

In such cases, it is better to start CPT prophylaxis in the first or initial visit and then start ART. This will allow for the side-effects of ART to be differentiated from those of ART.

Dosing of co-trimoxazole preventive therapy

Co-trimoxazole can cause anaemia and neutropenia. In some cases, rashes may also be present. But overall, the incidence of side-effects is low if weight band is followed (Table 27).

WHO's 2006 guidelines on CTX provides a detailed guidance on grading and management of side-effects. A simplified version for drug associated is presented in **Table 28**8.

Table 27. Dose of co-trimoxazole prophylaxis treatment as per weight band

Weight band/ population	Oral suspension (240 mg/5 mL)	Single strength tablet (480 mg)	Double strength tablet (960 mg)
1--4 kg/infant	2.5 mL	¼ tablet	NA
5--8 kg/infant	5 mL	½ tablet	¼ tablet
9--16 kg/child	10 mL	1 tablet	½ tablet
17--30 kg/child-adolescent	15 mL	2 tablets	1 tablet
> 30 kg/adults or adolescents	20 mL	2 tablets	1 tablet
Adults (any weight)		2 tablets	1 tablet

Table 28. Grading and management of drug rashes due to co-trimoxazole[18]

Severity level	Characteristics	Management
Grade 1 (mild)	Localized rashes. Dry with erythema and fine papular lesions; itching and affects < 50% of the body surface	Continue CTX; close monitoring; symptomatic treatment with antihistamines +/- topical steroids (NOT oral steroids)
Grade 2 (moderate)	Diffused rashes or target lesions. Dry with erythema and fine papular lesions; itching and affects > 50% of the body surface	**Stop CTX and follow desensitization protocol**; symptomatic treatment with antihistamines +/- topical steroids (NOT oral steroids); trial of desensitization after symptoms completely resolved. Can continue CTX if with careful and repeated observation and follow-up. Provide symptomatic treatment, such as antihistamines if required
Grade 3 (severe)	Diffused rashes and vesicles. Mucosal involvement; blistering; usually limited to one site or location	**Stop CTX and should not be re-challenged with CTX**; admission to hospital for supportive management (IV fluids, wound care, pain control, infection control, monitoring for super-infection); patient should NEVER be re-challenged with CTX or other sulpha-containing drugs; document and report adverse event and issue patient alert card
Grade 4 (potentially life threatening)	Extensive or generalized bullous lesions OR ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis	**Stop CTX and should not be re-challenged with CTX**; admission in hospital for supportive management (IV fluids, steroids, wound care, pain control, infection control, monitoring for super-infection); patient should NEVER be re-challenged with CTX or other sulpha-containing drugs; document and report adverse event and issue patient alert card

Source: Adapted from DAIDS AE Grading Table Corrected Version 2.1July 2017.

Management of PLHIVs with co-trimoxazole allergy

A rash may occasionally develop, usually about 7--14 days following initiation of CPT. It is often a relatively mild maculopapular rash with or without itching. Rarely, rash may develop with severe exfoliation of the skin and Stevens-Johnson syndrome. Assess the severity of rashes and then manage accordingly (Table 13).

Desensitization is effective in most patients with mild to moderate rash. It is seen from majority of studies and programme experiences around the globe that approximately 70–75% (Number needed to treat (NNT), 4.55 (95 CI 3.03-9.09) of patients who are allergic to sulpha drugs have been successfully desensitized.[19]

There are two types of desensitization protocols dependent upon the need to start CTX (Table 29).

Table 25. Standard co-trimoxazole desensitization protocol (8 days)

Day	Dose of TMP-SMX suspension (40/200 mg per 5 mL)
Day 1	0.5 mL (4/20 mg TMP-SMX)
Day 2	1 mL (8/40 mg of TMP-SMX)
Day 3	2 mL (16/80 mg of TMP-SMX)
Day 4	3 mL (24/120 mg of TMP-SMX)

[18]U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for grading the severity of adult and pediatric adverse events, Corrected Version 2.1. July 2017 (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf, accessed 18 October 2019).
[19]Lin D, Li W-K, Rieder MJ. Cochrane database (https://www.cochrane.org/CD005646/HIV_this-review-examines-strategies-to-enable-the-continued-use-of-the-antibiotic-cotrimoxazole-in-patients-with-hivaids-to-treat-or-prevent-opportunistic-infections-in-patients-who-previously-experienced-hypersensitivity-to-this-drug, accessed 17 October 2019).

Day 5	4 mL (32/160 mg of TMP-SMX)
Day 6	5 mL (40/200 mg of TMP-SMX)
Day 7	1 single strength tablet (80/400 mg of TMP-SMX)
Day 8	2 single strength or 1 double strength tablet (16/800 mg of TMP-SMX

Other prophylaxis in PLHIV

Table 30. Type of prophylaxis of OIs in PLHIVs

Name of OI	Type of Prophylaxis	What to start	Adult dose	When to start	When to stop
Pneumocystis pneumonia (PCP)	Primary	Co-trimoxazole	One double strength tablet (Sulfamethoxazole800 mg + Trimethoprim 160 mg)	CD4 < 350 cells/cmm or WHO clinical stage 3 or 4 conditions	CD4 > 350cells/ cmm (at least on two occasions, done 6 months apart) and devoid of any WHO clinical stage 3 and 4 conditions
	Secondary	Co-trimoxazole	One double strength tablet (Sulfamethoxazole 800 mg + Trimethoprim 160 mg)	After successful treatment for PCP (21 days)	CD4 > 350cells/ cmm (at least on two occasions, done 6 months apart) and devoid of any WHO clinical stage 3 and 4 conditions
Cryptococcal meningitis	Primary	Recommended as part of advance disease management for PLHIVs who have CD4 <100 cells/mm^3			
	Secondary	Fluconazole	Tab Fluconazole 200 mg	After successful treatment of cryptococcal meningitis (induction phase of 2-3 weeks and consolidation phase of 8 weeks)	CD4 > 200 cells/ cmm (at least on two occasions, done 6 months apart)

Reproductive health services

Sexually transmitted infections (STIs)

Screening for syphilis using rapid plasma reagin (RPR) should be performed as a routine investigation for all pregnant women. It is part of the ANC package.

PLHIV should be assessed for symptoms of STIs using the enhanced syndromic management of STIs. Sexual partners should be treated as well. Risk reduction counselling and provision of condoms are an integral part of STI treatment.

Patients who have persistent signs and symptoms of STIs after syndromic treatment should be referred to a specialist at HNGV.

Family planning and pre-conception counselling

Pregnancy should be determined for all women of reproductive age at every visit (based on history of last menstrual period and, if uncertain, irregular, or delayed, then refer to mother and child health (MCH) section in the CHC or hospital for a urine test).

Many PLHIVs would be interested to conceive and may seek appropriate advice regarding the outcomes. It is necessary to provide proper counselling and services to address this issue. For patients who do not have an immediate desire to become pregnant, dual contraception should be provided immediately with follow-up appointments scheduled to ensure no interruption in contraception provision.

Table 31outlines contraception options for PLHIVs based on the ARVs they are using.

Table 3126. Basket of contraception based on WHO 2018 guidelines

Contraceptive methods		ARVs					TB medications
		NRTI	NNRTI	PI	INSTI		Rifampicin
			EFV or NVP	LPV/r	DTG	RAL	
Depot medroxy progesterone acetate (DMPA)		✓	✓	✓	✓	✓	✓
Norethisterone enantate (Net-EN)		✓	±	±	✓	✓	±
Implants (Norplant II)		✓	±	±	✓	✓	±
Combined oral contraceptive pills		✓	±	±	✓	✓	×
Intra uterine devices (CuT-380Ag)	Initiation	± (May be recommended for PLHIVs who are stable on ART). Not recommended for all PLHIVs with advanced disease					
	Continuation	±	±	±	±	±	±
Condoms		✓	✓	✓	✓	✓	✓
Emergency contraceptive pills		✓	✓	✓	✓	✓	✓
Fertility awareness-based methods (FAB)		Can use if menstrual cycle is regular, though reliability is not as good as hormonal contraceptive methods or IUD. Encourage to use in combination with condoms to prevent STI/HIV transmission					
Lactational amenorrhoea method (LAM)		Effective for women who are less than 6months postpartum, are exclusively breastfeeding, and have not resumed menses. Encourage to use in combination with condoms to prevent STI/HIV transmission					
Spermicides and diaphragm		×	×	×	×	×	×

Note: Condoms are usually combined with other methods of contraception for triple prevention namely, HIV/AIDS, STIs and hepatitis B and C.

Dolutegravir was not part of WHO 2018 recommendations for family planning for PLHIVs. The reference for DTG interactions has been taken from DAIDS (https://aidsinfo.nih.gov/drugs/509/dolutegravir/0/professional, accessed 30 September 2019).

PLHIVs, who intend to become pregnant and wish to have a healthy baby, should be counselled accordingly. Table 32 provides guidance for the preconception services that would be required.

Table 32. Preconception messages and services for PLHIVs

Scenario	Messages	Pre-conception services
Women or couples with intention to conceive	▪ All PLHIVs qualify for ART, with initiation preferably	ART for all PLHIVs, including those intending to become pregnant Baseline investigations

	within two weeks of HIV diagnosis ▪ Deferring pregnancy until confirmed viral suppression reduces risk of vertical transmission to the baby, improves infant outcomes, and reduces risk of cross-transmission to the sexual partner ▪ Unprotected sex should be limited to days when ovulation is expected (based on basal temperature monitoring, fertility calendar based on menstrual cycles, and/or fertility calendar app) ▪ Routine ANC and delivery by a skilled birth attendant improves outcomes for mother and baby	▪ Hb (with management of anaemia) ▪ Syphilis screening ▪ Cervical cancer screening STI symptom screening Nutritional assessment, counselling and support Folic acid supplementation Standard VL after 6months on ART to confirm viral suppression
Additional messages for discordant couples: male partner HIV positive	▪ Defer unprotected sex until confirmed viral suppression in the HIV positive partner ▪ In situations where viral suppression is challenging, consider specialist referral for additional options such as sperm washing and artificial insemination	
Additional messages for discordant couples: female partner HIV positive	▪ Defer unprotected sex until confirmed viral suppression in the HIV-positive partner ▪ Discuss self-insemination during the peri-ovulatory period, where appropriate/as preferred ▪ In situations where viral suppression is challenging, consider specialist referral for additional options such as artificial insemination	

Chapter 6

Management of opportunistic infections

Pneumocystis pneumonia

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii*, a fungus and OI. The nomenclature of the organism has changed; *Pneumocystis carinii* now refers only to the Pneumocystis that infects rats, and *P. jirovecii* refers to species that infects humans. However, the abbreviation PCP is still used. It is commonly noted that initial infection with *P. jirovecii* usually occurs in early childhood. Almost two-thirds of healthy children have antibodies to *P. jirovecii* by age 2–4 years.[20]

The transmission routes follow normal pattern of airborne infections. However, the disease could also be acquired through re-activation (like TB) from a latent infection. PCP used to be the most common infection before the era of ARVs. Literature suggests that almost 70–80% of PLHIVs would be affected by PCP during the course of the HIV disease.[21,22,23,24]

Clinical manifestations

Table 33. Clinical features of PCP in HIV infected

Feature	Mild	Moderate	Severe
Clinical	• Normal while resting • With exertion, there may breathlessness and increased heart rate • Diffused dry cellophane rales on auscultation may be present • Fever is sometimes present	• Some discomfort while at rest, but essentially normal • Widespread rales are usually present • Fever is present • Other features as of mild disease	• Breathless, increased heart rate even when at rest • All clinical features are exaggerated and may have evidence of lung collapse (spontaneous pneumothorax)

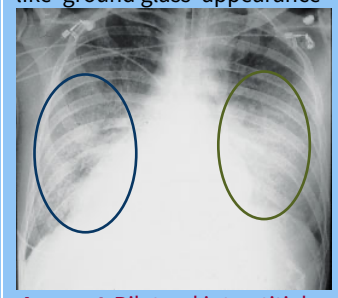
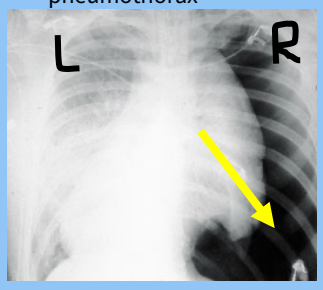
[20]Pifer LL, Hughes WT, Stagno S, Woods D. *Pneumocystis carinii* infection: evidence for high prevalence in normal and immunosuppressed children. Pediatrics. 1978;61(1):35–41 (http://www.ncbi.nlm.nih.gov/pubmed/400818, accessed 16 October 2019).

[21]Keely SP, Stringer JR, Baughman RP, Linke MJ, Walzer PD, Smulian AG. Genetic variation among *Pneumocystis carinii hominis* isolates in recurrent pneumocystosis. J Infect Dis. 1995;172(2):595–8 (http://www.ncbi.nlm.nih.gov/pubmed/7542688).

[22]Helweg-Larsen J, Tsolaki AG, Miller RF, Lundgren B, Wakefield AE. Clusters of *Pneumocystis carinii* pneumonia: analysis of person-to-person transmission by genotyping. QJM. 1998;91(12):813–20 (http://www.ncbi.nlm.nih.gov/pubmed/10024946).

[23]Huang L, Beard CB, Creasman J et al. Sulfa or sulfone prophylaxis and geographic region predict mutations in the *Pneumocystis carinii* dihydropteroate synthase gene. J Infect Dis. 2000;182(4):1192–8 (http://www.ncbi.nlm.nih.gov/pubmed/10979917).

[24]Sassi M, Ripamonti C, Mueller NJ et al. Outbreaks of *Pneumocystis* pneumonia in 2 renal transplant centers linked to a single strain of *Pneumocystis*: implications for transmission and virulence. Clin Infect Dis. 2012;54(10):1437–44 (http://www.ncbi.nlm.nih.gov/pubmed/22431811).

	• Oral thrush may be an accompaniment		
Investigations • **DaO_2 (mm of Hg)** • **PaO_2 (mm of Hg)**	< 35 >70	35–45 > 70	> 45 50 – 70
X-ray	Usually non-specific and normal	May show some abnormalities like 'ground glass' appearance  **Image 1.**Bilateral interstitial infiltrates in an HIV-infected patient with PCP	• Typically, diffuse, bilateral, symmetrical "ground-glass" interstitial infiltrates emanating from the hila in a butterfly pattern. • Spontaneous pneumothorax  **Image 2.** PCP associated right-sided pneumothorax

Treatment of PCP[25]

I. For mild to moderate: Total duration of treatment is 21 days

Preferred therapy:

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) PO (3 divided doses), *or*
- TMP-SMX 2 DS tablets PO three times daily.

Alternative therapy:

- ❖ Dapsone 100 mg PO daily plus TMP 15 mg/kg/day PO (3 divided doses), or
- ❖ Primaquine 30 mg (base) PO daily plus Clindamycin PO (450 mg every 6 hours or 600 mg every 8 hours), or
- ❖ Atovaquone 750 mg PO twice daily with food.

[25] https://aidsinfo.nih.gov/guidelines/brief-html/4/adult-and-adolescent-opportunistic-infection/321/pneumocystis-pneumonia, accessed 18 October 2019.

II. For moderate to severe: Total duration of treatment is 21 days

Preferred therapy:

- TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given every 6 or 8 hours, may switch to PO formulations after clinical improvement.

Alternative therapy:

- Pentamidine 4 mg/kg IV once daily infused over ≥60 minutes; may reduce the dose to pentamidine 3 mg/kg IV once daily in the event of toxicities, or
- Primaquine 30 mg (base) PO once daily plus (Clindamycin [IV 600 mg every 6 hours or 900 mg every 8 hours] or [PO 450 mg every 6 hours or 600 mg every 8 hours]).

Note: Adjunctive corticosteroids are indicated in moderate to severe cases of PCP (see indications and dosage recommendations below).

Adjunctive Corticosteroids

For moderate to severe PCP based on the following criteria:

- PaO_2<70 mmHg at room air, *or*
- Alveolar-arterial DO_2 gradient ≥35 mmHg.

Dosing schedule:

- Prednisone doses (beginning as soon as possible and within 72 hours of PCP therapy) (AI)
  - Days 1–5: 40 mg PO twice daily
  - Days 6–10: 40 mg PO daily
  - Days 11–21: 20 mg PO daily
- IV methylprednisolone can be given as 75% of prednisone dose.

Cryptococcal meningitis (CM)

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the etiology. *C. neoformans* is found worldwide, whereas *C. gattii* is found most often in Australia and similar subtropical regions and Timor-Leste. Before the advent of ART, approximately 5- 8% of HIV-infected patients in many countries were diagnosed with disseminated cryptococcosis.[26]

[26]Aberg J, WG. P. Cryptococcosis. In: Dolin R MH, Saag MS, editor. AIDS therapy. New York, NY: Churcill Livingstone; 2002:498–10.

Clinical manifestations

The clinical manifestations range from a variety of features. Many of them are non-specific such as fever, malaise and headache. There may be features of meningeal irritation like neck rigidity and photophobia. Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure.

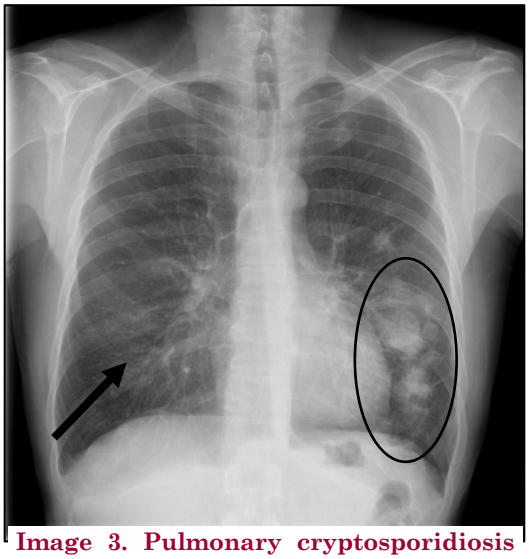


Image 3. Pulmonary cryptosporidiosis in HIV infected

Source: Radeopedia.org

Unfortunately, cryptococcosis is usually disseminated when diagnosed in an HIV patient and can affect any organ. Skin lesions may show many different manifestations, including umbilicated skin lesions mimicking molluscum contagiosum. Isolated pulmonary infection may be possible. Symptoms and signs include cough and dyspnoea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation (circle), though nodular infiltrates have been reported (arrow).

Pulmonary cryptococcosis may present as acute respiratory distress syndrome and mimic *Pneumocystis* pneumonia.

PLHIVs including adults and adolescents should receive cryptococcal screening if clinically suspected. The management algorithm for PLHIVs with cryptococcosis is given in Fig. 8.

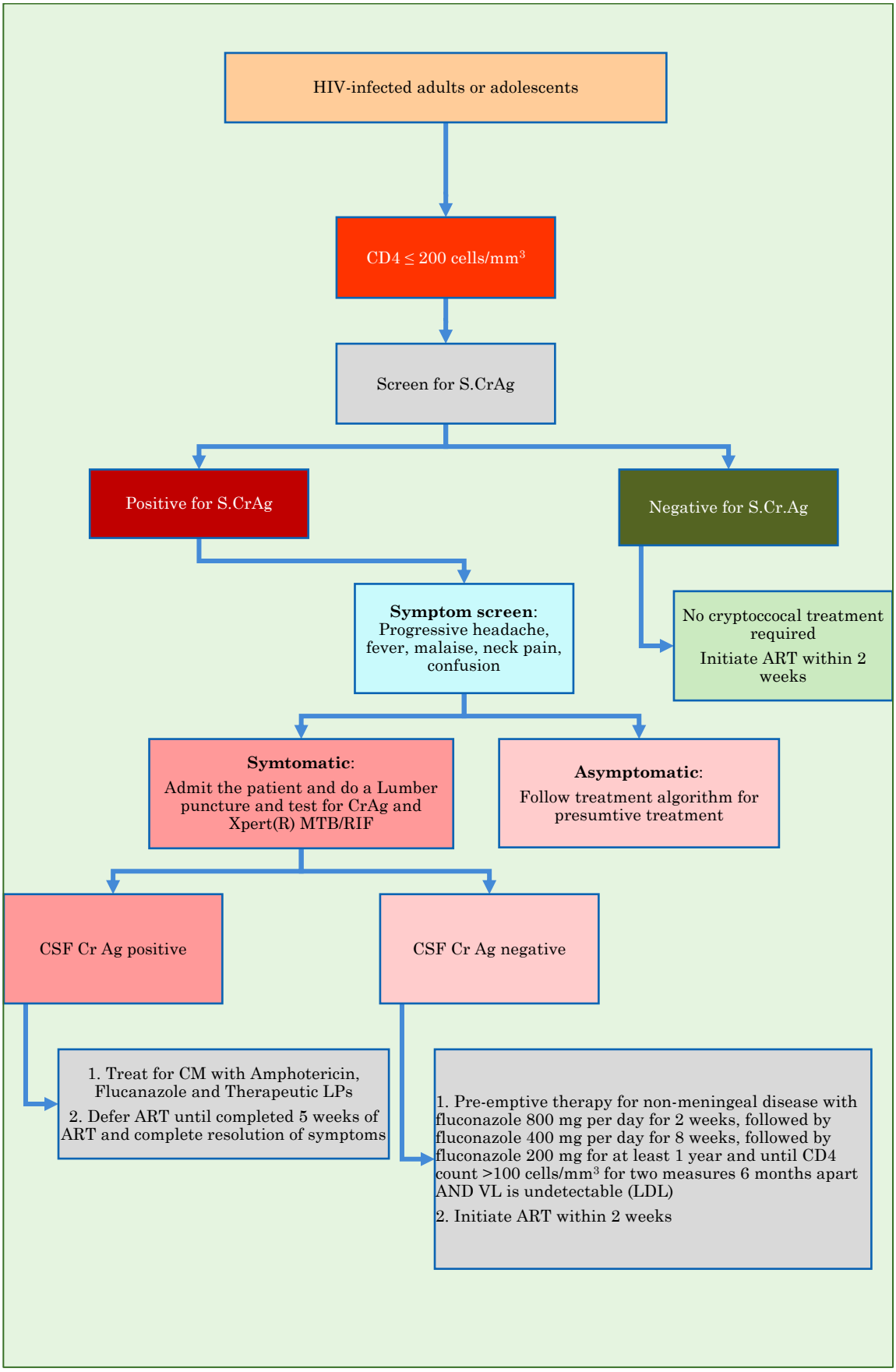


Fig.8. Management algorithm for PLHIVs with suspected cryptococcosis

Source: Adapted from AIDSInfo - Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV (https://aidsinfo.nih.gov/guidelines/brief-html/4/adult-and-adolescent-opportunistic-infection/333/cryptococcosis).

Note:

1. LP is recommended for all S.CrAg positive patients irrespective of symptoms with management based on LP results. If LP is not available to rule out meningeal disease, then patients should be treated for possible CM, even if asymptomatic.
2. Patients with CM are at high risk of developing life-threatening IRIS; deferring ART has shown to improve survival for these specifics.
3. Fluconazole use during pregnancy increases the risk of birth defects. All pregnant women who screen positive with serum CrAg should be offered a lumbar puncture (irrespective of symptoms) to determine if they have cryptococcal meningitis.
4. Fluconazole requires a dose adjustment for impaired renal function, when CrCl mL/min then use 50% of the standard recommended dose.
5. When using high-dose fluconazole, check ALT after 1week of treatment and based on symptoms thereafter.

Management of CM[27]

Treatment for cryptococcosis consists of three phases: initiation, consolidation and maintenance therapy (Table 34).

Table 34. Treatment options for CM in PLHIVs

Population	Regimen	Initiation	Consolidation	Maintenance	Remarks
Adults	Preferred	Amphotericin B 0.7- 1mg/kg/day+ Flucytocin 100 mg/kg/day + Fluconazole 800 mg per day (1 week)[2]	Fluconazole 800 mg per day (2 weeks)	Fluconazole 200 mg/day for at least 1 year and until CD4 count> 100 cells/mm^{3}for two measures6 months apart AND VL isundetectable[2]	Defer ART until after completing 5 weeks of CM treatment and symptoms have resolved
	Alternate	Fluconazole1,200 mg daily (2 weeks)			
Children and adolescents	Preferred	Amphotericin B 0.7–1.0 mg/kg/day +Flucytocin 100 mg/kg/day+ Fluconazole 12 mg/kg/day (up to max 800 mg/day)	Fluconazole 6-12 mg/kg/day up to 800 mg/day	Fluconazole6m g/kg/day up to 200 mg/day	
	Alternate	Fluconazole12 mg/kg/day (up to max 1200 mg/day)		Fluconazole12 mg/kg/day up to 800 mg/day	

Source: 1. Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

2.https://aidsinfo.nih.gov/guidelines/brief-html/4/adult-and-adolescent-opportunistic-infection/333/cryptococcosis.

Further, if Amphotericin B is used, then the following protocol should be used for monitoring the treatment.

Adults

- Use at least 1 L of normal saline (NS) with 20 mmol of KCl over 2--4 hours before each controlled infusion of Amphotericin B (Deoxycholate) given with 1 L of 5% dextrose
- Add two tablets of 8 mEqKCl orally twice daily

[27]https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/333/cryptococcosis, accessed 19 October 2019.

- An additional one 8 mEqKCl tablet twice daily may be added in the second week
- Include magnesium supplementation at 250 mg tablet of magnesium trisilicate twice daily (or 4 mEq tablets of magnesium chloride twice daily).

Adolescents and children

- Use 1 L of normal saline with 20 mmol of KCl over 2--4 hours before each controlled infusion of Amphotericin B. Darrows or Ringer's solutions can also be used
- Avoid KCl replacement in patients with pre-existing renal impairment or hyperkalaemia.

Managing hypokalaemia and raised creatinine levels

Obtain a routine baseline and twice weekly potassium and creatinine:

- If K < 3.3 mmol/L, administer 1 L of normal saline with KCl 40 mmol in normal saline or 1--2 tablets of 8mEq KCl every 8 hours. Add magnesium. Monitor potassium daily
- If creatinine level increases > 2-fold from baseline, omit dose of Amphotericin B, increase hydration to 1 L every 8 hours. If there's improvement, re-start Amphotericin B at 0.7 mg/kg/day on alternate days. If no improvement, discontinue Amphotericin B, give fluconazole 1600 mg/day to complete induction. Monitor creatinine daily.

Therapeutic lumbar punctures are a critical component of the management of CM and should be standard of care. For all patients with symptomatic CM, perform daily therapeutic lumbar punctures:

- If opening pressure is ≤ 40 cm: draw off enough CSF to reduce pressure to 20 cm
- If opening pressure is > 40 cm: draw off enough CSF to reduce pressure by 50%
- Continue daily LPs until pressure is normal for three consecutive days
- Restart LPs, if symptoms return
- If measuring intracranial pressure is not possible (even using a giving set and tape measure), then perform daily therapeutic LPs until severe headache subsides, removing 10--20 mL of CSF each time.

Prevention of other infections

This section deals with the other OIs.

Common conditions frequently causing fever in PLHIVs

There are many conditions that cause fever among the PLHIVs, and the common ones are presented in Table 35.

Table 35. Management of recurrent or persistent 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, total and differential leukocyte count, CSF examination
Prophylaxis	CTX also reduces the incidence of some bacterial infections, malaria and toxoplasmosis
Treatment	According to findings

Lymphadenopathy (Progressive generalized)

Lymphadenopathy is common in HIV infected. It should be treated and handled appropriately and with care. The common causes of lymphadenopathy are presented in Table 36.

Table 36. Differential diagnosis of lymphadenopathy in PLHIVs

Broad disease category	Specifics
Malignancies	Kaposi's sarcoma, Lymphomas (non-Hodgkin's mostly), metastasis, skin neoplasms
Infections	
▪ **Viral**	Adenovirus, cytomegalovirus, hepatitis, herpes zoster, HIV, infectious mononucleosis (Epstein-Barr virus), rubella
▪ **Bacterial**	Brucellosis, cat-scratch disease (Bartonella), chancroid, cutaneous infections (staphylococcal or streptococcal), lymphogranuloma venereum, primary and secondary syphilis, TB, tularaemia, typhoid fever
▪ **Granulomatous**	Berylliosis, coccidioidomycosis, cryptococcosis, histoplasmosis, silicosis
▪ **Other**	Fungal, helminthic, lyme disease, rickettsial, scrub typhus, toxoplasmosis
Autoimmune disorders	Dermatomyositis, rheumatoid arthritis, Sjogren's syndrome, still's disease, systemic lupus erythematosus
Miscellaneous/unusual conditions	Angio-follicular lymph node hyperplasia (Castleman disease), histiocytosis, kawasaki disease, kikuchilymphadenitis, kimura disease, sarcoidosis
Iatrogenic causes	Medications, serum sickness

Source: Adapted from Gaddey HL, Riegel AM. Unexplained lymphadenopathy: evaluation and differential diagnosis. Am Fam Physician. 2016 Dec 1;94(11):896--903.

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 noncontiguous sites (excluding inguinal sites) for three or more months)
- RPR for syphilis.

Treatment

- According to findings.

Respiratory infections

The common organisms causing respiratory infections range from common to many uncommon ones as well.

Opportunistic causes of respiratory infections in PLHIVs:

- 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:

- Based on clinical symptoms and findings
- Sputum examination
- Chest X-rays.

HIV and TB

Please refer to

Chapter.

Bacterial pneumonia

Table 37. Bacterial pneumonia in PLHIVs

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	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. Orthopnoea, fatigue and malaise are also common. Physical examination shows: fever, tachypnoea, 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 nonproductive cough. Chest often clear. Unusual bacterial organisms: *S. aureus*, other Gram –bacteria, *Legionella*. Acute severe pneumonia. Often in severely immune depressed patients.
Diagnosis	Chest X-ray shows lobar consolidation. A typical presentation includes multi-lobar, nodular, reticulonodular patterns Sputum examination (Gramstain and AFB)
Prophylaxis	Daily CTX may reduce the incidence of bacterial pneumonia
Treatment	*Typical bacterial pneumonia*: First-line: amoxicillin (50 mg/kg/day po divided over 3 doses x7 days) Second-line: amoxicillin/clavulanate (625 mg po tid to qid x 7days) 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) orceftriaxone (1 to 2 g IV od) with erythromycin (50 mg/kg/day IV divided in 4 doses) or doxycycline (100 mg po bid), for one 1week.

Pneumonia due to Pneumocystis jiroveci (PCP)

This part was dealt in detail earlier. For any other type of pneumonia, it is recommended that the PLHIV be referred to a specialist centre (Referral Hospital, HNGV for expert opinion)

Oral lesions, odynophagia and dysphagia

The most common mouth problems in HIV/AIDS patients are thrush, ulcerations,

angular cheilitis and oral hairy leucoplakia.

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

The diagnosis of oro-oesophageal conditions is usually clinical.

Table 38. Management options for mouth pain in PLHIVs

Infection or condition	Likely cause	Symptoms and signs	Diagnosis	Treatment and prophylaxis	Comments
Oral thrush or candidiasis WHO stage 2	*Candida albicans*	Two 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	Clinical features and laboratory: Wet mount microscopy using KOH preparation CD4 count is usually < 500/mm^3  **Image 1. Oral candidiasis**	*Topical*: Miconazole nitrate (10 mg gum patch od x 7 days) *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)	Maintain 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: WHO stage 2 disease, if recurrent	*Herpes simplex* CMV Malignancies Multiple aetiology	There are two 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 aetiology): well-circumscribed lesions with a whitish covering surrounded by a reddish halo; small or	Clinical features and CD4 count is usually <350/ mm^3 for *H. simplex*  **Image 2.Vesicles due to Herpes simplex**	*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 200 mg 5 times daily x 10 days) is given systematically as clinical differential diagnosis	Same as above

Infection or condition	Likely cause	Symptoms and signs	Diagnosis	Treatment and prophylaxis	Comments
		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		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	Multiple aetiology, but mostly fungal in origin	Cracking, pain, and sometimes bleeding from the corners of the mouth. It is fungal in origin complicated by inflammation	Clinical features are usually pathognomonic  **Image 3.Angular cheilitis**		
Oral hairy cell leucoplakia	Epstein-Barr virus	Unilateral or bilateral adherent white or grey patches on lingual lateral margins. Patches are irregular folds and cannot be scraped off	Clinical andCD4 count is <500/mm^3	Rarely symptomatic and do not need treatment, but is indicative of immune suppression	Maintain good oral hygiene

Infection or condition	Likely cause	Symptoms and signs	Diagnosis	Treatment and prophylaxis	Comments
			 **Image 4.Oral hairy cell leucoplakia due to EBV**		
Oesophagitis (oesophageal candidiasis) – WHO stage 4	Candida albicans	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	Suspected presence of oro-pharyngeal thrush, odynophagia Oesophagoscopy  **Image 5.Oesophageal candidiasis**	*Adult*: Fluconazole – oral 200mg day 1, Then, 100 mg daily; doses up to 400 mg/day may be used based on patient's response. Treat for a minimum of **3 weeks and for at least 2 weeks** following resolution of symptoms *Paediatric*: Fluconazole – oral, 6mg/kg stat day 1 then 3mg/kg/day for 14--21 days or Ketoconazole 3.3--6.6mg/kg/day x 14--21 days	Maintain oral hygiene

Image courtesy: Image 1 - St Mary's Hospital Medical School/Science Photo Library. Image 2 - Photograph from David H. Spach, MD, University of Washington, Seattle. Image 3 - frank60/ Shutterstock.com. Image 4- Mark Rogers Darling/ JCan Dent Assoc 2018;84:i8. Image 5 –Saleem N/ http://www.journalmc.org.

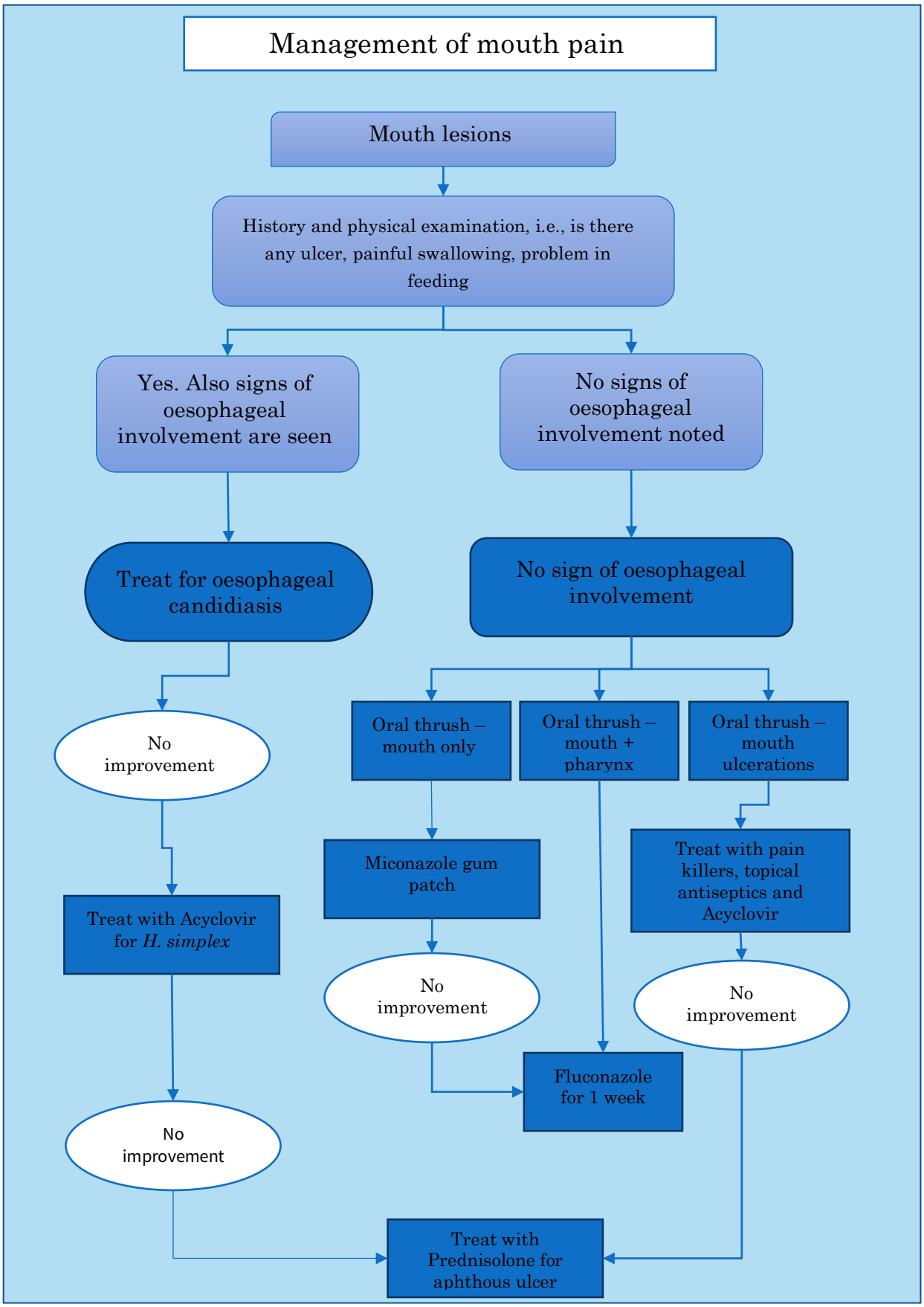


Fig. 9. Management of mouth pain in PLHIVs

Source: Adapted from fact sheet 653: HIV and the Mouth – AIDS infonet(http://www.aidsinfonet.org/fact_sheets/view/653, accessed 18 November 2019).

Diarrhoea in HIV infection

Diarrhoea is a common challenge among PLHIVs. In earlier days, chronic diarrhoea was one of the markers of AIDS defining illness. In practice, diarrhoea is perhaps the commonest problems noted among PLHIVs.

In any case of diarrhoea,

- Assess hydration status
- Provide nutritional advice such as continued diet with cooked food and frequent rehydration 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).

Table 39 provides a snapshot view of the management for acute and chronic diarrhoea.

Table 39. Management of diarrhoea in PLHIVs

Condition	Causative organisms	Symptoms and signs	Treatment
Acute diarrhoea *Definition:* *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*	Dysentery: *Shigella*, Enterohaemorrhagic *E. coli*, *Salmonella* non-typhi species, *Campylobacter* or *Entamoeba histolytica* Viruses, *E. coli*, *Clostridium difficile*, *Staphylococcus aureus* or *Yersinia*	Two syndromes may be possible: • Dysentery: Diarrhoea with blood and/or mucous in the stools, with or without fever • Watery or non-specific diarrhoea, with or without fever	• Assess hydration status. If moderate, treat with ORS and boiled water. If severe, refer for hospitalization • Assess the diarrhoea duration. If less than 3days, do not give antibiotics • In presence of blood and/or mucous: treat with ciprofloxacin (500 mg po bid) and metronidazole (400 or 500 mg po tid), for 7days. *Caution*: antidiarrhoeals are contra-indicated in this case • In watery or nonspecific diarrhoea: treat with CTX (960mg po bid x 7 days) if the patient is not under CTX prophylaxis or with amoxicillin (500 mg po qid x 7 days) • As antidiarrhoeals, use loperamide (4 mg as loading dose then 2 mg after each stools with a maximum of 16 mg/day)
Chronic diarrhoea Definition: > 3 loose or watery stools/day for > 30 days, continuously or episodically; More common during the later stages of the HIV infection	*Isosporabelli*, Cryptosporidiosis, *Cyclospora*, *Microsporidium*species, *Mycobacterium* avium complex, HIV itself *Entamoebahistolytica*or CMV; *Giardia intestinalis*	Usually watery, with or without fever, leading to malabsorption and wasting syndrome. Blood and/or mucous might be present if chronic amoebiasis; infection by giardia presents as nonspecific diarrhoea with bloating and flatulence	• 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 hospitalization • If presence of blood and/or mucous, treat with ciprofloxacin and metronidazole as acute diarrhoea In presence of watery or nonspecific 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 antidiarrhoeal and start ARV

Skin lesions in HIV infection

Skin lesions are common in PLHIVs. There are many reasons for the plethora of skin lesions such as lack of hygiene, immunosuppression, etc. The lesions include Kaposi sarcoma, thrush, several bacterial infections and herpes. Others, like photodermatitis, may be linked to immune reconstitution inflammatory syndrome due to revival of immune response to ARV drug therapy or the drugs themselves.

The common HIV-associated skin diseases are:

- *Viral infections*: herpes simplex, herpes zoster, molluscumcontagiosum (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, photodermatitis
- *Drug reactions*: ARV (i.e., Nevirapine), antibiotics (i.e., CTX, streptomycin).

The diagnosis is clinical.

Skin manifestations are usually seen below CD4 count of < 500/mm.[3]

Some common skin infections and their treatment are presented in Table 40.

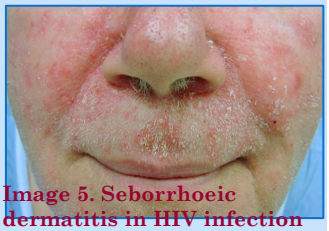
Table 40. Common skin infections and their treatment

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) and paracetamol 500 mg three times a day for 3--4 days
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 (WHO 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  **Image 1. Herpes zoster in HIV infection**
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:* Topical treatment 1st line: gentian violet or Whitefield's ointment topically (x 2–4 weeks) 2nd line: Clotrimazole 1% cream topically (x 2–4 weeks) Systemic treatment in severe cases fluconazole 100mg weekly for 4 weeks or give 100mg daily for 7 days *Vaginitis:* Clotrimazole pessary (200 mg od every night x 3 days or 100 mg od every night x 6 days) or fluconazole if persistent or recurrent
Tinea pedis & Tineacorporis (cutaneousring worm)	
Symptoms	*Tines pedis* 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 *Tines corporis* 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	*Topical treatment* 1st line: Whitefield's ointment or gentian violet topically (x 2–4 weeks) 2nd line: Clotrimazole 1% cream topically (x 2–4 weeks) *Systemic treatment* in severe cases 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	*Topical treatment* *No supra-infection*: C/C solution or ointment, topically (bid x 2 wks); Mild supra-infection: C/C ointment + Neomycin, topically (bid x 2 weeks) Systemic treatment, if severe supra-infection with cloxacillin (500 mg po qid x 7 days)
Scabies (common in Timor-Leste)	
Epidemiology and context	Scabies is a ectoparasitic infection of the skin that is caused by the mite *sarcoptesscabiei var. hominis*. Pandemic throughout the world, it is estimated there may be around 150 million cases,[28] but is particularly problematic in population with low hygiene, overcrowding. social disruption and shortage of water. In HIV-infected populations, prevalence has been reported as between 0.5% and6% in adults and 2% and 10% in children.[29] Transmission is mainly by skin to skin contact with infected individuals. Normally transmission is rare through innate objects and fomites, but is common in immunocompromised individuals  **Image 2. Sarcoptes scabiei**
Symptoms	Two main forms of presentation may be seen:1) Classical; and 2) Atypical or crusted form *Classical scabies*: 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. Interdigital web spaces of the fingers, the wrists, axillary areas, female breasts (particularly the skin of the nipples), peri-umbilical area, penis, scrotum and buttocks  **Image 3. Classical scabies** *Crusted scabies (Norwegian scabies)*: Presentation could be also hyperkeratosis of the knees, elbows and trunk. Scabies is usually atypical in advanced disease; it may be far more extensive than usual including areas above the neck
Treatment	*Mild to moderate scabies* Topical treatment: Permethrin 5% (two applications) or Benzyl benzoate 25% topically to whole body except face nightly for 3 nights. If there is poor response to treatment, or permethrin treatment is not feasible, then two doses of oral ivermectin at 200 µg/kg/dose (10 mg in a 50 kg person) is recommended (each 1week apart) Remember to also treat clothes, bed linen and all family members. *Severe or crusted scabies* Both topical and systemic treatment is recommended Topical: 5% permethrin crème (several applications) every 2--3 days for 1–2 weeks Systemic: ivermectin (200 µg/kg/dose) for three doses (days 1, 2 and8); five doses (1, 2, 8, 9 and15) or seven doses (1, 2, 8, 9, 15, 22 and29). Physician discretion is advised based on severity of infection
Pruritic papular eruption (PPE)	
Epidemiology	Papular pruritic eruption is one of the most common skin conditions associated with HIV disease in tropical and subtropical regions, with reported prevalence of 11–46% Pathophysiology of papular pruritic eruption is not well understood. Some suggests, hypersensitivity to arthropod bites and a form delayed hypersensitivity to arthropod antigens in the reconstitution syndrome

[28]Hay RJ. Scabies – learning from animals. J EurAcad Dermatol Venereol. 2004; 18:129–30.
[29]Patton LL, Phelan JA, Ramos-Gomez FJ, Nittayananta W, Shiboski CH, Mbuguye TL. Prevalence and classification of HIV-associated oral lesions. Oral Dis. 2002; 8(S 2):98–10.

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 Scabies, eosinophilic folliculitis and drug eruptions should always be considered in the differential diagnosis  Image 4. **PPE in HIV infected**
Treatment	Primary treatment is ART Vaseline moisturizers mixed with Hydrocortisone 1% ointment (x 2weeks) Povidone-iodine solution 0.5% (x 2 weeks) if evidence of superadded infection is present. Add tab doxycycline for any infected dermatitis Other therapeutic measures include: • Phototherapy – with UVB and PUVA • Pentoxyphyllin
Epidemiology	Seborrhoeic dermatitis is a chronic condition that can affect people at any age. It tends to wax and wane and is prone to recurrence after treatment Seborrhoeic dermatitis has been reported to be associated with several conditions, including HIV. In HIV-infected patients, prevalence is much higher and occurs early in the course of HIV disease, with a mean CD4 count at presentation of higher than 500/mm^3
Symptoms	*Adults*: Seborrhoeic dermatitis on the scalp manifests as dry, flaking desquamation (dandruff)or yellow, greasy scaling with erythema. In adolescence and adulthood, it usually begins as mild greasy scaling of the scalp with erythema and scaling of the nasolabial folds or the postauricular skin  **Image 5. Seborrhoeic dermatitis in HIV infection** *Children*: In infants, seborrhoeic dermatitis may present as thick, greasy scales on the vertex of the scalp - cradle cap seborrhoeic dermatitis In older children, it manifests as dry, flaking desquamation(dandruff) or yellow, greasy scaling with erythema Differential diagnoses are psoriasis, eczema and *Tinea capitis* *In HIV infected*, the occurrence is much more common and severe. It may be extensive and cover the whole body. It may be more resistant to treatment and prone to frequent relapses and recurrence
Treatment	*Mild seborrhoeic dermatitis* HIV-infected children and adults should be treated with topical ketoconazole 2% or clotrimazole 1% two to three times per week for4weeks, with a maintenance treatment once per week or as needed *Severe seborrhoeic dermatitis* HIV-infected children and adults unresponsive to first-line therapy should be treated with a combination therapy of topical antifungals (e.g., clotrimazole 1% or ketoconazole 2%) and topical corticosteroids ART should be the support required to reduce the frequency of recurrence and relapses
Psoriasis	
Epidemiology	Extensive psoriasis is observed in HIV patients; however, the incidence may not be increased

<table>
<tr><td>Symptoms</td><td>Common ones are:
• Rashes or patches of red, inflamed skin often covered with loose, silver-coloured scales. In severe cases, the plaques will grow and merge into one another, covering large areas
• Itchy, painful skin that can crack or bleed
• Small areas of bleeding where the involved skin is scratched
• Problems with fingernails and toenails, including discoloration and pitting. The nails may also begin to crumble or detach from the nail bed
• Scaly plaques on the scalp

Image 6. Psoriasis in HIV infection</td></tr>
<tr><td>Treatment</td><td>Mild seborrhoeic dermatitis
HIV-infected children and adults should be treated with topical ketoconazole 2% or clotrimazole 1% 2–3 times per week for4weeks, with a maintenance treatment once per week or as needed
Severe seborrhoeic dermatitis
HIV-infected children and adults unresponsive to first-line therapy should be treated with a combination therapy of topical antifungals (e.g., clotrimazole 1% or ketoconazole 2%) and topical corticosteroids
ART should be the support required to reduce the frequency of recurrence and relapses</td></tr>
<tr><td colspan="2">Kaposisarcoma (KS)</td></tr>
<tr><td>Epidemiology</td><td>KS, a tumour of endothelial cell origin, is an AIDS-defining illness caused by the humanherpesvirus-8 (HHV-8). It remains the most common
malignancy in PLHIVs, especially in sub-Saharan Africa
The advent of ART has had a profound influence on the epidemiology of HIV-associated KS, particularly in developed countries, and has been associated with a substantial reduction in KS incidence
Sexual route seems to be the main route of transmission for KS</td></tr>
<tr><td>Symptoms</td><td>Adults
Characteristic appearance of skin lesions, which can present as macules, papules, nodules or plaques, ranging in colour from faint pink to purple to brown. These lesions may also be present on the oral and genital mucosa, with or without accompanying internal organ involvement. Associated dissemination to lymphatics may occur, with or without painful lymphoedema and/or lymphadenopathy

Image 7. KS in HIV

Children
The presentation and outcome of KS in children may differ from that in adults. For example, children often present without characteristic skin lesions and at higher CD4 count levels. This has implications regarding staging and treatment of paediatric KS and use of adult staging criteria as the basis for selecting treatment may not be applicable in all cases (WHO, 2014)[30]

Visceral: digestive (usually asymptomatic) or pulmonary, lymph nodes</td></tr>
<tr><td>Classification/ case definitions</td><td>Two basic types:
Mild/moderate and severe
<table><tr><th>Mild/moderate KS</th><th>Severe KS</th></tr><tr><td>• Confined to skin and/or lymph nodes
• No symptomatic visceral disease</td><td>• Symptomatic visceral disease (pulmonary[a] or gastrointestinal[b])</td></tr></table></td></tr>
</table>

[30]Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. Geneva:World Health Organization; 2014.16--25.

	• No significant oral disease (i.e., does notinterfere with chewing or swallowing) • No significant oedema affecting function • Not functionally disabling or immediately life-threatening • Extensive oral KS lesions, which interfere with chewing or swallowing • Painful or disabling tumour-associated facial/genital/ peripheral oedema or ulcerated tumours • Life-threatening or functionally disabling disease • Progressive[c] or persistent KS despite ART

Note: [a] Symptomatic pulmonary KS, suggested by shortness of breath, hemoptysis or moderate/severe cough, which cannot be attributed to other pulmonary conditions.
[b] Symptomatic gastrointestinal KS, suggested by bleeding from mouth or rectum, which cannot be attributed to other gastrointestinal conditions.
[c] Progressive disease is defined as: an 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 symptomatic tumour associated oedema or effusion is also considered to represent disease progression.
Source: Adapted from *ACTG (1997) and WHO Classifications (2014).*

Staging criteria

The AIDS Clinical Trials Group (ACTG) staging classification was developed in the pre-ART era to establish a common language to use in describing AIDS-associated KS and the probability of survival
The adult classification is based on three criteria: tumour extent (T), the status of the patient's immune system as measured by CD4 cell count (I) and presence of systemic symptoms (S). Each factor is further grouped into good risk (0) or poor risk (1)

Criteria	Good prognosis	Poor prognosis
Tumour (T)	(T0) Tumour confined to skin and/or lymphnodes and/or minimal oral disease[a]	(T1) Tumour-associated oedema or ulceration; extensive oral KS; gastrointestinal KS; KS in othernon-nodal viscera
Immune system (I)	(I0) CD4 cells ≥150/µL	(I1) CD4 cells <150/µL
Systemic illness (S)	(S0) No history of OIs and/or thrush Absence of 'B' symptoms[b] Performance status: Karnofsky score ≥70	(S1) History of OIs and/or thrush Presence of 'B' symptoms[b] Performance status: Karnofsky score <70 Other HIV-related illness (e.g., neurologicaldisease, lymphoma)

Note: a 'Minimal oral disease' defined as non-nodular KS confined to the palate
b 'B' symptoms: unexplained fever, drenching night sweats, >10% involuntary weight loss, or diarrhoea persisting more than 2weeks.
Source: Adapted from Krown et.al (1997).

In children, there is no uniform criteria for staging. However, the following is commonly used:

- Stage I: <10 KS lesions isolated to the skin without significant associated oedema
- Stage II: ≥10 KS lesions isolated to the skin, or lesions involving the palate/oral mucosa, subcutaneous nodules, lymph nodes and/or bone marrow (i.e., two cytopoenias not otherwise explained)
- Stage III: Disseminated KS involving the lymphatics resulting in lymphoedema (i.e., "woody" oedema) in the extremities and/or groin

	• Stage IV: Systemic KS, defined as pulmonary KS with noted infiltrates/effusions on chest radiography, abdominal involvement with intra-abdominal nodes, hepatomegaly and/or ascites and/or cardiac involvement with cardiomegaly and associated pericardial effusion *Source:* Adapted from Mitsuasu (1987) and Stephan et. al (2011).
Treatment	In HIV-infected adults, adolescents and children diagnosed with mild/moderate KS, **immediate ART initiation** is recommended *Severe/symptomatic disease* In HIV-infected adults, adolescents and children diagnosed with severe symptomatic KS, immediate ART initiation in combination with systemic chemotherapy is recommended *"Recommended chemotherapy regimens in adults, adolescents and children may include vincristine with bleomycin and doxorubicin (ABV), bleomycin with vincristine (BV), and when available or feasible, liposomal anthracyclines (doxorubicin or daunorubicin), paclitaxel or oral etoposide, at sites with the infrastructure, staff and resources to administer chemotherapy drugs and provide appropriate monitoring and supportive care" (sic.)* (WHO 2014) However, in Timor-Leste, the chemotherapeutic regimens are very few. The above-mentioned drugs are not available in the country. Thus, as of current, the recommended treatment for KS is ART.

Molluscum contagiosum	
Epidemiology	Molluscum contagiosum is a skin infection of viral origin. It usually affects young children, but also sexually active young adults and the immunosuppressed, such as people infected with HIV Incidence of molluscum contagiosum is estimated to be between 2% and 8%, while in the HIV infected, it is estimated to be 5–18%[31] Superficial viral infection of the epidermis caused by a pox virus and spread by skin-to-skin contact
Symptoms	Lesions are pearly white or skin-coloured papules with a central umbilication. It can occur anywhere on the body including the external genitalia, but is most commonly seen on the face and trunk in children In PLHIVs, the lesions are usually persistent, frequently recur, have a fulminant clinical presentation and a longer duration of clinical manifestation. They may be disseminated, but with a predilection for the head, neck and genital area  **Image 8. Molluscum contagiosum in HIV infection**
Treatment	ART should be the primary treatment of extensive and/or unusually distributed molluscum contagiosum in HIV-infected patients. The disease is self-limiting and, in many cases, could resolve on its own

Eosinophilic folliculitis	
Epidemiology	Prevalence of HIV-associated eosinophilic folliculitis varies greatly across different populations. Before the widespread use of ART in the developing countries, this was commonly seen in moderate to severe immune suppression The development of HIV-associated eosinophilic folliculitis is strongly associated with advanced immunosuppression, especially CD4 counts < 250 cells/mm,[3] and low CD4 nadir (< 50 cells/mm[3])

[31]Husak R, Garbe C, Orfanos CE. Mollusca contagiosa in HIV-patients. clinical manifestations, relation to the immunological status and prognostic significance. [German] Mollusca contagiosabei HIV-Infektion. Klinische Manifestation, BeziehungzumImmunstatus und prognostischeWertigkeitbei 39 Patienten. Hautarzt. 1997; 48(2):103–9.

Symptoms	HIV-associated eosinophilic folliculitis manifests as 2–3 mm erythematous, highly pruritic wheallikepapules, most frequently affecting the shoulders, trunk, upper arms, neck and forehead.Lesions are follicular and are often markedly excoriated Severe pruritus may cause sleep impairment, distress and even depression. However, the diagnostic challenge is differentiating between other dermatoses. The table below provides a differentiating feature for the types of dermatoses:

Criteria	Eosinophilic folliculitis	Papular pruritic eruptions	Scabies
Itching	Severe and throughout day and night	Severe and throughout day and night	Night-time itching and partner itching
Skin lesions	• Oedematous, wheal like papules • Excoriations	• Hyperpigmented and skin-coloured papules • Severe excoriations and scarring, and sometimes prurigo-like lesions	• Small papules, papulovesicles • “Burrows”
Distributions	• Neck, forehead, cheeks and trunk	• Predominantly extensor surface of extremities and trunk	• Finger web spaces, palms, forearms, axilla, areola and nipple, umbilicus, external genitalia • No facial lesions
Histopathology	• Characteristic	• Suggestive, but variable	• Suggestive unless mite is visualized

Treatment	ART should be the primary treatment of eosinophilic folliculitis in HIV-infected patients All HIV-infected adults (including pregnant women), adolescents and children who have been initiated on ART and who subsequently develop HIV-associated eosinophilic folliculitis should not discontinue the ART Additional symptomatic therapy is recommended for the duration of the persistent symptoms with, depending on severity: • Oral antihistamine such as promethazine HCl, chlorpheniramine maleate or cetirizine, add • Topical corticosteroids if no response to antihistamine; add • Oral fluconazole if response is poor; add • Permethrin 5% crème applied above the waist

Management of neurological disorders in HIV infection

The assessment of the patient with headache should include the presence orabsence 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 and aphasia) due to toxoplasmosis, tuberculoma, cryptococcoma, lymphoma and PML)
- Changes in mental status (loss of concentration, personality change, confusion and cognitive impairment) and dementia due to TB meningitis, CM and HIV dementia
- Visual disturbances due to CMV(floaters, scotoma and flashing lights).

Neurological complications in HIV patients may be due to:

- HIV(HIV encephalopathy)
- OIs(Toxoplasmosis, cryptococcal meningitis
- Neurosyphilis
- Malignancies (primary CNS lymphoma)
- Drugs (e.g., EFV, etc.)

Box 1. Common neurological complications in HIV infection

HIV infection itself may cause encephalopathy and the neurological complications could be due to other infections as well.

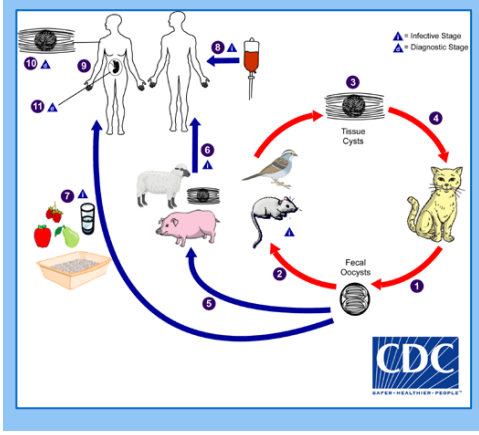
Some of these conditions require advanced investigations for diagnosis, but the most common seen in resource-limited settings may be clinically strongly suspected (toxoplasmosis) or diagnosed only with CSF examination (meningitis).

Malaria used to be an endemic disease in Timor-Leste. With substantial effort, the country has been able to reach the doorstep for elimination and less than 10 cases of malaria are being detected per year. Thus, in the differential diagnosis of meningeal conditions malaria should be the last option.

CD4 is very useful in narrowing the differential diagnosis. Patientson ARVs and cotrimoxazole prophylaxis may be at lower risk of some 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 (Table 41).

Table 41. Management of neurological disorders

Toxoplasmosis (WHO Stage 4 disease)	
Epidemiology and life cycle	Toxoplasmosis is a zoonosis caused by the obligate intracellular parasite, Toxoplasma gondii, and has a worldwide distribution. Majority of the infection is caused in cats and humans, but can infect any mammal and birds  Most of the horizontal transmission to humans is caused by ingestion of tissue cysts in infected meat, or by ingestion of water or food contaminated with sporulated oocysts from the environment, and less frequently directly from feline faeces In patients with HIV infection, most cases of toxoplasmosis are reactivation disease occurring when the CD4 T-lymphocyte (CD4) cell count is <50 cells/mm^3 Although not known, it is presumed that in Timor-Leste, the prevalence should be high owing to presence of numerous feline species and poor hygiene levels
Symptoms and diagnosis	Central nervous system (CNS) manifestations are the most common presentation of toxoplasmosis and include toxoplasma cerebral abscess and encephalitis Common symptoms include: • Constellation of severe headache, fever and focal neurological signs (such as hemiparesis) is typical • Altered mental status such as confusion, change in behaviour, seizures, coma, eye pain and reduced vision • Involvement of other organs such as lungs, eyes, heart, liver and pancreas lead to retinochoroiditis, pneumonitis, myocarditis and other manifestations of disseminated infection Physical examination would demonstrate neurological abnormalities Usual presentation is below CD4 count of < 100 cells/mm^3 *Diagnosis of toxoplasma encephalitis is most often presumptive, rather than definitive*
Treatment	Toxoplasma encephalitis ▪ Sulfadiazine 1000 mg four times a day (or 1500 mg four times a day, if weight is more than 60 kg)plus ▪ Pyrimethamine 200 mg loading dose followed by 50 mg daily (or 75 mg daily, if weight is more than 60 kg) plus ▪ Folinic acid 10 mg daily ▪ Duration: 6–8 weeks or more If condition deteriorates, alternative diagnosis may be considered and dexamethasone 4 mg four times a day tapered over a few days should be used.
Prophylaxis	Please refer to section on CTX prophylaxis

Bacterial meningitis	
Epidemiology	Bacterial meningitis may be common in many HIV infections, especially if the CD4 counts are below 100 cell/mm^3 Although cryptococcal and TB meningitis would be common in HIV infected in Timor-Leste (Programme data), bacterial meningitis would rank third in the series. Unfortunately, mortality from any of these diseases is high. Most common causative organism is *N. meningitis (Meningococcus)*, followed by *Streptococcus pneumoniae, Haemophilus influenza,* etc.
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)
Diagnosis	CSF examination: • Turbid appearance

	• Poly morpho nuclear cells > 500/mm^3 • Low glucose • Increased protein usually > 1g/L
Treatment	Ceftriaxone 2g IV od x 7 days
Peripheral neuropathy (PNP)	
Epidemiology	Nearly 33% of people infected with HIV/AIDS experience some peripheral nerve damage. Peripheral neuropathy can by caused by HIV virus itself by certain drugs used in the treatment of HIV/AIDS (Didanosine, Zalcitabin, Stavudine, etc.) or other complications (dapsone, INH, metronidazole, vincristine, ethambutol, etc.) or as a result of OIs (e.g., CMV, candidiasis [thrush], herpes, TB). Neuropathy could also result from other associated causes, such as alcohol consumption and vitamin B deficiency
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 neuralgia • Burning, tingling, pins and needles in drugs associated peripheral neuropathy
Diagnosis	• Usually clinical in resource-constraint settings • Nerve conduction studies are a good compliment and confirmation
Treatment	Combination ART using safer drugs is the way to go. Current regimens of Tenofovir+Lamivudine+Efavirenz is not known to cause PNP, dolutegravir based regimens are also not known to cause acute PNP In coinfection with TB, pyridoxine (vit B_6) is a regular complement and reduces the incidence of PNP in coinfected patients Alcohol intake is very high in Timor-Leste and is one of the major causative factors for PNP. Adequate counselling is a must on reducing the risk of PNP due to alcohol For intractable pain, amitriptyline (25 to 75 mg po) at bedtime (can increase up to200 mg, if necessary) For *post-herpetic neuralgia*: carbamazepine (200 mg po bid) for 2–4 weeks could be added 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

Palliative care

Palliative care is the provision of appropriate relief from physical and psychological discomfort in the absence of cure. However, in HIV infection, the need for palliative care arises more often not only due to absence of cure, but also mainly to support during the treatment of many types of OIs that develops during the course of infection. Palliative care extends, if necessary, to support in bereavement.

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.

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.

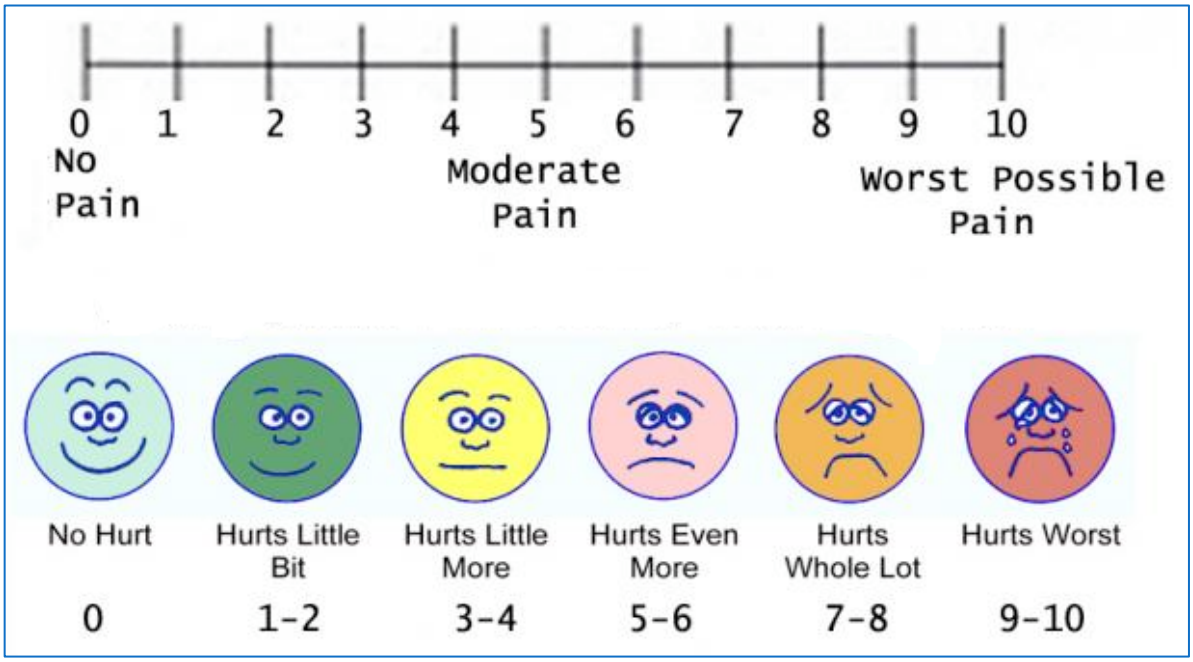


Fig. 10. Visual analogue scale with Wong-Baker faces for assessment of pain

The analgesic ladder (WHO) defines three levels of pain with adapted painkillers for each level(Fig. 11):

- Nonopioids such as aspirin, paracetamol and ibuprofen
- Weak opioids such as codeine and dextropropoxyphene
- Strong opioids such as morphine and tramadol.

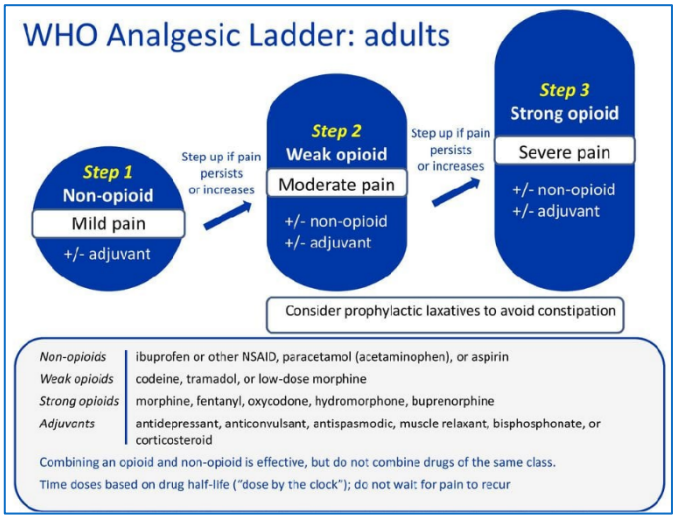


Fig. 11. WHO analgesic ladder for pain

The adjuvants that can be used to enhance the efficacy of these drugs are carbamazepine, diazepam, amitriptyline and prednisolone.

Follow the protocol given below for pain control in PLHIVs:

- If possible, give oral painkillers and not injectables
- 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 individualized for the patient.

Table 42 provides the guide to pain management using oral non-steroidal anti-inflammatory drugs (NSAIDs).

Table 27. Commonly used NSAIDS in management of intractable pain in PLHIVs

Drug	Dose
1. Paracetamol/Acetaminophen	650 mg every 4 hourly oral
2. Aspirin	650 mg every 4 hourly oral
3. Ibuprofen	200–800 mg every 6 hourly oral
4. Diclofenac sodium	50–75 mg every 8–12 hourly oral
5. Aceclofenac	100–200 mg every 12 hourly oral

Table 28.Commonly used opioids in pain management in PLHIVs

Drug	Dose
1. Codeine phosphate	60 mg every 3–4 hourly oral
2. Tramadol HCl	50 mg every 6 hourly oral
3. Oxycodone hydrochloride	10 mg every 3–4 hourly oral
4. Morphine sulphate (plain)	30 mg every 3–4 hourly oral
5. Morphine sulphate (sustained release tabs)	30 mg every 12 hourly oral
6. Morphine sulphate (injectable)	10 mg every 3–4 hours i.v

Apart from this, there may be situations where there are special needs to individual patients. Table 44 provides guidance to managing some special situations.

Table 44. Management of pain in special situations in HIV infection

Situations	Management
Burning pains; abnormal sensation pains; severe shooting pains with relatively little pain in between, pins and needles	Pregabalin 75 mg twice a day or start low-dose amitriptyline at 12.5 mg at night and then increase to 25 mg after 2 weeks and then increase to 50 mg after another 2 weeks
Muscle spasms in end-of-life care or paralyzed patient	Diazepam 5 mg orally
Herpes zoster (or shooting pain following it) Refer patients with ophthalmic zoster	Low-dose amitriptyline 12.5–25 mg daily *Early eruption*: acyclovir if available; apply gentian violet/povidone iodine if ruptured vesicles
Gastrointestinal pain from colic only after intestinal obstruction has been excluded (i.e., vomiting, no stool and gas passing, visible bowel movements)	Use dicyclomine HCl 10–20 mg every eight hourly oral along with paracetamol 500--650 mg every eight hours (or Mefenamic acid 250–500 mg)
Bone pain or renal colic or dysmenorrhoea	Ibuprofen (200–400 mg and paracetamol (325 mg) combination 3–4 times a day or Mefenamic acid (250–500 mg) 3–4 times a day
If pain is from: ▪ Swelling around tumour ▪ Severe oesophageal ulceration and cannot swallow ▪ Nerve or spinal cord compression ▪ Persistent severe headache (likely from increased intracranial pressure)	When giving end-of-life care and referral is not desired, one can consider use of steroids under careful clinical supervision

Additional methods for pain control

Combine these with pain medications if the patient agrees and it helps:

- Emotional support
- Physical methods:
  - Touch (stroking, massage, rocking and vibration)
  - Ice or heat
  - Deep breathing.
- Cognitive methods: distraction such as radio, music, and imagining a pleasant scene
- Prayer (with respect to patient's practice)

- Traditional practices which are helpful and not harmful—get to know what can help in the local setting.

Some special conditions in HIV management

Immune reconstitution inflammatory syndrome (IRIS)

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 subclinical, undiagnosed and later unmasked by the host's regained capacity to mount inflammatory response (Table 45).

IRIS does not indicate a failure of ART, as it shows an immunological and virological response to ART(Fig.12).

Under programmatic conditions and field level, the following working definition could be adopted for use:

"IRIS is a paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started ART with reconstitution (improved functioning) of their immune system. The immune system, once it regains some function, is now able to respond against the foreign antigen"

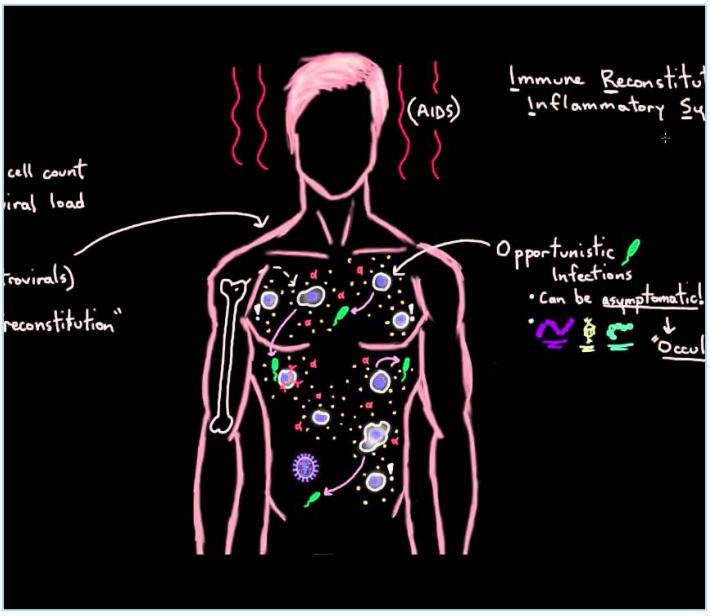


Fig. 12. Immune reconstitution inflammatory syndrome

Table 4529. Classification of IRIS

Categories	Target antigen
Infection–unmasking	Viable replicating infective antigen
Infection-paradoxical	Dead or dying organisms
Autoimmune	Host
Malignancies	Possible tumour or associated pathogen

Source: Devesh J. Dhasmana, Keertan Dheda, Pernille Ravn, Robert J. Wilkinson and Graeme Meintjes. IRIS in HIV infected patients receiving antiretroviral therapy pathogenesis, clinical manifestations &management. Drugs,2008; 68 (2):191–208.

Diagnosis criteria

Mostorallofthefollowingfeaturesshouldbepresentinordertomakethediagnosisof 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 that cannot be explained by an acute drug-resistant infection, a bacterial superinfection, ADRs, 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 two months after ART initiation (in 2/3 of patients). IRIS can also occur within a few days after initiating ART, or as late as three years after its commencement.

Pathogens involved

The most frequently reported associated infections are mycobacterium tuberculosis (MTB), cryptococcus, KS, localised herpeszoster, mycobacterium avium complex (MAC), and CMV. The clinical features of IRIS are strongly related to the type of pre-existing OI.

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 especially important so that it can be identified quickly and managed correctly.

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 1 mg/kg/day (maximum 60 to 80 mg/day), and 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 (Table 46).

Table 46. Management protocol in case of IRIS

Severity of IRIS	Definition	Management

Mild	Resolves over time in most patients
	Symptomatic treatment is often enough
		• Treat the OI and manage the associated symptoms
		• Treat IRIS-associated inflammation:
		  ○ NSAIDS for discomfort associated with mild inflammation/fever
		  ○ Inhaled steroids for bronchospasm or cough associated with mild pulmonary inflammation
		• Surgical intervention:
		  ○ Drainage of abscesses
		  ○ Excision of inflamed and painful lymph nodes

Severe	• Threatens a patient's functional state
	• Cause permanent disability
		• Treat the OI and manage the associated symptoms
		• Manage the IRIS-associated inflammation:
		  ○ If NOT cryptococcal meningitis or KS: give 1--2 mg/kg prednisone for 1–2 weeks. Follow with a period of individualized tapering of the dose
		  ○ Do not use corticosteroids for the management of CM or KS-related IRIS
		• Closely monitor patients on corticosteroid therapy for:
		  ○ Hyperglycaemia
		  ○ Hypertension

	• Potentially lead to death Examples: • Decline in pulmonary capacity from TB or MAC infection • Neurologic complications from cryptococcal infection • Loss of vision from CMV retinitis infection	○ Mental status changes ○ Avascular necrosis ○ Worsening of an existing infection ○ Predisposition to a new infection (e.g., TB and CMV)

Chapter 7

TB and HIV

TB diagnosis and treatment

HIV is the most powerful known risk factor for reactivation of LTBI to active disease. In PLHIVs, there is also a higher risk of rapid TB progression to active disease soon after infection with *Mycobacteriumtuberculosis*. A person infected with HIV has 10 times higher risk of developing TB, than those who are uninfected. TB can occur at any point during progression of HIV infection, but the risk of developing TB rises sharply with worsening immune status. Available evidence show that PLHIVs are nearly 29 times (26–31 times) more likely to develop TB as compared to people without HIV in the same country.[32]

HIV status	Life time risk of developing TB
Negative	5–10%
Positive	50% (or 10–30% per year[33])

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 EPTB have a worse prognosis than HIV+smearpositive 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-coinfected 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 among the HIV+ individuals.

General principles of management of HIV-TB coinfected patients

- Intensified case finding using 4-symptom complex for TB screening; fast-tracking and referral of symptomatic patients for Xpert® MTB/RIF test and other appropriate investigations, as required, for TB diagnosis
- If a patient with active TB is diagnosed with HIV, the priority is to start TB treatment in accordance with the national TB treatment guidelines
- Co-trimoxazole prophylaxis should be given to all HIV–TB patients.

Diagnosis of TB in HIV positive patient

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

[32]Tuberculosis prevalence surveys: a handbook. Geneva: World Health Organization; 2011.
[33]Maartens G, Wilkinson RJ. Tuberculosis. Lancet online. August 2007 (www.thelancet.com, accessed 14 September 2019).

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 resembling primary TB or EPTB or disseminated disease. Bacterial co-pathogens are frequent in HIV-coinfected patients (Table47).

Table 47. Features of PTB in different stages of HIV infection

Features of PTB	Stage of HIV infection	
	Early	Late
Clinical picture	Chronic cough (any duration) 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 immuno deficiency increases (less cavitation, inflammation and endobronchialirritation). However, chronic cough lasting more than 2–3 weeks is also highly predictive of TB disease in PLHIVs	
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

Table 48. Differential diagnosis of PTB in HIV-infected adult patients

Differential diagnosis	Details
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 may be negative
Pneumocystis pneumonia	• Sub-acute and insidious onset • Later stage of HIV infection (CD4 count <200/mm^3) • Dry cough, mucoid sputum (if any), progressive dyspnoea • Chest X -ray: bilateral d i f f u s e infiltrates (ground glass appearance) or may be normal or may have findings of spontaneous pneumothorax
Kaposi'ssarcoma	• Typical lesions found on the skin and mucous membranes (oral cavity) • Cough, haemoptysis and dyspnoea • Pleural fluid is blood-stained

Diagnosis of PTB in HIV+ patient

Intensified case finding (ICF) involves systematic screening for active TB among high-risk populations at each visit to a health facility. PLHIV should be regularly screened for TB during every visit to the ART centres using the 4-symptom (4S) complex---current cough, fever, weight loss and night sweats---

among adults. In children, the 4S complex includes current cough, fever, poor weight gain and history of contact with a TB case(Fig. 13). The 4S screening has a sensitivity of 85%.[34]

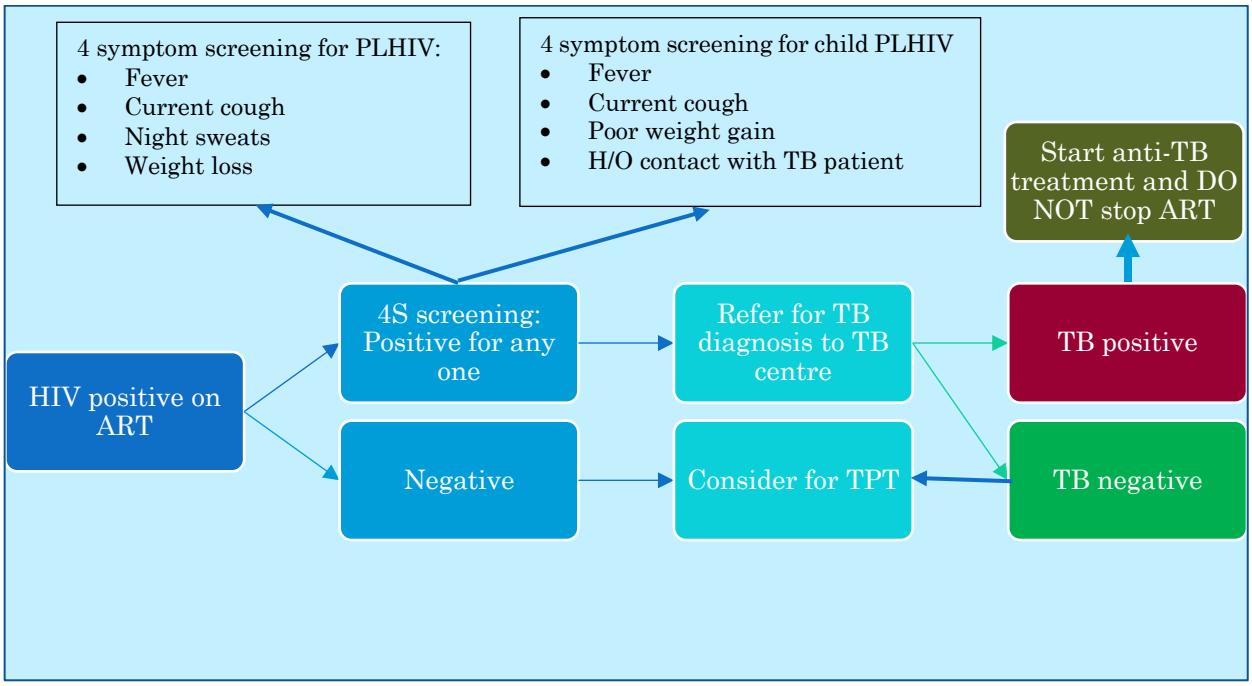


Fig. 11. HIV-TB coinfection: algorithm for screening HIV positive individuals

Diagnosis of EPTB

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.

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(Table 49).

Table 49. Differential diagnosis of EPTB in HIV-infected adult patients

	High suspicion of TB, if	Probably not TB, if
Lymph node TB	• 2cm or more in size, symmetrical/localized painless swelling, firm/fluctuant/fistulated cervical location, weight 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	Bilateral: heart failure, pneumonia Clinical KS/other malignancy Aspirate or fluid is: • cloudy/pus

[34]Getahun H et al. Development of a standardised screening rule for tuberculosis in people living with HIV in resource constrained settings: individual participant data meta-analysis of observational studies. PLoS Medicine, 2011; 8(1):e1000391.doi:10.1371/journal.pmed.1000391Meta-analysis of 12 studies and 8,148.

	• Aspirate of fluids is clear and straw coloured and clots on standing in a tube • Weight loss, night sweats and fever • Rivalta test+[35]	• fails to clot
Disseminated TB	Weight loss, fever and cough Abnormal CXR (including military pattern) Large spleen/liver Night sweats, anaemia	Differential diagnosis with salmonella, malaria, cryptococcus, kala-azar, lymphoma Rigors, very breathless (RR>30/min), severe diarrhoea, blood in stool, positive cryptococcal antigen, malaria smear or likely 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	Noninfectious, cardiac problems Rigors: bacterial pericarditis murmur: probable valvular disease High blood pressure
TB meningitis	• Weight loss, night sweats, fever CSF clear with high protein, low glucose and lymphocytes and negative for Ag crypto or Indian ink • Evidence of TB elsewhere	Other causes of meningitis, especially cryptococcal meningitis, bacterial meningitis, etc.

TB treatment regimens

There are several possible regimens depending on the patient's diagnostic category (Table 50).

Table 30. TB treatment regimens

Diagnostic category	Patient category	Treatment regimens	
		Intensive phase	Continuation phase
New case	All new patients: • PTB smear positive • PTB smear negative • EPTB	2 RHEZ	4 RH

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, and then consider the possibilities given in Table 51.

Table 51. Possibilities for treatment failure

Original diagnosis	Possibilities
Sputum smear negative PTB	Incorrect diagnosis. For example: • Other pathogens (pneumocystis pneumonia, bacterial pneumonia, mycoses, e.g., cryptococcus, Kaposi'ssarcoma,CMV), heart failure • Chronic obstructive airways disease • DR-TB • IRIS
Sputum smear positive PTB	• Superimposed infection with other pathogens • DR-TB • Lung abscess (empyema) • IRIS

[35]The Rivalta Test is a simple and inexpensive method that can be used in resource-limited settings to differentiate a transudate from exudates.

For a patient with suspected EPTB, who has 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 is 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.

IRIS may occur in 33% of patients diagnosed with TB and who have been started on ART. It typically presents within three months of the initiation of ART but can occur as early as five days. Patients with TB-associated IRIS most commonly present with fever and with worsening of pre-existing lymphadenopathy or respiratory disease. The symptoms are like the paradoxical reactions seen in immuno-competent patients on ATT but occur more frequently.

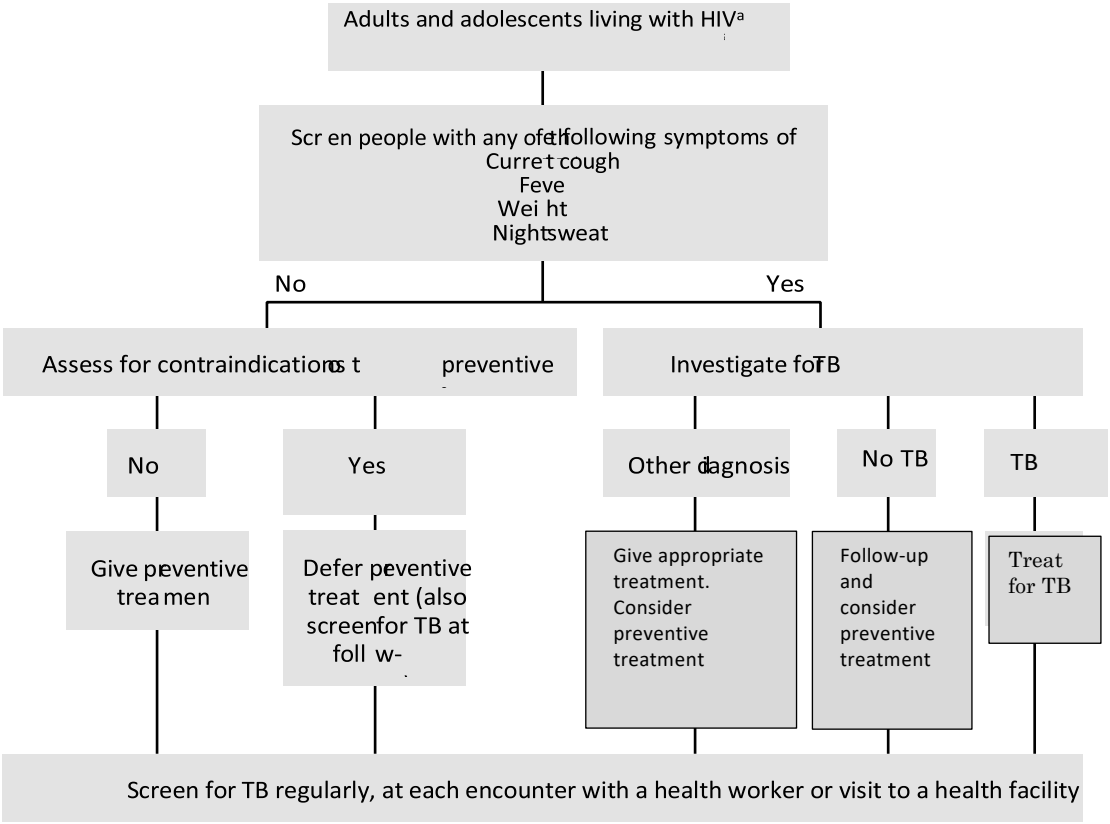
Most cases resolve without any intervention and ART can be safely continued. Serious reactions, such as tracheal compression caused by massive adenopathy or respiratory difficulty, may occur.

Therapy may require the use of anti-inflammatory drugs, including corticosteroids.

TPT guideline on adults and adolescent living with HIV

The algorithm for TB screening (Fig. 14) in adults and adolescents living with HIV is based on recommendations published in the recently updated WHO guidelines on LTBI.

Fig. 14. Algorithm for screening adults and adolescents living with HIV for TB



Note:

[a] 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 in which care is provided. [b] Chest radiography can be done if available, particularly for people living with HIV on ART, but is not required to classify patients into TB and non-TB groups.
Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. History of TB and current pregnancy should not be contraindications for starting preventive treatment.
[d] Xpert MTB/RIF should be used as the initial diagnostic test for TB.

Children living with HIV

Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a case of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age.

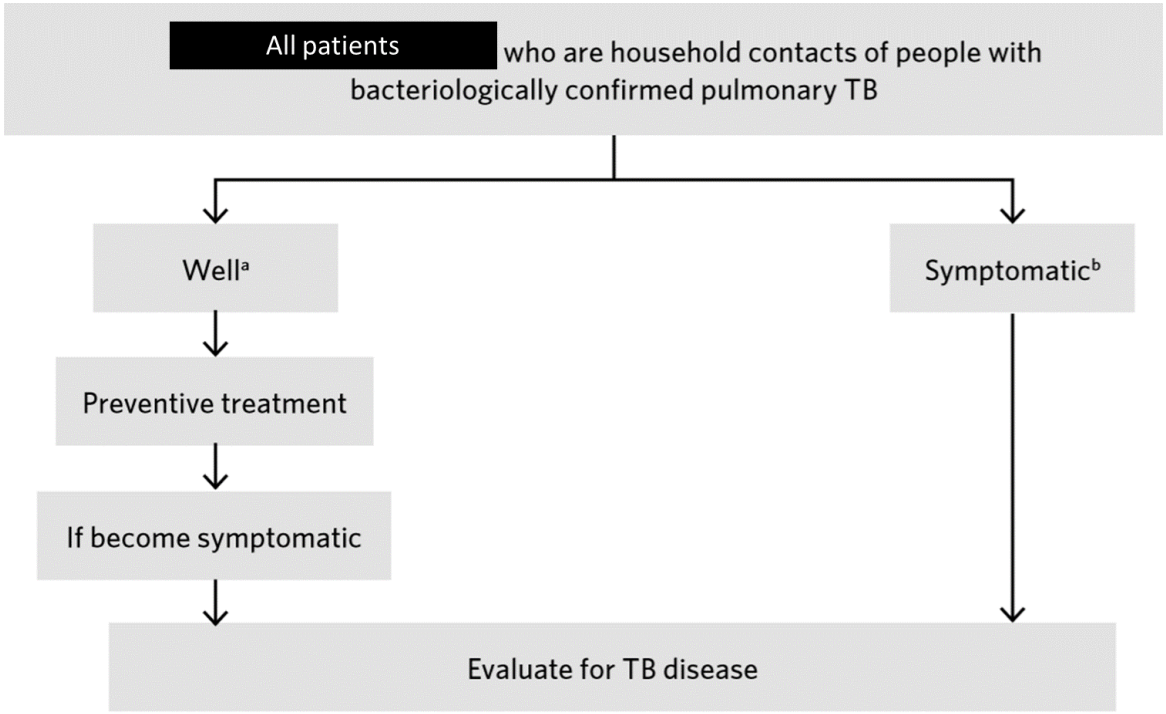
Poor weight gain is defined as reported weight loss, very low weight-for-age (< –3 z-score), underweight (weight forage < –2 z-score), confirmed weight loss (> 5% since the last visit or growth curve flattening)

Children and infants < 1 year of age should be given preventive treatment only if they have a history of household contact with a TB case and active TB has been excluded in investigations.

HIV-negative household contacts of a person with PTB

On reviewing the evidence and considering the field conditions in Timor-Leste, and high TB incidence rate (498/100000), the country consultation process during the guidelines revision workshop in May 2019 concluded that the implementation of a simple algorithm for ruling out active TB in household contacts before preventive treatment initiation would be feasible in the country. The algorithm can be used by health workers at peripheral level. Research on symptom-based screening of children's TB contacts indicates that this contact management strategy is safe and more feasible in resource-limited settings than contact screening based on diagnoses. The algorithm should, therefore, be used for HIV-negative household contacts of persons with pulmonary TB of all ages (Fig. 15).

Fig. 15. Algorithm for screening HIV-negative household contacts of a person with pulmonary TB



Note. [a] Patients must be free of any TB and non-TB related symptoms to be considered well. [b] The most common TB-related symptoms are persistence of cough, fever, weight loss and night sweats.

Treatment for LTBI

Based on recommendations published in the recently updated WHO guidelines on LTBI, the NTP will use the following drug regimens for at-risk populations that should receive LTBI treatment:

PLHIVs

- Weekly rifapentine plus isoniazid for 3 months (3HP)

A new systematic review was conducted to compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid with that of isoniazid monotherapy. The review covered 4 RCTs, of which 2 RCTs involved adults with HIV from South Africa, Peru and in several countries with a low incidence of TB. No significant difference was found in the incidence of active TB between participants (adults with HIV infection, adults without HIV infection and children) given a 3-month weekly regimen of rifapentine plus isoniazid and 6 or 9 months of isoniazid monotherapy. Furthermore, the risk for hepatotoxicity was significantly lower with the 3-month weekly regimen of rifapentine plus isoniazid in adults with HIV.

HIV-negative household contacts of a person with PTB

- Weekly rifapentine plus isoniazid for 3 months (3HP) for children above 2 years

This is based on recommendations published in the recently updated WHO guidelines. The advantage of 3HP is minimum number of doses (12) among other regimens, and hence higher acceptability, well-tolerated, high treatment completion rate, and higher efficacy than other INH and INH-Rifampicin combined regimens. 3HP would likely be most suitable in Timor-Leste settings where the need of preventive treatment coverage and its completion is relatively higher than other regions.

It is crucial to strengthen household contact investigations in contacts above 2 years by using the following regimen:

- Weekly rifapentine plus isoniazid for 3 months (3HP) for children above 2 years. In case, rifapentine is not available, daily rifampicin plus isoniazid for 3 months (3RH) should be provided.

For children contacts below 2 years, daily rifampicin plus isoniazid for 3 months (3RH) should be provided. This regimen is based on recommendations published in the recently updated WHO guidelines indicating that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid.

For adult contacts 3HP is recommended considering the ease of administration (once weekly, 12 doses instead of daily 90 doses of 3RH). In the long term 3HP (1 HP when it is formally recommended by WHO) may be the regimen to aim for considering treatment duration.

The shorter treatment duration is expected to facilitate the implementation of LTBI treatment in the country-specific conditions in Timor-Leste.

ART initiation in HIV-TB coinfection

In the absence of ART, TB therapy alone neither significantly increase the CD4 cell count, nor significantly decrease the HIV VL. Thus, CD4 counts measured during active TB are likely to reflect the actual level of immunosuppression. As with all PLHIVs, those who are diagnosed with TB/HIV coinfection should be on ART and CPT as part of the standard package of care for PLHIVs (Table 52).

Table 52. Timing of ART initiation in HIV--TB coinfection

Criteria	Action
Patients who are not yet on ART	• Start TB treatment immediately • Initiate ART as soon as anti-TB medications are tolerated, preferably within 2 weeks; for TB meningitis consider delaying ART for up to 8weeks • Monitor closely for IRIS
Patients who are already on ART	• Start TB treatment immediately • Continue ART, making any required adjustments to the ART regimen based on drug–drug interactions • Monitor closely for IRIS
Patient being treated concurrently for TB and HIV requires close monitoring for toxicity	• MDR-TB and HIV coinfection should be managed in settings where close toxicity monitoring and follow-up by experienced clinicians are possible • Patients on TDF and aminoglycosides are at high risk for renal toxicity and require close monitoring

The ART regimens would need to be modified in case of HIV--TB coinfection. With the Dolutegravir-based regimens now in place , concomitant use of rifampicin needs dose adjustment.. The preferred ART regimens are summarized in Table 53.

Table 53. Preferred ART regimens in HIV--TB coinfection

Age	First-line ART regimen in HIV--TB coinfection
< 4 weeks	Start anti-TB treatment immediately; start ART after 4weeks of age, once tolerating anti-TB drugs
4 weeks < 3 years	• ABC + 3TC + LPV/r + RTV (additional ritonavir) • After completion of TB treatment, revert to the recommended first-line regimen (ABC + 3TC + LPV/r)
3–10 years	ABC + 3TC + EFV
> 10 years	• Give TDF/3TC/DTG FDC am + DTG 50mg pm for duration of rifampicin-containing TB treatment and for an additional 2 weeks after TB treatment is completed, then revert to TDF/3TC/DTG FDC OD • Alternate TDF + 3TC + EFV
Pregnant women	• TDF+3TC+DTG • Put on TB treatment as early as possible after detection. Follow adult guidelines for all other issues

Chapter 8

Post-exposure prophylaxis (PEP)

PEP is short-term use of ART to reduce the likelihood of HIV infection after potential exposure. Health care workers(HCWs) are prone to accidental exposure to blood and other body fluids or tissues in their day to day working. There are many factors that contribute to the increased risk of occupational HIV exposure. First, with the scale-up of HIV testing services (HTS) and ART services more and more people with HIV are coming in contact with health care personnel (HCP). Second, as PLHIVs receiving ART benefit from living longer, they are more likely to survive and their chances of coming in contact with the HCP are increasing, and thus the increased chances of accidental exposure to HIV-infected blood and other body fluids.

In order to avoid exposure to HIV, precautions should be taken when handling possibly contaminated body fluids including the use of appropriate barriers such as gloves, gowns and goggles; care with sharps including minimizing blind surgical procedures and proper handling and disposal of sharps; safe disposal of contaminated waste; safe handling of soiled linen; adequate disinfection procedures and universal hepatitis B vaccination of nonimmune at risk groups including HCWs, police, prison staff and rescue workers. These are collectively referred as '*Standard Precautions*'.

Some definitions

'***Exposure***', which may place an HCP at risk of blood-borne infection, is defined as:

- A percutaneous injury (e.g., needle-stick or cut with a sharp instrument)
- Contact with the mucous membranes of the eye or mouth
- Contact with nonintact skin (when the exposed skin is chapped skin or afflicted with dermatitis)
- Contact with intact skin when the duration of contact is prolonged with blood or other potentially infectious body fluids.

'Occupational exposure' refers to exposure to potential blood-borne infections (HIV, HBV and HCV) that occurs during performance of job duties.

'Non-occupational exposure' refers to exposure to potential blood-borne infections (HIV, HBV and HCV) outside of the workplace setting like unsafe sex and sexual assault.

'Post-exposure prophylaxis (PEP)' refers to the comprehensive management instituted to minimize the risk of infection following potential exposure to blood-borne pathogens (HIV, HBV and HCV).This includes first aid, counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, depending on the risk assessment, the provision of short term (4 weeks) of ARV drugs, with follow-up and support, including maintaining confidentially.

Table 54. Risk of exposure from different body fluids

Exposure to body fluids considered 'at risk'	Exposure to body fluids considered 'not at risk,' unless these fluids contain visible blood
• Blood • Semen • Vaginal secretions • Cerebrospinal fluid • Synovial, pleural, peritoneal, and pericardial fluid • Amniotic fluid • Other body fluids contaminated with visible blood	• Tears • Sweat • Urine and faeces • Saliva • Sputum • Vomitus

For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of HIV infection after human bites has been rarely reported.

The average risk of acquiring HIV infection following different types of occupational exposure is low compared to the risk of acquiring infection with HBV or HCV. In terms of occupational exposure, the important routes are needle stick exposure (0.3% risk for HIV, 9–30 % for HBV and 1–1.8% for HCV) and mucous membrane exposure (0.09% for HIV). The estimated per act probability of acquiring HIV from an infected source by exposure route is presented in Table 55.

Table 55. Risk of transmission of HIV virus through different routes from an infected source

Exposure route	Risk per10000 exposures	95% CI
Parenteral exposure		
Blood transfusion (infected blood)	9250 (92.5%)	8900-–9610
Needle-sharing injection drug use	63 (0.63%)	41–92
Percutaneous needle stick	23 (0.23%)	0–46
Sexual exposure		
Receptive anal intercourse	138 (1.38%)	102–186
Insertive anal intercourse	11 (0.11%)	4–28
Receptive penile vaginal intercourse	8 (0.08%)	6–11
Insertive penile vaginal intercourse	4 (0.04%)	1–14
Receptive oral sex	Low	0–4
Insertive oral sex	Low	0–4
Vertical transmission		
Mother-to-child transmission	2260 (22.6%)	1700–2900

Source: Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014;28(10):1509-–19. doi: 10.1097/QAD.0000000000000298. PMID: 24809629; PMCID: PMC6195215.

Practices that influence risk of occupational exposure

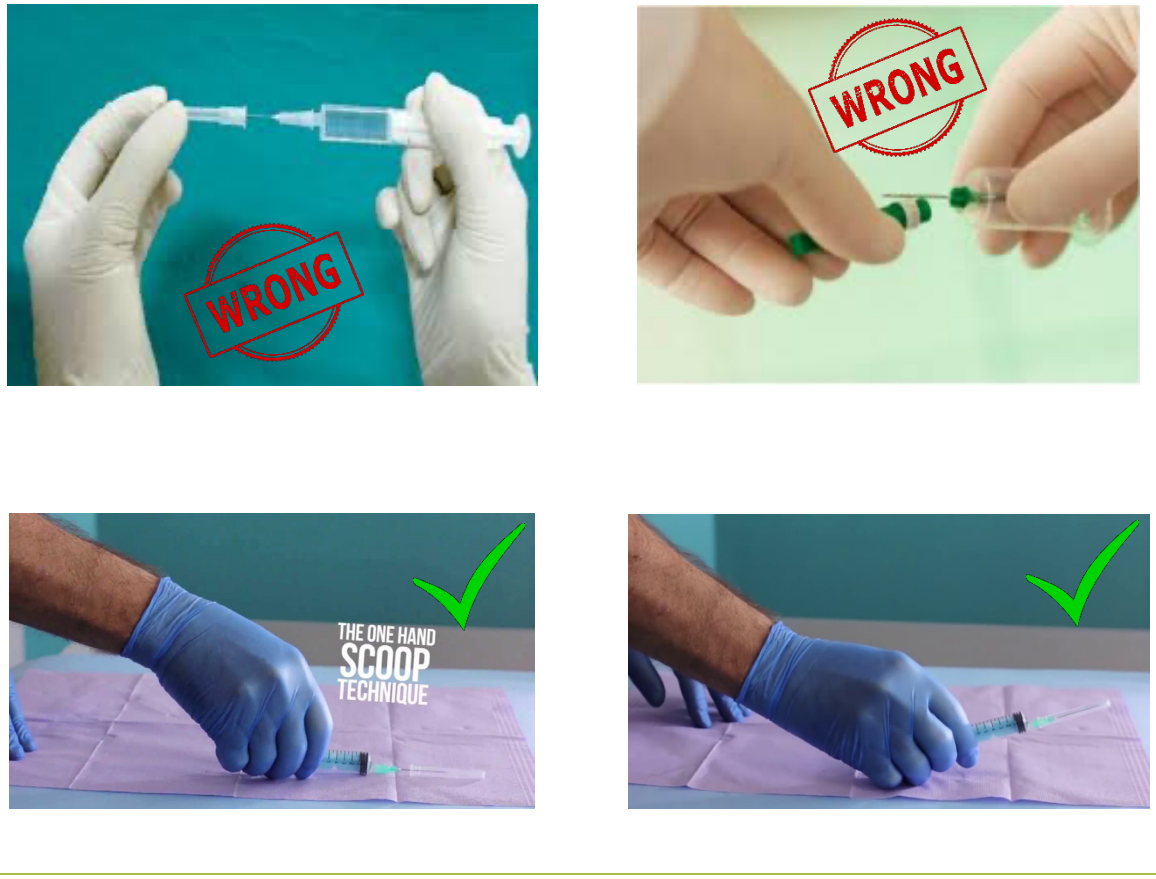
Certain work practices increase the risk of needle stick injury such as:

- Recapping needles (most dangerous)
- Transferring a body fluid between containers
- Handling and passing needles or sharps after use
- Failing to dispose of used needles properly in puncture-resistant sharps containers
- Poor healthcare waste management practices.

Steps to protect oneself from occupational exposure

- Strict compliance with Standard Precautions (earlier referred as Universal precautions)Annex 11: Standard Precautions in Health Care
- Avoid the use of injections where safe and effective alternatives are available, e.g., oral, drugs
- Avoid recapping needles
- Plan for safe handling and disposal of needles after use
- Promptly dispose of used needles in appropriate sharps disposal containers
- Report all needle stick and sharps-related injuries promptly to ensure that you
    - Receive appropriate follow-up care
    - Participate in training related to infection prevention
    - Use devices with safety features provided by the institute (wherever possible)

- Record and monitor injuries with an injury register in each location of healthcare setting.



Photograph 1. Recapping of needles - the right and wrong way

Management of exposure person

Step 1: Management of exposure site--First Aid

For skin—if the skin is pierced by a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin with water and soap and rinse
- Do not scrub
- Do not use antiseptics or skin washes
- Don't use bleach, chlorine, alcohol and betadine.

After a splash of blood or body fluids:

Unbroken skin:

- Wash the area immediately
- Do not use antiseptics.

For eye:

- Irrigate exposed eye immediately with water or normal saline
- Sit in a chair, tilt the head back and ask a colleague to gently pour water or normal saline over the eye
- If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again
- Do not use soap or disinfectant on the eye.

For mouth:

- Spit fluid out immediately
- Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times
- Do not use soap or disinfectant in the mouth
- Consult the designated physician of the institution for management of the exposure immediately.

Step 2: Establish eligibility for PEP



Assess the chances of HIV or HBV/HCV transmission risk. If reasonable risk is found, the person should be eligible for PEP.

PEP should be ideally started within 2 hours after exposure. It is effective till 72 hours and not effective at all after 72 hours.

A designated person/trained doctor must assess the risk of HIV and HBV transmission following an accidental exposure. This evaluation must be made rapidly, so as to start any treatment as soon as possible after the accident. The assessment must be made thoroughly (because not every accidental exposure requires prophylactic treatment).

The exposed individual should have confidential counselling and assessment by an experienced physician. S/he should be assessed for **pre-existing HIV infection**.

Step 3: Counselling for PEP

For an informed consent, exposed persons (clients) should receive appropriate information about what PEP is and its risk and benefits. It should be clear that PEP is not mandatory. The client should understand details of window period, baseline test, drugs that are used, their safety and efficacy, and issues related to these drugs during pregnancy and breastfeeding.

S/he should be counselled on safe sexual practices till both baseline and 3months' HIV test are found to be negative.

Step 4: Assessing need for PEP and prescribing PEP

The decision on the need for PEP for HIV (following an occupational exposure in health care worker) will depend on the exposure as well as source person's HIV status and the extent of disease, if the source has been confirmed positive.

Step 5: Recommended regimens

A three-drug HIV PEP Kit is available. It contains two separate combinations:

- Tab tenofovir disoproxil fumarate(TDF) 300mg + lamivudine (3TC) 300mg and tab dolutegravir 50 mg to be taken once daily. The duration is for 28 days
- It also contains: Pregnancy detection kit and emergency contraception pill (Levonorgestrel – 75 mg).

Chapter 9

HIV-Hepatitis coinfection

HIV and HBV have similar transmission routes. Acute HBV infection in HIV positive people is associated with increased risk of chronicity, reduced chances of spontaneous clearance, higher rates of replication and reactivation, and therefore increased incidence of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Additionally, HIV/HBV coinfection has been associated with rapid HIV disease progression and poorer HIV treatment outcomes. Other complications of HIV/HBV coinfection include increased incidence of drug-related hepatotoxicity, drug--toxin interactions and ART-related immune reconstitution hepatitis.

The term **Acute HBV infection** refers to new-onset hepatitis B infection that may or may not be icteric or symptomatic. Diagnosis is based on detection of hepatitis B surface antigen (HBsAg) and IgM antibodies to hepatitis B core antigen (anti-HBc). Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs (antibodies to hepatitis B surface antigen), usually within 3 months.

The term **Chronic HBV infection** is defined as persistence of hepatitis B surface antigen (HBsAg) for 6 months or more after acute infection with HBV. Around 20–40% of PLHIVs will fail to clear HBV beyond 6months and will become chronically infected.

Evaluation of HIV and hepatitis B coinfected persons

The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg. Those found positive for hepatitis B surface antigen should be evaluated further following the guidelines for evaluation of those with hepatitis B infection.

Look for signs of cirrhosis and hepatic decompensation like jaundice, conjunctival haemorrhages, anaemia, spider angioma, palmar erythema, petechiae, clubbing, gynaecomastia, testicular atrophy, parotid enlargement, asterixis (liver flaps, flapping tremors), caput medusa, ascites, oedema, longitudinal veins alongside of abdomen, hepatomegaly, hepatic bruit, venous hum and splenomegaly.

The lab investigations, besides routine haemogram and chemistry, should specifically include liver function tests (LFT), prothrombin time, alpha-fetoprotein (AFP), ultrasound and upper GI endoscopy. The virological examination should include HBeAg--marker of HBV replication and infectivity, anti-HBe antibody and HBV DNA quantitative (Real-time PCR).

A non-invasive technique to assess liver cirrhosis like transient elastography (FibroScan®) is available in HNGV in Timor-Leste. FibroScan® is a specialised ultrasound machine that measures fibrosis (scarring) and steatosis (fatty change) in liver. Fatty change is when fat builds up in your liver cells. It is a very good tool to measure the stiffness of liver and thus give a fair assessment of the stage of liver cirrhosis. Table 56provides guidance to the level of fibrosis based on FibroScan® results.

Table 56. Interpreting FibroScan(R) results in different liver diseases

Disease	F0--F1	F2	F3	F4
Hepatitis B	2–7 kPa	8–9 kPa	8–11 kPa	18 kPa or higher
Hepatitis C	2–7 kPa	8–9 kPa	9–14 kPa	14 kPa or higher
HIV/HCV coinfection	2–7 kPa	7–11 kPa	11–14 kPa	14 kPa or higher
Cholestatic disease	2–7 kPa	7–9 kPa	9–17 kPa	17 kPa or higher
Nonalcoholic fatty liver disease (NAFLD or NASH)	2–7 kPa	7.5–10 kPa	10–14 kPa	14 kPa or higher
Alcohol-related disease	2–7 kPa	7–11 kPa	11–19 kPa	19 kPa or higher

Source: Understanding your FibroScan® Results. Memorial Sloan Kettering Cancer Centre. Patients and Caregivers (https://www.mskcc.org/cancer-care/patient-education/understanding-your-fibroscan-results,accessed 29 September 2019).

In case of non-availability of FibroScan® machine, APRI score, i.e., Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) can be calculated to estimate the hepatic fibrosis based on a formula derived from AST and platelet concentrations. The formula is as follows:

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

Another method is to use FIB-4 score, index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations and age. The formula for calculating the score is given above.

Treatment of HIV and hepatitis B coinfected patients

A detailed algorithm of WHO recommendations on the management of persons with chronic hepatitis B infection is given in Annex 10. Management of chronic hepatitis B infection – WHO .

The indications for antiviral treatment in chronic hepatitis B (CHB) are as below:

- All adults, adolescent, children with CHB and clinical evidence of compensated/decompensated cirrhosis (or APRI score >2 in adults) should be treated, regardless of ALT, HBeAg status, HBV DNA levels
- Treatment is recommended for adults with CHB, who do not have clinical evidence of cirrhosis (or based on APRI score ≤ 2 in adults), but are aged > 30 years and have persistently elevated ALT levels and evidence of high-level HBV replication (HBV DNA > 20000 IU/ mL) regardless of HBeAg status
- If HBV DNA testing is unavailable, but patients have persistently elevated ALT, treat for hepatitis B regardless of HBeAg status.

The management guidelines for HIV and hepatitis B coinfection are summarized in Table 57.

Table 57. Management guidelines for HIV and hepatitis B coinfection

Criteria	Details
When to start ART?	All persons diagnosed with HIV infection should be initiated on ART regardless of CD4 count or WHO clinical staging or age group or population sub-groups
Choice of regimen	Nucleoside analogues with activity against both HIV and HBV such as 3TC and TDF should be included in the first-line ART regimen for HIV-infected patients who are HBsAg-positive (and HBeAg-positive, if known) In view of higher incidence of hepatotoxicity with NVP in coinfected patients, it is preferable to use EFV unless contraindicated DTG can be used when introduced and scaled up. However, it is planned to be introduced in a phased manner and thus not being put as the preferred drug in the regimen

Preferred regimen	TDF +3TC +EFV (TDF may be replaced by AZT in case of TDF toxicity or contraindications)
Second-line regimen	TDF and 3TC should be continued as part of the second-line ART following initial ART failure, even if it was used in the first-line regimen
HBV resistance	Ideally, 3TC should be used either with TDF or not at all, because HBV resistance to 3TC develops quickly. HBV resistance to 3TC develops in 50% of patients after two years and in 70% after four years of treatment, if 3TC is the only active anti-HBV drug in the ART regimen
Therapy outcomes	HBV seroconversion (loss of HBeAg and development of HBeAg) occurs in 11–22% of HBeAg-positive HIV-infected patients who are treated with 3TC containing regimen for one year
Hepatic flares	HBV flares on ART start soon after the initiation of ART as a manifestation of IRIS. Discontinuation of 3TC may also result in hepatic flares

Prevention of HBV infection

The risk of HBV infection could be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg and immunized, if not infected. Those already infected with HBV (HBsAg positive) do not require HBV vaccine. Those who are surface antigen negative need to be vaccinated against hepatitis B, besides following other precautions(Table 58).

Table 58. Treatment regimen for hepatitis B infection

Vaccine type	Dose (intramuscular)	Schedule
Adjuvanted HBV vaccine	Standard dose (0.5–1mLas appropriate	'0' dose followed by dose on 1, 2 and 6 months
Nonadjuvanted HBV vaccine	Double the dose	

HIV and HCV coinfection

Viral hepatitis C infection is associated with significant morbidity and mortality. Chronic HCV infection can cause a wide spectrum of liver disease, potentially leading to severe liver damage, including cirrhosis, organ failure and hepatocellular carcinoma. It accounts for nearly 12–32% of all cases of liver cancer and 10–20% cases of liver cirrhosis, both of which have high treatment costs and poor outcomes.

HIV-positive persons at risk of HCV coinfection should be identified and offered HCV treatment. The recent introduction of direct acting antiviral therapies (DAAs) for treatment of HCV has simplified the management of HIV/HCV coinfection, making it possible to manage uncomplicated HIV/HCV infection safely even in primary care settings.

Screening

HCV serology should be offered to individuals at risk of HCV infection. These include:

- People who inject or use drugs (limited in Timor-Leste)
- Persons who have had tattoos, body piercing or scarification procedures from settings of doubtful infection prevention precautions
- Children born to HCV positive mothers.

Up to 45% of individuals who are infected with HCV spontaneously clear the infection. HCV positive individuals should be offered nucleic acid HCV RNA testing to establish presence of chronic HCV infection.

Prevention

General measures for prevention of bloodborne infections are effective in preventing HCV transmission as given below:

1. Recommendations for healthcare settings

- Hand hygiene: including surgical hand preparation, handwashing and use of gloves
- Safe handling and disposal of sharps and waste
- Effective disinfection and sterilization
- Provision of safe blood and blood products
- Training of healthcare providers.

2. Recommendations for prevention of sexual transmission

- Correct and consistent condom use
- Access to prevention services for sex workers and other people at risk (including screening and treatment STIs, frequent testing for HIV and HCV)
- Treatment of HIV/HCV coinfection.

Chapter 10

Other comorbidities in HIV and their management

Screening and management for NCDs in PLHIVs

There is high incidence of mortality and morbidity associated with NCDs such cardiovascular diseases (CVDs), diabetes, liver diseases, kidney diseases, etc. because of high inflammatory state due to HIV infection, and side-effects of some ARVs also.

Traditional risk factors for cardiovascular diseases include: 1) tobacco use; 2) alcoholism; 3) poor food habits; 4) obesity; 5) physical inactivity; 6) familial history; 7) age, etc. Many of the factors can be modified, but many are hereditary.

This section provides a brief overview of the management of NCDs. For more details, the reader is referred to more comprehensive management guidelines for each of these diseases.

CVDs

CVDs such as hypertension, cerebrovascular accidents, myocardial infarction are common in HIV infected, if risk factors are present. Smoking is the single-most common cause of increase in cardiovascular diseases and as such measures to address this issue will be of importance to prevent untimely deaths and morbidity.

Lifestyle modification including tips to quit cigarette smoking is beneficial. Table 59provides 'leads' to address this issue.

Table 59. Suggested steps in lifestyle modification in adult PLHIVs with CVD risk

Smoking cessation
❖ Smoking cessation has multiple short-and long-term benefits, including • Reduced premature aging/wrinkling of skin • Improved fitness and quicker recovery from common infections • Reduced risk of respiratory infections and chronic lung disease • Reduced risk of high blood pressure, diabetes, kidney disease, heart disease, and stroke • Improved infant outcomes (for pregnant women who smoke) • Reduced risk of cancers: lung, bladder, breast, mouth, throat, oesophagus • Better response to ART (better viral suppression) • Reduced risk of developing TB or dying from TB
❖ Tobacco dependence treatment and cessation programmes should combine behavioural/counselling support with pharmacotherapy treatment where necessary and available. For further details on cessation interventions, refer to the Tobacco control guidelines for Timor-Leste
Dietary changes and weight loss
❖ Weight loss to maintain a healthy BMI (nutritionists to be engaged in patient care)
❖ Drink at least 8 glasses of water per day
❖ Reduce/abstain from alcohol
❖ Decrease sugar intake
❖ Reduce red meat intake
❖ Cut down consumption of fatty foods, fat for flavouring and fried foods
❖ Increase intake of whole grains, vegetables, fruit and beans
❖ Increase intake of fish
❖ Consume less than 5 g (just under a teaspoon) of salt per day
Physical activity
❖ Active lifestyle with moderate-intensity physical activity
❖ 30 minutes of aerobic activity such as brisk walking, at least 5 days per week

Hypertension is common in Timor-Leste. It is diagnosed when the average systolic blood pressure is 140 mmHg or higher, or when the average diastolic blood pressure is 90 mmHg or higher, taken on two or more separate days.[36] The suggested screening steps and management measures are presented in Table 60**.**

Table 60. Management of hypertension for adult PLHIVs

Screening
❖ BP should be measured and recorded for every adult at every visit
Diagnosis
❖ Hypertension requiring intervention is defined as BP ≥ 140/90 mmHg on two or more separate days
Investigations of patients with hypertension
❖ Urine analysis to access kidney disease and diabetes ❖ Creatinine, Na, K: to assess for kidney disease (Referral Hospitals (RHs) and HNGV) ❖ Blood glucose: to assess for diabetes (All CHCs, RHs and HNGV) ❖ Complete blood count: anaemia may indicate chronic kidney disease ❖ Lipid profile: dyslipidaemia is a cardiovascular risk factor (Available in RHs and HNGV) ❖ ECG: to assess for cardiac pathology including cardiomegaly, ventricular dysfunction, ischemic heart disease, etc. (Available in RHs and HNGV)
Management of hypertension
❖ If baseline BP is 120--139/80-89 (prehypertension) • Lifestyle modification, along with monthly BP monitoring ❖ If baseline BP is 140--159/90--99 • Lifestyle modification (Table 20) for up to 6 months, along with monthly BP monitoring ❖ If does not meet treatment target with lifestyle modifications, then add drugs to lifestyle modification • In PLHIVs without kidney disease or diabetes, first-line antihypertensive therapy is a thiazide diuretic such as hydrochlorothiazide starting at 12.5 mg OD (maximum dose 25 mg OD) OR a calcium channel antagonist such as amlodipine starting at 2.5 mg OD (maximum 10 mg OD) • In PLHIVs with kidney disease or diabetes, the first antihypertensive should be an ACE-I such as Captopril or Enalapril 2.5--10 mg OD (maximum dose is 20 mg BD); with referral to a physician, if available • Introduce one drug at a time. If the target blood pressure is not reached within one month after initiating therapy, the dosage of the initial medication should be increased. Titrate to maximum recommended dosage (if tolerated) before adding an additional drug • If inadequate response once dose has been titrated, an additional agent may be required, e.g., hydrochlorothiazide starting at 12.5 mg OD (maximum dose 25 mg OD) • If inadequate response to two agents, consider consultation with or referral to a physician *Note*: Calcium-channel blockers have known drug interactions with PIs and NNRTIs and should be used with caution. ACE-I and thiazide diuretics do not have significant interactions with ARVs. ❖ If baseline BP ≥ 160/100 mmHg • Initiate lifestyle modifications and introduce antihypertensive medications concurrently

[36]WHO Western Pacific Region, Korean Ministry of Health and Welfare and Community Care Project, Korea. Diagnosis and management of patients with hypertension. a non-communicable disease education manual for primary care professionals and patients. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=2ahUKEwi_zJD426vlAhWUTX0KHRZ1C0kQFjABegQICxAG&url=https%3A%2F%2Fapps.who.int%2Firis%2Frest%2Fbitstreams%2F1147546%2Fretrieve&usg=AOvVaw39eYMws6ehuvtTfKRAZfDK.

Grading of hypertension

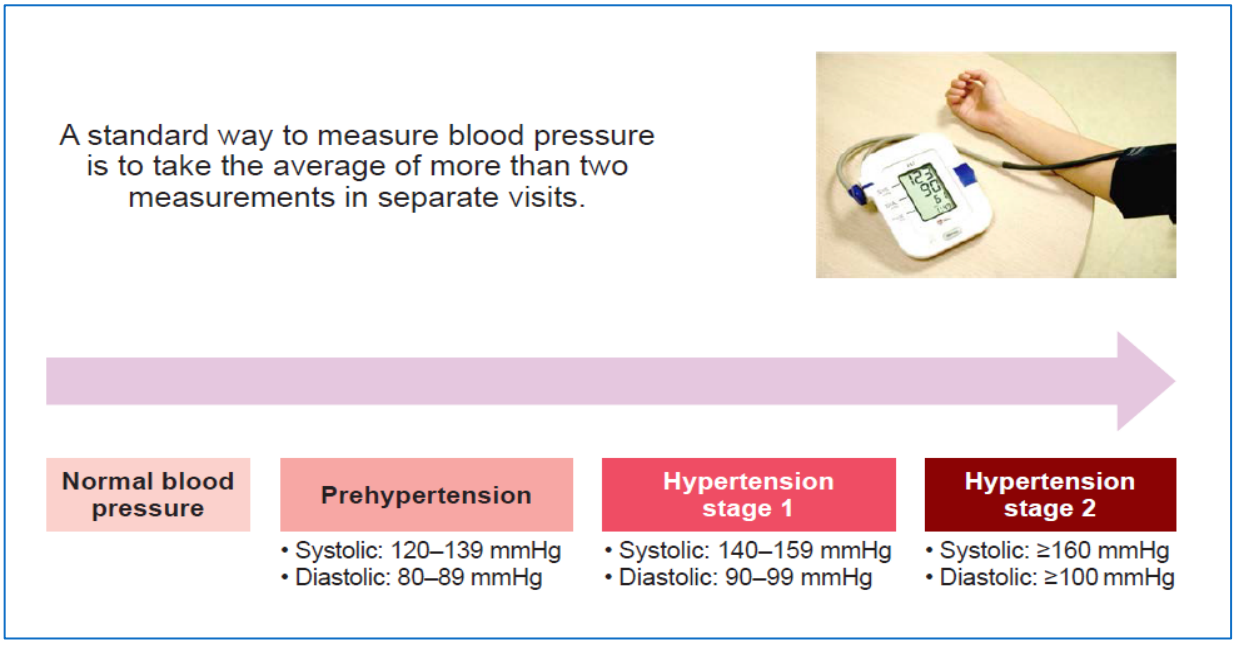


Fig.12. Stages of hypertension - WHO

Source: WHO Western Pacific Region, Korean Ministry of Health and Welfare and Community Care Project, Korea. Diagnosis and management of patients with hypertension. a non-communicable disease education manual for primary care professionals and patients. 2017

Diabetes

Diabetes is common in Timor-Leste. Part of WHO Package of Essential Noncommunicable Disease Interventions (PEN), diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads to major damage to the heart, blood vessels, eyes, kidneys, and nerves over a period. The most common is type 2 diabetes (NIDDM[37]), occurring in adults. The body becomes resistant to insulin or doesn't make enough insulin. In the past three decades, the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. Management of diabetes in adult PLHIVs is given in Table 61.

STEPS survey done in Timor-Leste in 2014 shows that 1.5% of all respondents had raised fasting blood sugar levels.[38]

Table 61. Management of diabetes in adult PLHIVs

Screening
❖ Blood glucose (fasting or random) should be evaluated at baseline for all PLHIVs, then annually if baseline screening is normal; urine dipstick for protein and glucose can be used if blood glucose testing is not available
Diagnosis
❖ Diabetes Mellitus is defined as fasting blood sugar ≥ 7.0 mmol/L (126 mg/dL), or random blood sugar ≥ 11.1 mmol/L (199.9 mg/dL), or HbA1c> 6.5%, or oral glucose tolerance test ≥ 11.1 mmol/L (199.8 mg/dL) ❖ Abnormal results should be repeated to confirm the diagnosis, particularly for patients without symptoms of diabetes (such as 3 Ps -- polyuria, polydipsia, polyphagia, weight loss)
Management of diabetic patients
Treatment targets: HbA1C ≤ 7.0% or fasting blood sugar levels of 4 – 7 mmol/L (70-126 mg/dL)

[37]NIDDM – Noninsulin dependent diabetes mellitus.
[38]Noncommunicable diseases risk factors: STEPS survey Timor-Leste.WHO SEARO, MoH TL and UNTL. 2014 (https://apps.who.int/iris/bitstream/handle/10665/204496/Timor-Leste_2014_STEPS_FactSheet.pdf?sequence=1&isAllowed=y, accessed 18 September 2019).

- ❖ For patients with pre-diabetes (abnormal results but does not meet criteria above for diabetes) monitor FBS or HbA1C every three months and encourage lifestyle modifications
- ❖ For patients with diabetes, monitor $HbA1_C$ (or FBS if $HbA1_C$ not available) every three months
- ❖ Lifestyle modification (weight loss, nutritional support to manage portion sizes and calculate glycaemic index of various foods to help with control of blood sugar) for 3--6 months
- ❖ If does not meet treatment target with lifestyle modifications, then add drugs
  - Metformin
    - Obtain baseline creatinine; do NOT use metformin if creatinine clearance <45 mL/min
    - Start with low dose (500 mg OD or BD) and titrate up every 1--2 weeks until reaches 1 g BD (or maximum tolerated dose if less than 1 g BD)
  - If does not meet treatment targets with metformin for 3--6 months at maximum tolerated dose, then consider adding drug from another class (such as glibenclamide) and/or specialist consultation. Some patients may require insulin
    Note: DTG may increase metformin plasma levels: monitor blood glucose levels; dose reduction of metformin may be required, and maximum daily dose of metformin should be 1g
  - At every visit: A thorough history (to elicit features of hypoglycaemia, other CVD risk factors, neuropathy, diabetic foot ulcers) and a physical exam (for BP, neuropathy, foot ulcers)
- ❖ Additional routine screening for patients with diabetes
  - Annual ophthalmology examination for diabetic retinopathy (HNGV or RHs)
  - Annual urinalysis: start on an ACE-I/ARB if proteinuria develops (even if BP normal)
    Note: Patients with DM are at increased risk of developing TB.

Chronic kidney disease (CKD)

Kidney diseases are common in Timor-Leste. Anecdotal evidence suggests that it may be multifactorial causality. Low water intake, chronic urinary tract infection (UTI), and high total dissolved solids in water may be the primary cause. Familial kidney diseases have not been investigated, and so glomerulopathies cannot be commented upon.

In screening for CKDs, patients who are at a higher risk of developing renal disease include: 1) pre-existing renal disease; 2) hypertension; 3) diabetes mellitus; 4) severe wasting (weight below 60 kg in adults);5) age > 45 years; 6) WHO stage 3 or 4; 7) low CD4 count or high HIV VL; and 8) concomitant nephrotoxic agents. Additionally, glomerular disease directly related to HIV infection, commonly known as HIV-associated nephropathy (HIVAN), is an important cause of CKD among PLHIVs.

Prevention, early identification and management of kidney disease are important to reduce the burden of dialysis and other complications (Table 62).

Table 31. Management of chronic kidney disease in adult PLHIVs

Screening
❖ Urinalysis (for protein) and serum creatinine should be evaluated at baseline for all PLHIVs and monitored annually
Diagnosis
❖ Impaired renal function is defined as creatinine clearance < 90 mL/min, or dipstick proteinuria ≥ 1 ❖ Abnormal results should be repeated to confirm diagnosis ❖ CKD is defined as evidence of kidney damage that persists for at least 3months
Management of diabetic patients
❖ Management depends on the cause of the renal impairment; additional investigations and/or specialist consultation may be required ❖ Consultations with a physician is recommended ❖ Treat dehydration promptly and aggressively ❖ If on TDF-containing regimen, substitute with another ARV, if CrCl<50 mL/min with the exception of patients with HBV/HIV coinfection for renal dose adjustments of TDF and 3TC for patients with HIV/HBV coinfection) Avoid nephrotoxic drugs (e.g., aminoglycosides and NSAIDS) ❖ Evaluate for and treat hypertension ❖ All NRTIs, except ABC, require dose adjustments for renal impairment depending on the severity. NNRTIs, PIs and INSTIs do not require dose adjustments for impaired renal function *Note*: DTG may cause a small rise in serum creatinine levels, but this does NOT represent a decline in renal function.

Mental health screening and management

PLHIVs are susceptible to psychological disturbances due to HIV itself and perceptions regarding HIV in their environment. Common ones include psychological disturbances like depression and suicide, anxiety, internalized stigma, posttraumatic stress disorder (PTSD), cognitive difficulties such as dementia (HIV-associated dementia), and perceived lack of social support. Any of these can significantly interfere with a patient's sense of well-being and their adherence. However, depression and alcohol/drug addiction are most significantly seen in PLHIVs across the globe.

In Timor-Leste, the incidence of dementia is not known, but assumed to be widespread due to country context. It is a postconflict country with severe history of trauma in the past during their independence wars. Depression is the commonest mental disorder (unipolar disorder).

Depression

PLHIVs are more susceptible to episodic depression. It is estimated that the relative risk is 3--6 times higher for PLHIVs compared to general population. This has a profound effect not only with quality of life of PLHIVs, but also the treatment outcomes with ARVs and immune response (increase in CD4 levels).

All PLHIVs should receive basic screening for depression before initiating ART, and thereafter annually using the following two questions:

- *During the past 2weeks have you often been bothered by feeling down, depressed, or hopeless?*
- *During the past 2weeks have you often been bothered by little interest or pleasure in doing things?*

If the answer to any of the questions is 'yes', or the PLHIV has HIV VL > 1000 copies per mL, it is prudent to screen with an expanded questionnaire.

A simple depression questionnaire that could be used is presented in Table 63.

Table 63. Depression screening questionnaire

PHQ – 9 Depression screening questionnaire **Name** _____ **Date:** _____				
Ask the patient the questions below for each of the nine symptoms and circle the response for each question. After asking all questions, add the points for each column at the bottom. The total score is the sum of the column totals. Interpretation and management recommendations are provided at the bottom of the table.				
Question: *"Over the last 2weeks, how often have you been bothered by any of the following problems?"*	Not at all	Several days	More than half of the days	Nearly every day
1. Little interest in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling or staying asleep or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure and have let your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching TV	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed	0	1	2	3
9. Thought that you would be better off dead or hurting yourself	0	1	2	3
Total = _____	=	=	=	=

If you have checked off any of these problems, how difficult these problems made it for you to do your work, take care of things at home or get along with other people (✓)	□ Not difficult at all □ Somewhat difficult □ Very difficult □ Extremely difficult

Interpretation of PHQ-9 score and recommended management		
Total score	Provisional diagnosis	Recommended management
0–4	Depression unlikely	Repeat screening in future if new concerns that depression has developed
5–9	Mild depression	• Provide counselling support and continue to monitor; refer to mental health team, if available • If patient is on EFV, substitute with a different ARV after ruling out treatment failure
10–14	Moderate depression*	• Provide supportive counselling. Refer to psychologist, if available • If patient is on EFV, substitute with a different ARV after ruling out treatment failure • Begin antidepressant medication (or, if unfamiliar with use of antidepressants, then refer to an experienced clinician) • Refer to a medical officer, psychiatrist, or mental health team, if available
15–19	Moderate – severe depression	
20–27	Severe depression	

Note: *Symptoms should ideally be present for at least 2weeks for a diagnosis of depression and before considering treatment with antidepressant medication. Severe depression may require patients to start on antidepressants immediately.

Source: PHQ-9 Copyright © Pfizer Inc. All rights reserved. Reproduced with permission. PRIME-MD ® is a trademark of Pfizer Inc. (https://www.uspreventiveservicestaskforce.org/Home/GetFileByID/218,accessed 20 September 2019).

Depression is a known ADR with EFV, though it is often mild and temporary. Patients on EFV who develop any persistent symptoms of depression should be switched to another ARV after ruling out treatment failure.

Management of depression

Patients with mild depression should receive supportive counselling, which may include:

- Psychoeducation on the following key messages
  - Depression is common and can happen to anyone
  - Depressed people often have exaggerated negative opinions about themselves, their life and their future
  - Effective treatment is possible
- Counselling on self-management
  - Continuing ART as prescribed
  - Continuing activities that they used to find interesting/pleasurable
  - Maintaining a regular sleep cycle
  - Keeping physically active
  - Participating in community/social events
  - Returning to clinic if any thoughts of self-harm
- Addressing psychosocial stressors
  - Explore potential stressors in the patient's life
  - Assist in problem-solving to reduce stressors
  - Assess for and manage intimate partner violence
- Reactivation of or referral to social networks, including peer support groups
- Regular follow-up until symptoms improved and stable.

Use of antidepressant drugs

- Fluoxetine, a specific serotonin receptor inhibitor (SSRI), could be used and has shown to be effective in the overall management of depression among PLHIVs. It has low drug interactions with efavirenz and thus could be used as the first-line antidepressants
- Initial dose should be 10--20 mg per day in the mornings and then increase to 80 mg as a maximum dose for any patient. Usually, the following schedule is well tolerated with patients on TDF+3TC+EFV. With protease inhibitor, LPV/r, the interaction with fluoxetine is minimal. No dose adjustment is necessary[39]
    - Start with fluoxetine 10 mg in the morning for 2 weeks. Increase the dose to 20 mg from 3rd week till the 6th week. Response usually takes 6--8 weeks
    - If no appreciable improvement noted, i.e., no increase in scores PHQ-9 after 8 weeks, increase dosage to 40 mg and then wait for another 6 weeks for response
    - If low or no improvement noted, please refer the patient to a psychiatrist
- If there is good response with fluoxetine, then continue the same for at least 6 months before tapering off the dose. A weekly schedule is recommended. So, if the maintenance dose is 60 mg, then taper to 50 mg in week one, 40 mg in week two, 30 mg in week three and so on till reaching 10 mg in week five and the stop.

Nutritional assessment and counselling

In Timor-Leste, the prevalence of malnutrition is high. The assessment of nutritional status of children and adults is poor. The trends of malnutrition among under 5 over three nutrition surveys (DHS 2009--10, TLFNS 2013 and DHS 2016) are presented in the Fig. 17.

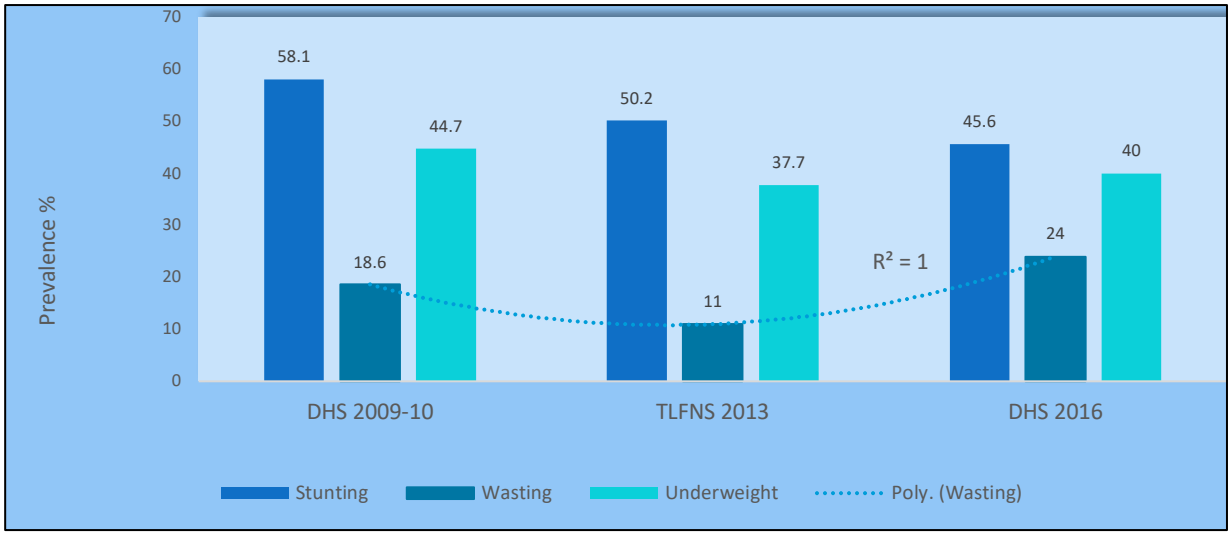


Fig. 13. Trends of malnutrition status of U5 children in Timor-Leste, 2009--2016

Proper and adequate nutrition is the mainstay of treating chronic diseases. Nutritionally adequate PLHIVs will always show improved outcomes. Good nutrition contributes to reducing risk and frequency of other infections, delaying progression of HIV infection to AIDS, a healthy appearance and weight, and reducing the side-effects of ART.

All PLHIVs must receive nutritional assessment, counselling and support, which needs to be customized to the individual, and should include:

[39] http://arv.ucsf.edu/insite?page=ar-00-02&post=10&param=4, accessed 19 September 2019.

1. **Nutrition assessment and diagnosis** (should be timed with routine clinic visits, preferably monthly for the first year of life, and then quarterly up to age of 5 years, and then every 3--6 months as appropriate)

    a. Anthropometric (Tables 68--70 provide interpretation and required actions for anthropometric results for children and adults)
    b. Biochemical (investigations as listed in Table 19 for baseline and Table 21 for follow-up investigations)
    c. Clinical (physical examination as described in Table 18 for initial evaluation)
    d. Dietary (24-hour recall for food type/frequency and household food security)
    e. Environmental and psychosocial
    f. Functional (ability to care for self, bedridden, etc.)

Critical nutrition practices

- Undertake periodic nutritional status assessments
- Increase energy intake through a balanced diet
- Maintain high levels of sanitation and food hygiene
- Practice positive living behaviours
- Carry out physical activity or exercises
- Drink plenty of clean, safe water
- Seek prompt treatment for all OIs and manage diet-related symptoms
- Manage drug--food interactions and side-effects.

Box 2. Critical nutrition practices

2. **Counselling and education**

    a. Benefits of maintaining good nutritional status for a PLHIV
    b. Mother infant and young child nutrition (MIYCN) including exclusive breastfeeding
    c. Reassuring the PLHIV that it is possible to attain/maintain good nutritional status
    d. Look well and live a healthy life
    e. Identifying locally available foods they can access given their own context, food safety and food preparation
    f. Helping the PLHIV to plan meals and snacks with a variety of foods in order to meet their energy and nutrient needs and treatment plans
    g. Identifying any constraints, the PLHIV may face and find ways to minimize them
    h. Helping the PLHIVs to understand the potential side-effects and food interactions of the medicines they are taking, and help them identify ways to manage these side-effects
    i. Exploring with the PLHIVs the cause(s) of poor appetite and appropriate responses (type of food, disease, pain, depression, anxiety, or side-effects of medications)
    j. Counsel on critical nutrition practices (Box 2).

3. **Support**

    a. Therapeutic and supplementary foods to treat clinical malnutrition (food by prescription, therapeutic feeds, fortified blended flour- Box 3). Tables 66and 67 provide malnutrition management recommendations for adults and children

Equipment for screening

- Mid upper arm circumference (MUAC) tape
- Salter weighing scale for infants and children
- Infant weighing trousers
- Weighing scale of men and women
- Height measurement for children, women and men

Supplies for acute malnutrition

- Therapeutic spread (Ready to use therapeutic food – RUTF)
- Therapeutic milk – F75 and F100
- ReSoMal and supplementary food.

Micronutrient supplements

- Vit A capsules (100 000 and 200 000 IU)
- Deworming tablet
- Micronutrients powder (MNP)
- Iron-folic acid
- Zinc tablets

Box 3. List of nutrition equipment and supplies available in Timor-Leste

b. Complementary foods for children aged 6--24 months to prevent malnutrition
c. Micronutrient supplements to prevent vitamin and mineral deficiencies
d. Point-of-use water purification to prevent waterborne disease
e. Food security and linkage to community services, such as household food support, home-based care, agricultural extension services, and economic strengthening and livelihood support.

MUAC is the commonest measure done for children and pregnant/lactating women (Table64).

Table 64.Interpretation and management of malnutrition using MUAC

MUAC level by age (in cm in children below 18 years)			Interpretation	Recommended measures
6–59 months	5–9 years	10–17 years		
< 11.5	< 13.5	< 14.5	Severe acute malnutrition (SAM)	• Irrespective of clinical signs, admission (referral) for stabilization/therapeutic rehabilitation • Treat diseases that may be there • Rule out TB by doing a 4S screening and investigate for paediatric TB
11.5–12.5	13.5–14.5	14.5–18.5	Moderate acute malnutrition	• May be treated as in-patient and provided supplementary nutrition • Treat diseases that may be there • Rule out TB by doing a 4S screening and investigate for paediatric TB
12.6–13.5	NA	NA	Mild acute malnutrition	• Provide nutritional education and counselling
> 13.5	NA	NA	Normal	• Education and counselling for care givers
Pregnant and breastfeeding women				
≤ 23			Malnourished	• Provide nutritional support
> 23			Normal	• Provide nutritional education and counselling

Source: Adapted from publications with permission from WHO, Kenya Institute of Medical Sciences, Nairobi and CDC.

Body mass index (BMI) is used as primary measure to assess malnutrition in adults. HIV illness itself causes muscle wasting and loss of body weight (thus was referred as 'slims disease'). The interpretation of BMI is provided in Table 65.

$$BMI = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

Table 65. Interpretation of BMI and recommended management

BMI level	Interpretation	Recommended measures
< 16	Severe malnutrition	• Refer for facility-based therapeutic intervention; rehabilitation with therapeutic foods; counselling on intake issues and possible metabolic issues • 4S screening for TB
16.0–18.4	Underweight (mild malnutrition)	• Nutrition counselling and supplementary feeding • 4S screening for TB
18.5–24.9	Normal	• Nutritional counselling, consistent exercise to build muscles
25.1–29.9	Pre-obesity (overweight)	• Nutritional counselling to reduce energy intake; aerobic physical activity to reduce weight • Screen for NCDs such as hypertension, coronary heart disease, diabetes, etc.
> 30.0–34.9 **> 35.0–39.9** **> 40**	Obesity class I Obesity class II Obesity class III	• Counselling to change lifestyle and reduce energy intake; aerobic physical activity to reduce weight • Screen for NCDs such as hypertension, coronary heart disease, diabetes, etc.

*Source:*https://www.who.int/nutrition/publications/bmi_asia_strategies.pdf,accessed 27 September 2019.

Weight for age growth charts are the recommended measurement tool for children under 5 years (5–60 months). However, WHO table could be used for detection and prompt treatment of SAM in Timor-Leste (Table 67).

Table 66. Assessment criteria and interpretation in infants and children aged 5--60 months

Ratio	Indicator	Z-score	Severity
Weight/Age	Underweight	< - 3	Severe
Height/Age	Stunting	- 3 to - 2	Moderate
Weight/Height	Wasting*	> - 2 to - 1	Mild
		> - 1	Normal
*Children with weight/height z-score of -2 or less should be supported with therapeutic/supplementary foods			

Source: Adapted from Ministry of Health, National AIDS & STI Control Program. Guidelines on use of antiretroviral drugs for treating and preventing HIV infection in Kenya. 2018 edition. Nairobi, Kenya: NASCOP, August 2018. Print. Permission sought.

Table 67. WHO diagnostic criteria for SAM in children 5--60 months of age

Indicator	Measure	Z score - Cut-off
Severe wasting	Weight for height	< -3 SD
Severe wasting	MUAC	< 115 mm
Bilateral oedema	Clinical sign	

Source: WHO child growth standards and the identification of severe acute malnutrition in infants and children. a joint statement by the World Health Organization and the United Nations Children's Fund. WHO Geneva and UNICEF, New York (https://www.who.int/nutrition/publications/severemalnutrition/9789241598163_eng.pdf,accessed 22 October 2019).

Moreover, the HIV-infected infants and children have requirement of some additional calories while the intake is calculated. Table 68provides the requirement for infants and children with HIV and malnutrition.

Table 32. Total calorie needs of HIV-infected children

Total energy needs of HIV-infected children (kcal/day)

	Daily energy needs of HIV uninfected children*	HIV infected and asymptomatic 10% additional energy	HIV infected and poor weight gain or other symptoms 20% additional energy	Severely malnourished and HIV infected (post-stabilisation) 50-100% additional energy**
6-11 mo	690	760	830	150-220 kcal/kg/day
12-23 mo	900	990	1080	150-220 kcal/kg/day
2-5 yrs	1260	1390	1510	150-220 kcal/kg/day
6-9 yrs	1650	1815	1980	75-100 kcal/kg/day
10-14 yrs	2020	2220	2420	60-90 kcal/kg/day

**Based on average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by age group. Joint FAO/WHO/UNU Expert Consultation, October 2001. ftp://ftp.fao.org/docrep/fao/007/y5686e/y5686e00.pdf*
***Management of Severe Malnutrition: a manual for physicians and other senior health workers. WHO, 1999.*

Source: Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months-14 years). Geneva: World Health Organization.2009. Print. (https://www.who.int/nutrition/publications/hivaids/9789241597524/en/,accessed 22 October 2019).

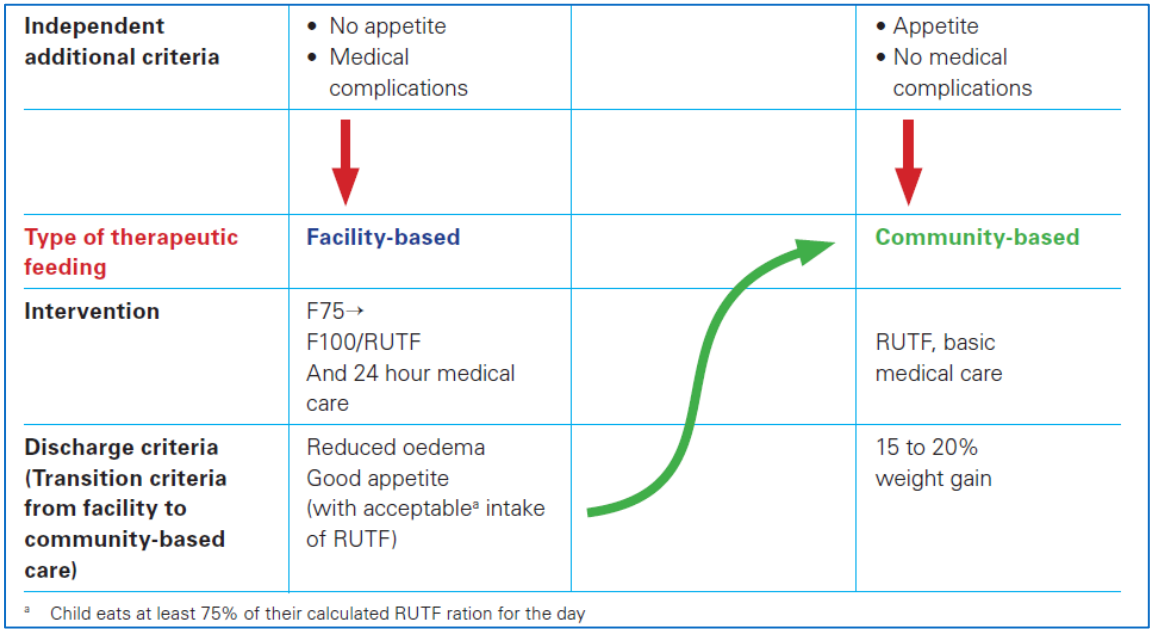


Fig. 18. Management of severe acute malnutrition in children

Source: Reproduced from WHO child growth standards and the identification of severe acute malnutrition in infants and children. ajoint statement by the World Health Organization and the United Nations Children's Fund. WHO Geneva and UNICEF, New York(https://www.who.int/nutrition/publications/severemalnutrition/9789241598163_eng.pdf.,accessed 22 October 2019).

Annex 1. 'Test and Treat' protocol for Timor-Leste

Goals and objectives

The overall goal of Timor-Leste's National Test and Treat policy for HIV/AIDS is '*to reduce the incidence of HIV infection by providing expanded prevention, diagnosis and treatment options*'.

The objectives of this policy are:

- Increase HIV testing for vulnerable population
- Increase access to treatment for people living with HIV/AIDS
- Ensure quality of universal HIV test and treat services
- Implement appropriate evidence-based communication and community strategies to increase public and health care provider awareness on Test and Treat services.

In order to meet the objectives, time-bound broad activities are planned (Table A1.1).

Table A1.1. Planned broad activities to reduce the incidence of HIV infection

Objectives/Activities	Timelines	Details
1. **Increase HIV testing for vulnerable population**		
Act 1: Map out the municipalities and areas reporting low HIV testing **Act 2: Expand ANC HIV testing across all municipalities in a phased manner** **Act 3: Expand HIV testing for all registered TB patients** **Act 4: Expand HIV testing for all STI and chronically ill patients across all municipalities in a phased manner** **Act 5: Expand HIV testing for key population to all municipalities in a phased manner** **Act 6: Reorganize the logistical management system for HIV test kits to ensure zero stockouts of HIV test kits** **Act 7: Conduct training for lab technicians, nurses, midwives and public health workers on HIV testing service and its reporting system** **Act 8: Conduct training for key population groups on HIV testing service and community-based HIV testing**	Phase I: July--Dec 2017 Phase II: Jan--June 2018	Phase I: Expand HIV testing for ANC/STI/KP Current – Five/four municipalities and SAR of Oecusse across Timor-Leste Expand to: 1. Ermera 2. Aileu 3. Ainaro 4. Manatutu Phase II: Expand to remaining municipalities: 5. Viqueque 6. Lautem 7. Manufahi
2. **Increase access to treatment for** PLHIVs		
Act 1: Introduce case-based surveillance system for HIV testing services and ART **Act 2: Conduct training on treatment care and support for doctors, nurses, lab technicians, midwives and public health workers in each municipality** **Act 3:Conduct specialized training for HIV VL testing and monitoring,** second-line **ART and adherence** **Act 4: Create awareness** on **HIV testing and treatment through media and other campaigns**	July--Dec 2017	Revise formats and reporting to be implemented across all ART centres and HIV testing centres by the end of Dec 2017 New format will be introduced from July to Sept 2017 and will be monitored with old formats till Dec 2017. Dual reporting for Sept–Dec. period to evaluate the quality of HIV case-based surveillance reports
3. **Ensure quality of universal HIV test and treat services**		
Act 1: Scale up internal and external quality assurance for HIV testing, CD4 and HIV VL	Phase I: July17--Dec 2018	Quality assurance protocols for HIV testing is already developed and in

Act 2: Set up CD4 and HIV VL interface for all current patients **Act 3: Shift to HIV VL as standards of monitoring and care in a phased manner**	Phase II: Jan-- Dec 2019	use. However, quality assurance protocols for CD4 and HIV VL will be developed during Phase I (July to Dec 2017) and will be piloted and scaled up across Timor-Leste in a consolidated manner from Jan–Dec 2018
4. **Implement appropriate evidence-based communication and community strategies to increase public and health care provider awareness on Test and Treat services**		
Act 1: Develop culturally appropriate and gender-sensitive IEC materials and communication strategies for creating awareness on 'Test and Treat' for HIV/AIDS **Act 2: Pilot the IEC materials and communication strategies in select municipalities** **Act 3: Revise the IEC materials and communication strategies based on inputs from pilot and implement across Timor-Leste** **Act 4: Measure the impact of communication materials and strategies**	July 17--Dec 18	IEC materials for 'Test and Treat' would be developed and used for awareness generation and behaviour change communication It is important that appropriate indicators be used to measure the impact of such communication strategies and materials

Quality of care

'Test and Treat' services for HIV/AIDS just do not mean expanded services and implementation alone. Expansion and scale up will be quality assured as per global standards of HIV care. Thus, starting from diagnosis of HIV to getting the appropriate regimen and monitoring the level of disease through either CD4 counts or HIV VL need to be of assured quality. A case in point will be of a person who was tested HIV positive, but not through a quality assured testing may truly not be HIV positive and may be put on ART. Such issues are not infrequent in large set ups in many countries, and controls must be put in place to ensure such things do not happen.

One of the ways of addressing the quality issue will be to have in-service training on clinical guidelines, counselling and attitude building to address stigma and discrimination for service delivery providers. This has the potential to promote uptake of testing and further improve adherence and retention in care.

A nonexhaustive list of priority training areas for service providers is given below:

- Clinical guidelines on managing HIV as a chronic illness
- Counselling and testing
- Key populations and their special needs (sensitization)
- Retention in care with special emphasis on adherence to ART and other medications
- Integration with other basic service package for HIV and STI prevention.

Quality is not a onetime affair and needs to be rigorously monitored regularly to maintain the standards.

Target audience

This policy document and its associated clinical guideline are intended for staff of Ministry of Health, Timor-Leste, specifically the National HIV/AIDS and STI programme, Maternal, Child and Adolescent health programme, National TB programme and other associated programmes of communicable

disease control and NCD control programme as well as civil societies implementing HIV/AIDS, TB and MCH programmes.

Ethical and legal considerations

This policy is based on human rights approach and in accordance with the Constitution of Timor-Leste. It is based on equality, right to privacy and confidentiality, and right to medical services for all Timorese population.

Monitoring and evaluation of this policy

The existing system of HIV reporting will be utilized to monitor the implementation of this policy. The indicators that will be used for monitoring the policy implementation are:

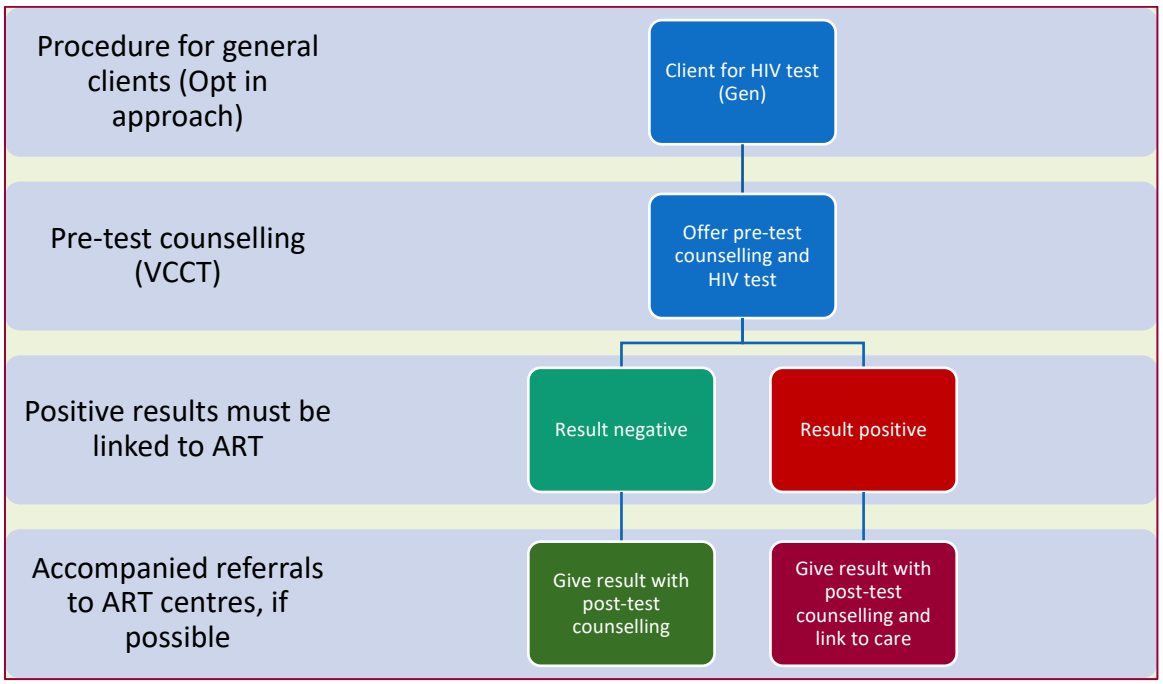
- Percentage of estimated HIV positive who know their status
- Percentage of HIV positives who are on ART
- Percentage of adults and children known to be on treatment 12 months after initiation of ART.

Revised eligibility for ART under Test and Treat policy

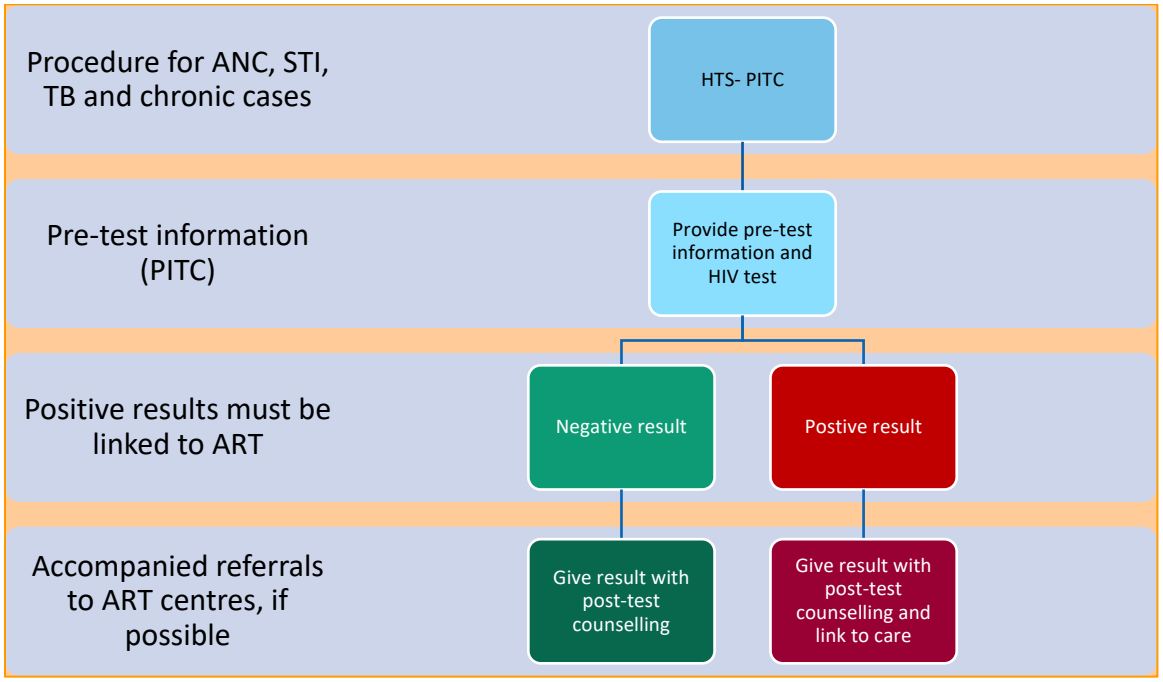
"*Any person irrespective of age or sex who has a confirmed HIV positive diagnosis from any designated laboratory in Timor-Leste*".

Annex 2. HTS protocol

A. For general clients



B. For ANC, TB and STI patients



Annex 3. Patient registration form

Patient Card (KartaunPasientes)

<table>
<tr><td rowspan="2">PID code:</td><td>Date of registration</td><td>Date of discharge</td><td>Outcome</td></tr>
<tr><td></td><td></td><td>☐LFU
☐Transferred
☐Dead</td></tr>
<tr><td colspan="2">First name:</td><td>Middle name:</td><td>Family name:</td></tr>
<tr><td>Address:

Phone No.

Contact for tracing:</td><td colspan="3">Electoral card:
Home:
Landline:
Mobile:
Name: Patient’s link: Phone No:
(use only in case of patient failing to call; confidentiality should not be breached)</td></tr>
<tr><td colspan="2">Date of birth:</td><td colspan="2">☐Male
☐Female</td></tr>
<tr><td>Marital status:</td><td colspan="2">☐Single
☐Married</td><td>☐Widow
☐Divorced</td></tr>
<tr><td>Profession:</td><td colspan="3"></td></tr>
<tr><td>Spouse:
Children:</td><td colspan="3">……..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: ……</td></tr>
<tr><td>Mode of entry:</td><td>HTS VCCT</td><td>HTS-PITC: TB</td><td>HTS-PITC: STI</td><td>EMTCT</td><td>Transferred from another ART centre</td><td>Other:</td></tr>
<tr><td>Date of first HIV+ test:</td><td colspan="2">Weight on enrolment</td><td>BMI</td><td colspan="3">Past TB dates</td></tr>
<tr><td>Past exposure to ARV drugs:

yes/no</td><td colspan="2">Date of ARV previous exposition:</td><td colspan="4">Names of ARV drugs taken previously:</td></tr>
<tr><td>Drug allergy:
yes/no</td><td colspan="2">Name of ARV drugs allergy:</td><td colspan="4">Non-ARV drugs allergy:</td></tr>
</table>

Annex 4. Patient monitoring form (Adult and paediatric)

DEPARTAMENTODOENÇASCONTAGIOZAS-PROGRAMAHIV/AIDS

ID code:……Naran:……Visita:☐ontime☐late☐unplanned

Date of consultation/hospitalization: ……../……../……..

Next appointment: ……../……../……..

If hospitalized, date of discharge: ……../……../……

Pulse:……/min
Temp:……..
BP:……..
Weight:……kg
Height:……..m

BMI or W/H%…….

Lab tests:
Date:…../……/……

HIV VL: ……..

CD4:……../mL

Hb :…….g/dL

S. Creat:……..

ALAT:……

WHO clinical stage:

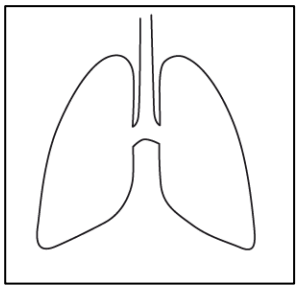
X-ray:……

Sputum:……

Main complaints:……

Anamnesis:……
……
……
……

Physical examination:
Pallor:
Lymphnodes:
Cardiovascular system: S1 S2 Murmurs
Respiratory system:
Neurological symptoms:
Abdomen
Urinary-genital symptoms:
Skin:



Diagnosis……
……
……

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

Main drugs (ARV)	**Dose**	**Code**	**Intolerance**
1. TDF+3TC+EFV			
2. TDF+3TC & NVP			
3. AZT+3TC&EFV			
4. AZT+3TC+NVP			
5. TDF+3TC+DTG			
6. AZT+3TC & DTG			
7. TDF+3TC & LPV/r			
8. AZT+3TC & LPV/r			
9. ABC+3TC & LPV/r			
Other drugs			
10. CTX Prophy.			
11. Fluconazole Prophy.			

(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 5. Monthlydata reporting form

Centre ID: Month/Year: Person responsible:

Criteria	Data
HIV testing services	
No. of patients tested during the period	
No. of new HIV positive during the period	
Cumulative No. of HIV positive patients	
HIV cohort report (on ART and diagnosed, but not started ART)	
No. of HIV positive patients in the active cohort at the end of the previous period	
No. of new HIV positive patients < 15 years enrolled during the period Male Female	
No. of new HIV positive patients >or = 15 years enrolled during the period Male Female	
No. of patients transferred in during the period	
Total No. of new HIV positive patients enrolled during the period	
Total No. of death during the period	
No. of HIV positive patients transferred out during the period	
No. of HIV positive patients LFU during the period	
Total No. of HIV positive patients in the active cohort at the end of the period	
ART programme	
No. of ARV patients at the end of the previous period	
No. of patients < 15 years initiated on ART during the period Male Female	
No. of patients ≥ 15 years initiated on ART during the period Male Female	
No. of patients on ART transferred in during the period	
Total No. of patients initiated on ART during the period	
Total No. of ART patients dead during the period	
No. of ART patients transferred out during the period	
No. of ART patients LFU during the period	
Total No. of ART patients in the active cohort at the end of the period	
Cumulative No. of ARV patients initiated since the beginning of the programme	
No. of ART patients < 15 years switched to second-line treatment during the period	
No. of ART patients≥ 15 years switched to second-line treatment during the period	
Total No. of ART patients switched to second-line treatment during the period	

Cumulative No. of ART patients on second-line treatment since the beginning of the programme	
EMTCT	
See EMTCT data reporting form	

Annex 6. Appointment and tracing registers

This register is used for improving the programmatic performance for improved impact.

Example of 'appointment agenda'

Week 9/05 to 13/05/11	ID code	Counsellor	Doctor	Lab
Monday 2–5pm	ID0011JF ID0687ML ID0541HT	X X X	X X	- HIV VL Hb,CD4
Tuesday	Off	Off	Off	Off
Wednesday 8–10 am	ID0225JK			Hb, LFT
Thursday	Off	Off	Off	Off
Friday 8 am–12pm	ID0225JK	X	X	

Example of 'tracing register'

ID code	Date of defaulting	Tracing activities	Outcome
ID0154DE	5 Jan 2019	Phone call: 5 Jan 2019 (no reply) Home visit: 22 Jan 2019	Died on 24 August 2019
ID0314TR	10 Jan 2019	Phone call:10 Jan 2011(will come on 15 Jan 2011) Phone call:15 Jan2011(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
ID0114AZ	2 Feb 2019	Phone call: 02 Feb 2019 (no reply) Home visit:10 Feb2 019 (wrong address) Contacted PLHIV group – Estrella Plus and Esperança Peer group mobilization: no success	Declared missed case on 10 Feb 2019 Declared LFUon2 May 2019

Annex 7. WHO clinical staging

WHO has developed tools 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. They should be used as additional tools and do not replace the need of HIV VL or CD4 count.

There are two clinical staging tables; one is developed for OIs in adults and adolescents, the second one is developed for OIs in children.

The purposes of the clinical tables are:

- 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 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 inpatients exhibiting the clinical events suggestive of HIV disease
- 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 A 7.1. WHO clinical staging of HIV infection in adults, adolescents and children

Stage	Adults and adolescents	Children
Primary HIV infection	• Asymptomatic • Acute retroviral syndrome	• Asymptomatic • Acute retroviral syndrome
Clinical stage 1	• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	• Moderate unexplained weight loss(<10% of presumed or measured bodyweight) • Recurrent RTIs (Sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papularpruritic eruption • Fungal nail infections • Seborrheicdermatitis	• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper RTIs (Otitis media, otorrhoea, sinusitis, tonsillitis) • Herpes zoster • Lineal gingival erythema • Recurrent oral ulceration • Papularpruritic eruption • Fungal nail infections • Extensive wart virus infection • Extensive molluscum contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	• Unexplained severe weight loss (>10% of the presumed or measured bodyweight) • Unexplained chronic diarrhoea for more than 1 month • Unexplained persistent fever (intermittent or constant for longer than1month) • Persistent oral candidiasis • Oral hairy leucoplakia (OHL)	• Unexplained moderate malnutrition 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 1month)

	• PTB • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, and bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8 g/dL, neutropenia (<0.5 x 109/L) and/orchronic thrombocytopaenia (<50 x109/L)	• Persistent oral candidiasis (after the first 6weeksof life) • OHL • Lymph node TB • PTB • Severe recurrent bacterial pneumonia • Acute necrotizing ulcerative gingivitis or periodontitis • Unexplained anaemia (<8 g/dL), neutropenia(<0.5 x 109/L) or chronic thrombocytopaenia (<50x 109/L) • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4	• HIV wasting syndrome • *Pneumocystis* (*jiroveci*) pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1month duration or visceral at any site) • Oesophageal candidiasis (orcandidiasis of trachea, bronchi or lungs) • EPTB • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extra pulmonary cryptococcosis, including meningitis • Disseminated nontuberculous mycobacterial infection (NTM) • Progressive multifocal leukoencephalopathy (PML) • Chronic cryptosporidiosis • Chronic isosporiasis • Disseminated mycosis (extra pulmonaryhistoplasmosis, coccidioidomycosis) • Lymphoma (cerebral or B-cell non-Hodgkin) • Symptomatic HIV-associated nephropathy or cardiomyopathy	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • *Pneumocystis* (*jiroveci*) Pneumonia • Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic Herpes simplex infection (orolabial or cutaneous of more than 1 month duration orvisceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • EPTB • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1month) • Central nervous system toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extra pulmonary cryptococcosis, including meningitis • NTM • PML • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis

	• Recurrent septicaemia (including nontyphoidalsalmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidioidomycosis, penicilliosis) • Cerebral or B-cell nonHodgkinlymphoma • HIV-associated nephropathy or cardiomyopathy

Annex 8. Assessment of patient during the first visit to ART centre

The initial visit provides the opportunity to establish a meaningful patient-provider relationship. The clinician should elicit concerns and expectations with open, non-judgmental, and clear communication. The details are presented as tabular format for ease of use (Table A8.1).

Table A 8.1. Assessment of patient during the first visit to ART centre

History	Comments	
Current history and complaints	• Main complaints and current symptoms • Include symptoms of TB and TB contacts	Ask about: • Coinfections such as hepatitis B and C, visceral leishmaniasis, etc. • Other comorbid conditions such as diabetes, hypertension, kidney diseases, liver diseases, etc. • 4 symptoms screening for TB and fill up the intensified case finding tool
	• Date of first positive HIV test • Past and current comorbidities (e.g., TB, cryptococcal meningitis, hypertension, diabetes, kidney and liver diseases) • Current medications, including herbal medicine/traditional medicine • Drug allergies, especially sulpha allergy (for using co-trimoxazole at later date • ARV exposure history • History of hospitalization • Family history of chronic disease or cancer	• Document history of TB • Document previous or current ARV use (including for EMTCT, PEP, PrEP and ART) • Establish current medications (prescription, nonprescription, and herbal) likely to adversely interact with ARVs • Establish reasons for hospitalization
Psychosocial history	• Ask about education, employment and family marital status • Any history of mental illness • Disclosure and self-stigma • Substance use including alcohol, tobacco, marijuana, narcotics, injection drug use, etc. • Nutritional history and adequacy of nutritional intake and household food security	• Establish and document social support structures • Establish possible presence of mental health concerns • Encourage disclosure to trusted close relations/friends and sexual partners • Elicit and begin to address possible barriers to adherence • Link to additional facility and community support resources, including psychosocial support groups, peer mentors, etc.
Sexual and reproductive history	• History of STIs • Any current symptoms • Current sexual practices • Partner HIV status and disclosure to sexual partner(s) • Pregnancy history and age of all living children • Menstrual history, family planning and plans for pregnancy	• Speak about secondary prevention (ART) and avoiding reinfection with STIs • HIV and ART status of sexual partner/s • Discuss intention of pregnancy and contraception needs • Encourage contact tracing and HIV testing for sexual partners and all children of HIV-infected women and

	• History of cervical cancer screening	all children whose mothers' HIV status is unknown

Notes:

- Assign and document the initial WHO clinical stage and manage presenting illnesses
- Growth and developmental milestone must be assessed and used for WHO staging in children
- Differentiate between patients with advanced disease versus those who are clinically well to guide acuity of follow-up.

Physical examination	Comments	
General impression, vital signs and anthropometric measurements	Assess general mood, measure and record weight, height, MUAC (in children and pregnant women), temperature, pulse rate, BP, respiratory rate, pulse oximetry (if patient has respiratory complaints or has difficulty in breathing)	• Calculate BMI as: weight (kg)/ heightm^2) • Use Z-scores for children • Monitor growth trends for children
General examination	Central nervous system (focal defects, retina); mental state examination (for mental status); abdomen (for liver or splenic enlargement); respiratory (for dullness to percussion; crackles or wheezes); cardiovascular (for peripheral pulses, oedema, heart sounds); if specific symptoms: genitourinary/anorectal system (for ulcers, discharge, condylomata/warts, prostate examination for men ≥ 45 years of age). Speculum examination with cervical cancer screening for females	• Prompt treatment of inter-current illness contributes towards success of ART and reduction in early morbidity and mortality • Asymmetric or rapidly enlarging lymph nodes will require fine needle aspiration cytology or biopsy • Cervical cancer screening (if not done in the past year) and appropriate management • Monitoring developmental milestones for children
Systemic examination	Central nervous system (focal defects, retina); mental state examination (for mental status); abdomen (for liver or splenic enlargement); respiratory (for dullness to percussion; crackles or wheezes); cardiovascular (for peripheral pulses, oedema, heart sounds); if specific symptoms: genitourinary/anorectal system (for ulcers, discharge, condylomata/warts, prostate examination for men ≥ 45 years of age). Speculum examination with cervical cancer screening for females	
Summary	Problem list with differential diagnosis and management plan for each problem (including investigations, treatment, referrals and follow-up)	• Assign and document the initial WHO clinical stage and manage presenting illnesses • Growth and developmental milestone must be assessed and used for WHO staging in children • Differentiate between patients with advanced disease versus those who are clinically well to guide acuity of follow-up

Note: Laboratory assessment is not a prerequisite to ART initiation. It should not cause delay in starting ART.

Annex 9. National referral system

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 to provide the best quality medical care (**Fig. A9.1.** A9.1).

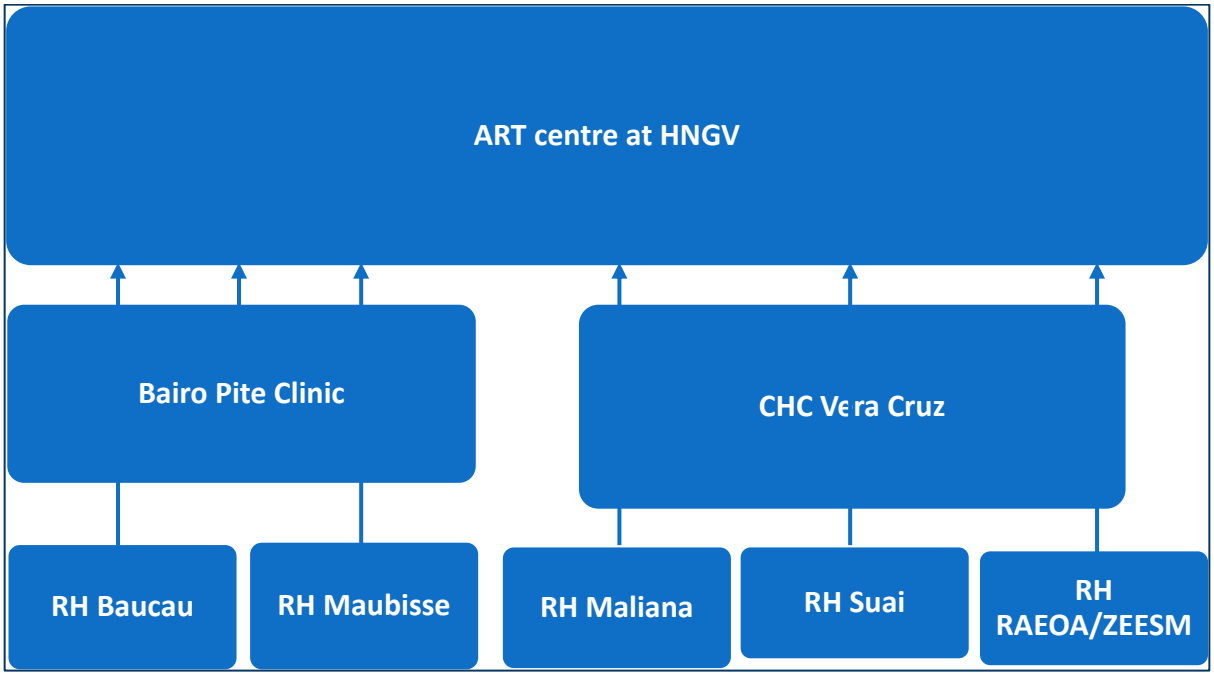


Fig. A9.1.Referral flow and confidentiality

National coding system

Documents provided will ***NOT*** mention names, but only **"PID and ART No."** The code is used only once and will ***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 (*shared confidentiality*). The code is attributed where the patient is attending the HIV services for the first time. The ID code will remain the same till the end. Specifically, it is recommended to have one unified ID code that will remain same even when patient is transferred from one site to other within Timor-Leste. It will be part of the counselling to educate the patient in remembering his/her ID code. An ART card will be provided to the patient with his/her ID code in writing and all the necessary details.

The definition of the national ID code follows the described rule below:

1. HNGV: HN-001, HN-002,HN-003...
2. Bairo Pite Clinic: BP-001, BP-002, BP-003…

3. CHC VERA Cruz: VC-001, VC-002, VC-003....
4. Regional Hospital (RH) Baucau:BC-001, BC-002, BC-003...
5. RH Oecusse: OC-001, OC-002, OC-003...
6. RH Maliana: ML-001, ML-002,ML-003...
7. RH Maubisse: MB-001, MB-002,MB-003...
8. RH Suai: SU-001, SU-002, SU-003...

Example 1

A patient has been diagnosed HIV positive at the HIV testing centre (HTC) of Maliana. After post-test counselling, the patient accepts to see the doctor and to enter in the HIV medical cohort of Maliana ART centre. Only when the patient comes for his first medical consultation, the ID code will be attributed to this particular patient. Hence, if the patient presents himself at Maliana ART centre, and he is the first to come in the centre, he will receive the code ML-001. Next time when he comes for a medical visit, the patient will present his ID code and the counsellor 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/her ID code will be ML-050.

Example 3

If the patient is tested HIV positive in Dili and after post-test counselling, the patient decides to go to Maliana for his/her 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 may be supported for their transport, accommodation, and food expenses. The peer network (Estrela Plus and Esperança) will work closely with MoH to support this endeavour.

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.

Infrastructure and services

Hospital Nationalin Dili (Hospital Nacional Guido Valadares, HNGV)

The ART centre at HNGV will also function as national referral centre for HIV/AIDS medical management. The overall in charge would be one of the designated physicians from the department of internal medicine (internist).

The ART centre is currently being managed by a medical doctor from the programme, and if required a specialist consultation is available for the patient.

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 most OIs that may occur in an HIV infected.

The HNGV is responsible to provide the following services:

- Pre-ART assessment
- OI management
- First-line ART initiation as per 'Test and Treat' policy
- Routine monthly medical monitoring of patient
- Early detection of failure -- clinical, immunological and virological failure monitoring
- Switch to second-line ART as appropriate
- Monitoring of patients on second-line ART.

1. HIV testing services (VCCT/PITC)
2. EMTCT
3. STI management
4. ART (First- and second-line)
5. Specialist consultation (Internal medicine, paediatrics, surgery, obstetrics&gynaecology, STI, eye, ENT, chest, gastroenterologyand neurology)
6. Coinfections - TB, hepatitis and VL
7. PLHIV support network (Estrela Plus and Caritas)
8. Laboratory support at National Labs (CD4, HIV VL and other routine investigations)
9. Radiology – X-ray, Ultrasound and CT scan.

Box A9.1. Services available at HNGV

HNGV will also be responsible for transitioning the patients from current first-line of tenofovir + lamivudine + efavirenz (TLE) to tenofovir + lamivudine + dolutegravir (TLD) based regimens as per protocol detailed in the section on first-line ART. The services currently available at HNGV are given in Box A9.1.

Bairo Pite Clinic (BPC)

BPC is a private NGO clinic that started the first ART services for PLHIVs in Timor-Leste (2002). It is in Dili and serves almost half of all PLHIVs on treatment.

BPC provides 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, etc.) for which the patient is referred to HNGV.

Other ART centres (6):

- Referral Hospital Baucau (HOREX)
- Referral Hospital Maubisse
- Referral Hospital Maliana
- Referral Hospital Suai
- Referral Hospital Oecusse (HRO)
- CHC Vera Cruz, Dili.

The referral hospitals are responsible to provide the following services:

- Referral to HNGV of all newly HIV positive diagnosed patients
- Pre-ART assessment
- OI management
- First-line ART initiation as per 'Test and Treat' policy
- Routine monthly medical monitoring of patient
- Early detection of failure -- clinical, immunological and virological failure monitoring

- Referral to HNGV/CHC Vera Cruz for expert opinion for challenging cases
- Transition to dolutegravir-based regimens (TLD and ZLD)
- Referral to national labs for HIV VL.

Reference to HNGV/CHC Vera Cruz for any reason will benefit financial or logistic support for transport, accommodation and basic food expenses in Dili as per available ART support mechanism.

Some referral hospitals (RH Maliana, Oecusse and Baucau) have functioning CD4 machines (PARTEC®). Thus, immunological monitoring is possible in these centres.

However, the referral hospitals are currently not responsible for:

- Treating complicated OIs and coinfections (HIV with hepatitis B)
- Assessing treatment failure
- Switching to second-line ART.

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.

HIV and ART consultations:

- Open twice*a week on fixed days
- On appointment for patient follow-up during these two 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/Obstetrics.

Note: *The frequency of weekly consultation will be revised according to the patients load in each ART centre.
**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 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	1—2	2
Bairo Pite Clinic	1—2	2
Referral Hospitals/CHC Vera Cruz	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 should be able to provide quality HIV medical services to HIV positive patients including first- and second-line ART, and also support transition to Dolutegravir-based ART in complicated cases.

It must be further noted that some patients are achieving adequate HIV VL suppression with the current regimens namely, TLE and ZLE. The clinical decision to shift the patients should be taken in close consultation with experts (TRG members as per Transition Plan)

The nurses of HNGV, BPC and CHC Vera Cruz should be able to follow the instructions and directions of the medical doctors and additionally able to provide adequate treatment literacy to the HIV positive patients as per protocol.

The medical doctors and nurses of the RH should be able to recognize:

- ARV drug side-effects
- First sign of OIs
- 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 appropriate counselling.

Patient circuits:

1. Outpatient department (OPD)

Patient should go directly to counsellor room

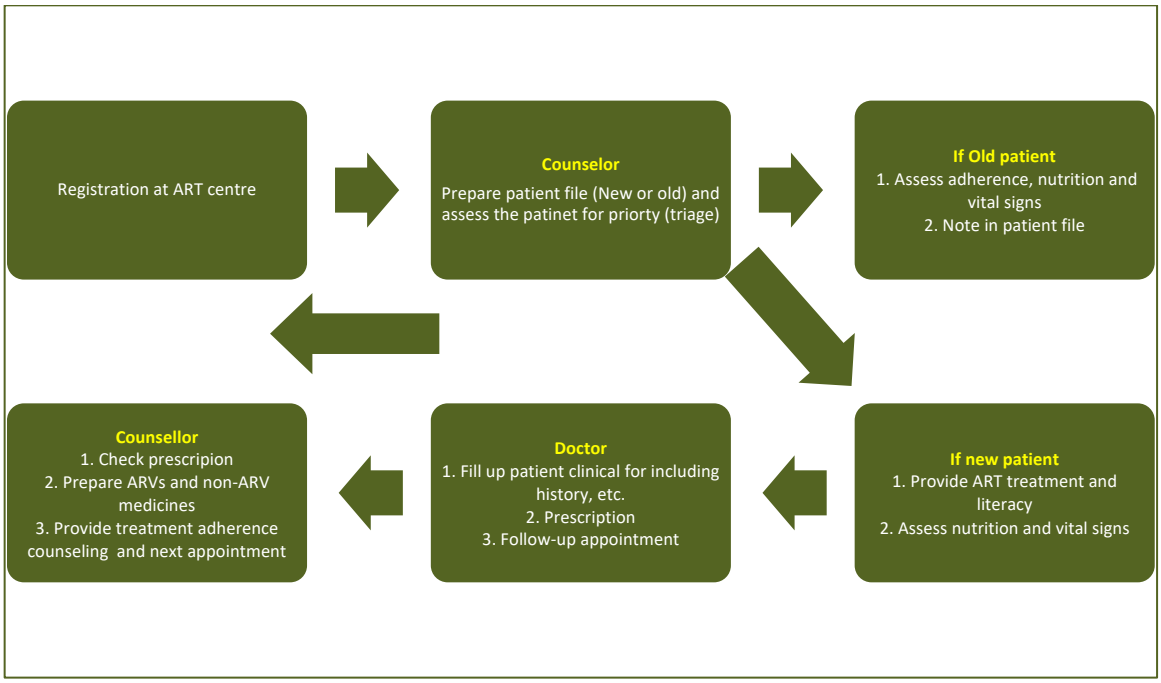


Fig. 14.2. Flow chart for patient circuit in ART centre (OPD)

- Registration(As per format **Annex 3.** Patient registration)
- Prepare patient file and medical follow-up form (**Annex 4.**Patient monitoring form (Adult and paediatric))
- Adherence counselling: problems to be recorded in the patient file
- Nutritional assessment: to be recorded in the file
- Vital signs to be registered on the new follow-up form
- Present complaints: in case of emergency, alert the doctor and prioritize the patient.

Patient should go to see the doctor in the **doctor room**(One patient at a time)

- Medical history to be recorded on the follow-up form
- Clinical examination to be recorded on the follow-up form
- Prescription to be recorded on the follow-up form and filled
- Appointment to be recorded on the follow-up form.

Patient should go back to the **counsellor room**

- Counsellor to take the prescription
- Counsellor to ask the OPD pharmacy for non-ARV items
- Counsellor to prepare ARVs prescribed
- Counsellor to supply drugs with therapeutic education to the patient
- Counsellor to write the next appointment in the appointment agenda and on the patient appointment card.

2. Inpatient department (IPD) and counselling

a. Cases with HIV status not known

The cases who are admitted to the wards under any of the departments such as surgery, obstetrics and gynaecology, paediatrics, etc. may be screened for HIV based on the discretion of the attending physician. The following protocol must be adhered to while ordering an HIV test:

- Informed consent to be recorded in the patient file (verbal consent is enough, but a mention of the same in the case sheet is required)
- Follow the 5 Cs of counselling namely, a) Consent; b) Confidentiality; c) Correct results; d) Counselling; and e) Connection (Linkage to ART, if detected to be HIV positive)
- Evaluate the patient for starting ART in consultation with ART physician
- Initiate the ART as per protocol
- Follow-up as per protocol.

The attending physician should call the HIV counsellor for counselling and testing. Follow provider-initiated testing and counselling (PITC) protocols (please refer to **Annex 1.** 'Test and Treat' protocol for Timor-Leste).

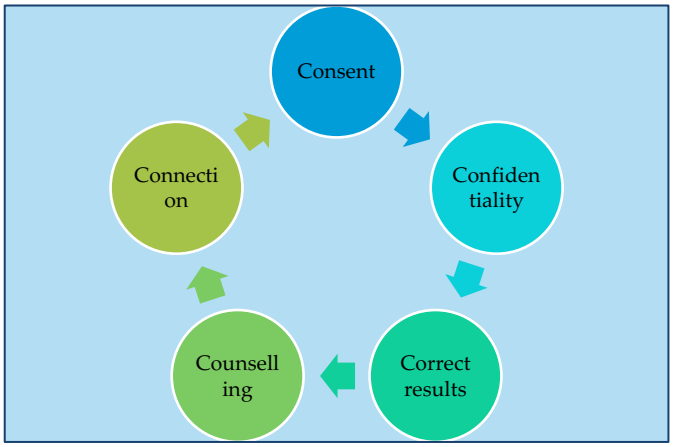


Fig. A9.3.5Cs of HTS counselling

be treated as highly confidential.

The medical records of an HIV positive individual should be '*sealed*' and kept in locked closet.

Sharing information within the health care team about a patient's HIV status is only permissible if the patient has given consent or if it is clinically indicated.

Disclosure in public interest: This can be one of the conditions of shared confidentiality even if explicit consent has not been taken. For disclosure to be justified, the risk of harm to others must be serious enough to outweigh the patient's right to confidentiality.

Box A9.2. Shared confidentiality

Note: Once patient is confirmed HIV positive, the doctor trained for HIV care and treatment should oversee HIV-related problems, but other issues (surgery, gynaecology, etc.) remain under the specialist responsibility.

At discharge, the patient should be referred to the counsellor room for administrative records, drugs supply and next appointment record.

b. IPD for known HIV+ cases

- Either patient is hospitalized through emergency and if the patient has disclosed positive results must be linked to ART
- Depending on his/her status, family should be encouraged to inform the counsellor or HIV doctor as soon as possible for better quality of care
- Either patient is hospitalized after OPD consultation as deemed necessary by the attending physician
- Patient should be hospitalized in the ward corresponding to his condition and the HIV doctor should 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 (Box A2: Shared confidentiality)
- At discharge, the patient should be referred to the counsellor room for administrative records, drugs supply and next appointment record.

3. Medical file and confidentiality

An individual code is given at each new HIV positive registration; this same code should be used in place of names whenever names should not be disclosed (i.e., blood tests, drugs prescription, etc.)

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 for other patients at large. Further it must be noted that practice for 'Standard Precautions'[40] is a must for handling infectious patients.

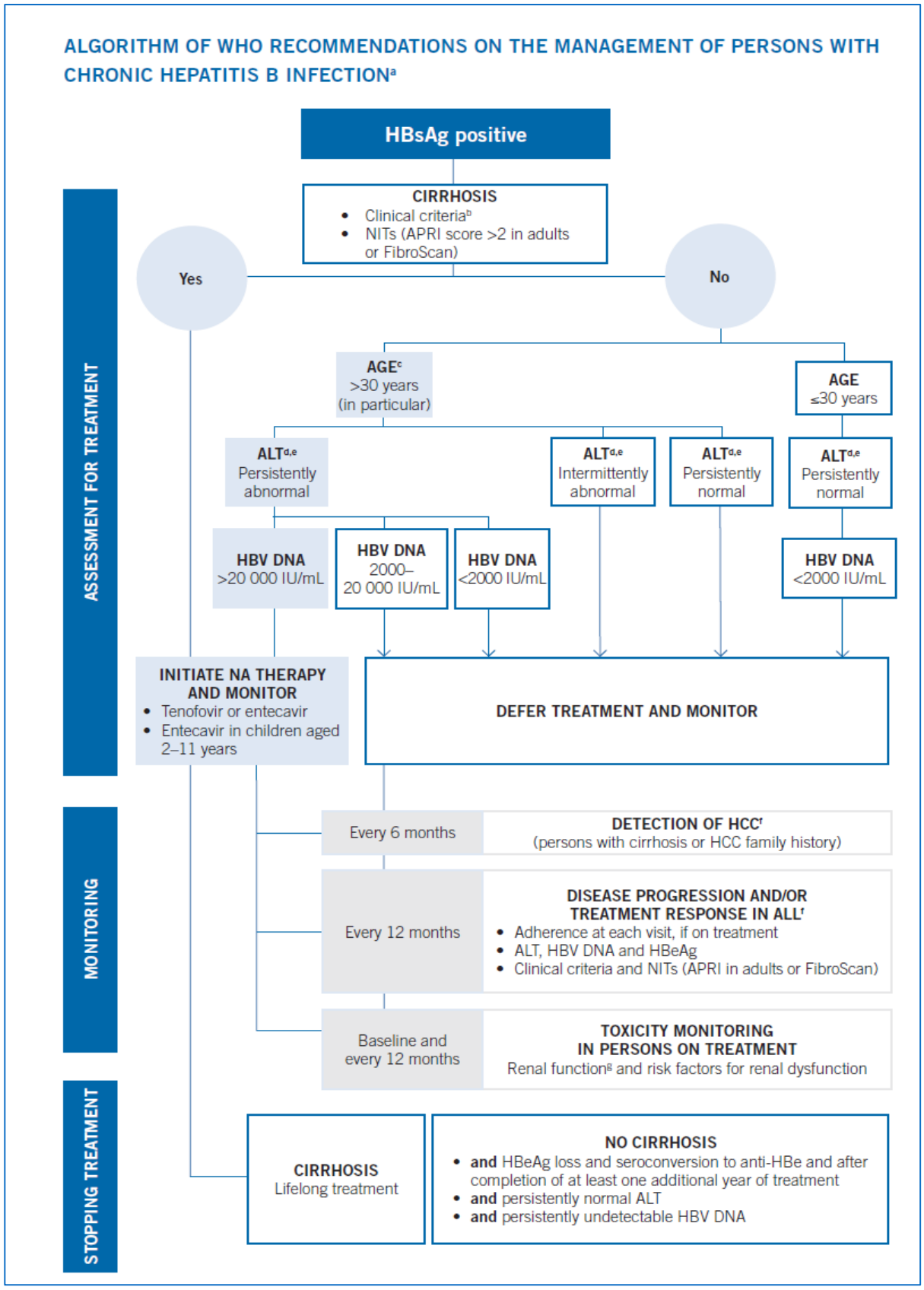
The medical files need to be kept securely. Patients should be encouraged to disclose their status if they are seen outside their regular HIV/AIDS consultations (e.g., in emergency in OPD). Attempts should be made to ensure confidentiality and only clinicians involved in their HIV/AIDS care should know the HIV status of the patients.

The ART pharmacy need to be integrated with the general one. A locked cabinet/cupboard is needed to securely store ARV drugs and OI medicines, if any. The keys of the cabinet need to be available any time (day and night and weekend).

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

[40]The set of principles advocated for prevention of infection control in health care set up are: a) Hand hygiene; b) Use of personal protective equipment such as gloves, gown, facial protection, etc.; c) Prevention of needle stick injuries from sharp instruments; d) Respiratory hygiene and cough etiquette; e) Environmental cleaning; f) Handling of linens; g) Waste disposal; and h) patient care equipment.

Annex 10. Management of chronic hepatitis B infection – WHO algorithm



Source: Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization. 2015. p.xxvi.

Annex 11. Standard precautions – WHO recommendations

Health-care facility recommendations for standard precautions

KEY ELEMENTS AT A GLANCE

1. Hand hygiene[1]

Summary technique:

- Hand washing (40–60 sec): wet hands and apply soap; rub all surfaces; rinse hands and dry thoroughly with a single use towel; use towel to turn off faucet.
- Hand rubbing (20–30 sec): apply enough product to cover all areas of the hands; rub hands until dry.

Summary indications:

- Before and after any direct patient contact and between patients, whether or not gloves are worn.
- Immediately after gloves are removed.
- Before handling an invasive device.
- After touching blood, body fluids, secretions, excretions, non-intact skin, and contaminated items, even if gloves are worn.
- During patient care, when moving from a contaminated to a clean body site of the patient.
- After contact with inanimate objects in the immediate vicinity of the patient.

2. Gloves

- Wear when touching blood, body fluids, secretions, excretions, mucous membranes, nonintact skin.
- Change between tasks and procedures on the same patient after contact with potentially infectious material.
- Remove after use, before touching non-contaminated items and surfaces, and before going to another patient. Perform hand hygiene immediately after removal.

3. Facial protection (eyes, nose, and mouth)

- Wear (1) a surgical or procedure mask and eye protection (eye visor, goggles) or (2) a face shield to protect mucous membranes of the eyes, nose, and mouth during activities that are likely to generate splashes or sprays of blood, body fluids, secretions, and excretions.

4. Gown

- Wear to protect skin and prevent soiling of clothing during activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions.
- Remove soiled gown as soon as possible, and perform hand hygiene.

5. Prevention of needle stick and injuries from other sharp instruments[2]

Use care when:

- Handling needles, scalpels, and other sharp instruments or devices.
- Cleaning used instruments.
- Disposing of used needles and other sharp instruments.

6. Respiratory hygiene and cough etiquette

Persons with respiratory symptoms should apply source control measures:

- Cover their nose and mouth when coughing/sneezing with tissue or mask, dispose of used tissues and masks, and perform hand hygiene after contact with respiratory secretions.

Health-care facilities should:

- Place acute febrile respiratory symptomatic patients at least 1 metre (3 feet) away from others in common waiting areas, if possible.
- Post visual alerts at the entrance to health-care facilities instructing persons with respiratory symptoms to practise respiratory hygiene/cough etiquette.
- Consider making hand hygiene resources, tissues and masks available in common areas and areas used for the evaluation of patients with respiratory illnesses.

7. Environmental cleaning

- Use adequate procedures for the routine cleaning and disinfection of environmental and other frequently touched surfaces.

8. Linens

Handle, transport, and process used linen in a manner which:

- Prevents skin and mucous membrane exposures and contamination of clothing.
- Avoids transfer of pathogens to other patients and or the environment.

9. Waste disposal

- Ensure safe waste management.
- Treat waste contaminated with blood, body fluids, secretions and excretions as clinical waste, in accordance with local regulations.
- Human tissues and laboratory waste that is directly associated with specimen processing should also be treated as clinical waste.
- Discard single use items properly.

10. Patient care equipment

- Handle equipment soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of pathogens to other patients or the environment.
- Clean, disinfect, and reprocess reusable equipment appropriately before use with another patient.

[1] For more details, see: WHO Guidelines on Hand Hygiene in Health Care (Advanced draft), at: http://www.who.int/patientsafety/information_centre/ghhad_download/en/index.html.
[2] The SIGN Alliance at: http://www.who.int/injection_safety/sign/en/

World Health Organization • CH-1211 Geneva-27 • Switzerland • www.who.int/csr

Source: Standard precautions in health care. Geneva: World Health Organization.2007 (https://www.who.int/docs/default-source/documents/health-topics/standard-precautions-in-health-care.pdf?sfvrsn=7c453df0_2).



National HIV/AIDS Programme
Department of Communicable Diseases
Ministry of Health
Democratic Republic of Timor-Leste