Content

Foreword

Lao PDR has responded to HIV/AIDS in an effective and timely manner in line with the international strategies, policies and lessons. HIV prevalence rate remains low (0.3%) among the population aged 15-49 years old based on 2017 estimates using the Asian Epidemic Model. In this model, it was estimated that about 11,716 people are living with HIV, of which about 5,631 people are receiving antiretroviral therapy by 2017.

Since 1990, the number of new infection have increased yearly. In 2017, it was about 1,400 new HIV infection reported. In the same year, there were about 311 AIDS cases reported and among them, 142 people died of AIDS. Most HIV patients presented in care when they were very sick. The mode of transmission is mainly through heterosexual transmission (87%). It was assumed that low condom use may have caused the HIV epidemic especially in high risk populations. Moreover, the national HIV /AIDS programme has many challenges in getting people to undergo HIV testing and provide treatment for those who have tested positive. Lao PDR endorsed the 90 – 90 – 90 fast track initiative to achieve by 2020, 90% of people living with HIV knowing their status, up from about 66% in 2016; 90% of people living with HIV are accessing antiretroviral treatment where current level is about 41% in 2016 and; 90% of patients receiving antiretroviral treatment having viral suppression which was estimated at 32% in 2016.

Since 2015, Lao PDR has implemented treatment policy by initiating antiretroviral therapy in people who have been diagnosed with HIV and AIDS in accordance with Treatment as Prevention policy. A lot of efforts has been made to improve counselling and testing by having same day result of HIV testing and getting people to antiretroviral therapy when tested positive. The “Treat All policy” has been implemented in all treatment sites to treat people regardless of their CD4 cell counts.

This edition intent to improve national policies and strategy in HIV diagnosis, care and treatment, and services of HIV/AIDS at health facilities in accordance with the global recommendations. This edition mainly refers to the 2016 World Health Organization guidelines on the use of antiretroviral therapy and other related WHO guidelines on HIV treatment and care. The Center of HIV/AIDS and Sexually Transmitted Infections with support from WHO had already published the Rapid Advice for the quick response of Treat All policy before the full updates of this treatment guidelines.

Process of guidelines development

This is the 5th edition of guidelines development on antiretroviral therapy. The new WHO recommendatons have been introduced to the Lao clinicans. All agreements have been reviewed by the national HIV/AIDS programme with technical assistance from WHO at both regional and country levels. The drafte of this guideline have been shared and discussed with local and international experts to finalize the draft through a consultation process.

Eligibility

All people living with HIV are encouraged to be given the same standard policy mentioned in this guideline. The guideline mainly applies for Lao people who are living with HIV. Patient center is very important to increase coverage of people on antiretroviral therapy. Currently, the HIV/AIDS services are provided free of charge including HIV testing and antiretroviral drugs. There may be some limitation to provide similar services for non-Lao residents or international migrants. The international migrants need to be refered by their home country to receive antiretroviral therapy.

Decentralization of antiretroviral therapy

Antiretroviral therapy is available in the central, provincial and district hospitals and administered by an experienced practitioner. In stable patients, it is recommended to be monitored at the community levels by using a back-up system. Medical practitioners at district levels can seek advice from skilled practitioners. Integration of antiretroviral therapy in other health services is recommended as well especially in ANC, delivery room and TB ward due to the very high number of lost follow-up cases.

HIV diagnosis and Testing

HIV testing is the gateway to HIV prevention, treatment, care and other support services. HIV testing services (HTS) refer to the full range of services that should be provided with HIV testing, including counselling (pre-test information and post-test counselling); linkage to appropriate HIV prevention, treatment and care, and other clinical services; and coordination with laboratory services to support quality assurance (QA) and the delivery of accurate results.

New recommendations on HIV diagnosis address the timing of and methods to virological testing (using nucleic acid testing) or DNA PCR, the use of rapid diagnostic tests in infants and young children, and retesting to verify diagnosis as a critical step before care and treatment is initiated.

- Retesting all people previously diagnosed HIV-positive before they enrol in care and initiate antiretroviral therapy (ART).
- Retesting is recommended in all HIV negative pregnant women in the third trimester, postpartum and during labour in low prevalence settings.
- Retesting is recommended in discordant couple or partners who have known on going HIV risk.
- Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure. This applies also to couples and partners from key populations.
- HIV-exposed infants should be tested with DNA PCR at the age of 4-6 weeks of birth so that treatment can be initiated immediately for those already infected with HIV. Mortality is very high among untreated infants infected with HIV in the first year of life. HIV exposed infants with non-detectable DNA PCR at 4-6 weeks should undergo DNA PCR test at 9 months of age to rule out HIV infection. If there is no access to DNA PCR testing, HIV exposed infants should receive at least an antibody test at 9 months of age. Infants whose HIV-antibody tests are reactive at nine months should continue DNA PCR test to identify HIV infection and the need for ART.
- Children with a parent living with HIV should be routinely offered HIV testing, if found either infected or at high risk of infection through breastfeeding, they should be linked to care for treatment and prevention.

- Infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen is collected to confirm the initial positive virological test result. Do not delay ART. Immediate initiation of ART saves lives and should not be delayed while waiting for the results of the confirmatory test.

The overarching goals of HTS are as follows:

- to identify people with HIV through the provision of quality testing services for individuals, couples and families;

- to effectively link individuals and their families to HIV treatment, care and support, as well as HIV prevention services, based upon their status; and

- to support the scaling up of high-impact interventions to reduce HIV transmission and HIV-related morbidity and mortality.

The diagnosis of HIV includes testing services in health-care facilities, free-standing sites and a wide range of community-based approaches, as well as HIV self-testing (HIVST). These approaches are described in detail in the 2017 WHO Consolidated guidelines on HIV testing services (1) and 2016 HIV self-testing and partner notification: Supplement to consolidated guidelines on HIV testing services. (2)
The use of HIV rapid diagnostic tests (RDTs) at the point of care has become an important strategy to expand access, increase the return of same-day results and enable immediate linkage and follow-up. Countries should choose a strategic mix of service delivery models to achieve equitable access to HIV testing services, based on the local context, nature of the epidemic, cost– effectiveness and available resources. The mix should facilitate diagnosis of as many people living with HIV as early as possible to enable timely enrolment in care and access to antiretroviral therapy (ART).

The WHO Five C's – consent, confidentiality, counselling, correct test results and connection to care and treatment – are principles that apply to all models of HTS and in all circumstances. (3) The Five C's are as follows:

• **Consent**: People receiving HTS must give informed consent to be tested and counselled. Verbal consent is sufficient; written consent is not required. They should be informed of the process for HIV testing and counselling and of their right to decline testing.

• **Confidentiality**: HTS must be confidential, meaning that what the HTS provider and the client discuss will not be disclosed to anyone else without the expressed consent of the person being tested. Confidentiality should be respected, but it should not be allowed to reinforce secrecy, stigma or shame. Shared confidentiality with a partner, family members, trusted other and a health-care provider is often highly beneficial.

• **Counselling**: Pre-test information can be provided in a group setting, but all people should have the opportunity to ask questions in a private setting if they request it. All HIV testing must be accompanied by appropriate and high-quality post-test counselling, based on the HIV test result and HIV status reported. QA mechanisms as well as supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling.

• **Correct**: Providers of HIV testing should strive to provide high-quality testing services. Quality management systems (including QA) should be in place for all HTS, regardless of where testing takes place, to ensure that people receive a correct diagnosis. QA should include both internal and external measures, and should receive support from the national reference laboratory. All people who receive a positive HIV diagnosis should be retested to verify their diagnosis before initiation of HIV care or treatment.

• **Connection**: Linkage to prevention, treatment and care services should include effective and appropriate follow-up, including long-term prevention and treatment support.

Provider initiative counselling and testing (PICT)

Provider initiative counselling and testing (PICT) is recommended for TB patient, STI patient, and pregnant women in antenatal care. To increase uptake of HIV testing during pregnancy, provider initiated routine testing, with a right to refusal (an "opt-out" approach) should be offered in all ANC sites. Testing in ANC should become routine practice so that women suspected of having HIV or women who get referred for the test through PITC don't feel stigmatized. The partners and family member (including children) of all people enrolled in HIV care and treatment should be offered HIV testing. ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong. Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure. This applies also to couples and partners from key populations.

Testing algorithm

For low-prevalence settings such as Lao PDR, the WHO recommends HIV diagnosis is made following three separate, sequential reactive tests:

- Low prevalence: In settings with less than 5% HIV prevalence in the population tested
- Diagnosis of HIV-positive: Three sequential reactive tests
    - The first-line assay (T1) should be the ***most sensitive*** assay available, with ***more specific assays*** used as second-line (T2) and third-line (T3)
    - Positive Predictive Value (PPV) based on 2 test results is too low to provide an HIV diagnosis
    - When T1+; T2+, a 3rd separate and distinct assay (T3) should be used to confirm the results and issue an HIV-positive diagnosis

A HIV positive result will only be confirmed after three sequential tests, conducted on three distinct assays, are reactive. Intensive pre-test counseling is no longer recommended and may create barriers to service delivery. Additionally, individual risk assessment and individualized counseling during the pre-test information session is no longer recommended.

Details of the testing algorithm and assay characteristics evaluated and selected for Lao PDR can see in annex 1.

Retesting prior to enrolment in care to verify HIV diagnosis

WHO recommends that all people newly or previously diagnosed with HIV should be re-tested before starting ART. Retesting aims to rule out possible technical or clerical errors. This includes specimen mix-up through mislabeling, transcription errors and random errors

either by the provider or the test device. While retesting will not exclude misdiagnosis related to poor choice of a testing algorithm, this risk should be minimal with adequate validation of the testing algorithm.

Retesting people on ART is not recommended in this , as there are potential risks of incorrect diagnosis. The effect of ART in suppressing viral replication may extend to suppression of the immune response and therefore of antibody production. Once a person is started on ART, low antibody titres – particularly if oral fluid-based rapid diagnostic tests are used – make it challenging to discern whether an individual is indeed HIV positive.

People undergoing HIV testing must be made aware of the risk of incorrect diagnosis if they do not disclose that they are on ART. All people receiving HIV testing should be asked if they have been tested previously and told that they are HIV infected and /or if they are now on ART or have ever received ART.

Retesting a person diagnosed to verify the diagnosis should include:

- retesting of a new specimen for each newly diagnosed individual, preferably conducted by a different provider using the same testing algorithm, prior to initiation of ART;
- retesting that is preferably conducted at a different site, ideally the site where the decision about ART initiation will be made.

Routine Screening in High Risk Populations

The vast majority of individuals do not require routine testing to verify an HIV-negative status, particularly in the absence of any ongoing risk. However, it is important to accurately identify individuals who test HIV-negative and may require routine testing in certain circumstances.

HIV-negative individuals with ongoing risk from the following populations who test HIV-negative warrant retesting:

- People with known recent HIV exposure should be re-tested after 2-4 weeks if negative
- People from key populations such as female sex workers, MSM with multiple partners, and injecting drug users should be recommended to come back for testing once per year, or on known exposure to HIV infection
- Testing is recommended regularly (at least once a year) in discordant couple or partners who have known ongoing HIV risk
- Routine testing is recommended in all HIV negative pregnant women. In Lao PDR, testing is recommended at two time points for all pregnant women: one at the first ANC encounter and one ideally in the third trimester. If the test in third trimester is missed, the woman can be retested during labor or post-partum to confirm HIV negative status.
- Individuals seen for a diagnosis or treatment of STI
- Outpatients with clinical conditions indicative of HIV infection
- Individuals taking PEP or PrEP

Pre-Exposure Prophylaxis

Oral pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs before HIV exposure by people who are not infected with HIV in order to block the acquisition of HIV. In the appropriate circumstances, PrEP should be given to people at substantial risk. Substantial risk is defined as high HIV incidence (more than 3 per 100 person years) especially in men

who have sex with men, transgender women, heterosexual partner men and women who have sexual partners with untreated or inadequately treated HIV infection.

PrEP should be considered for:

- HIV-negative pregnant and breastfeeding women, who:
    - Have partners with untreated HIV; or/and
    - Have partners that have been on ART for less than six months or who do not know the details for her partner's viral suppression if on ART treatment, including when the partner is known to have poor ARV adherence,

  These women are at high risk of acquiring HIV, and HIV acquired during pregnancy and breastfeeding is associated with an increased risk of HIV transmission to the infant. The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection. PrEP can protect the HIV-negative partner in a serodiscordant relationship when the HIV-positive partner is either not on antiretroviral therapy (ART) or has not yet achieved viral suppression. (4) Men who have sex with men, transgender people, and people who sell sex
    - Men who have sex with men, transgender people, and people who sell sex

PrEP regimen:

Daily dose is the current WHO-recommended option. The product used in Lao PDR for PrEP will be TDF 300 mg + 3TC 300mg PO daily. PrEP is highly effective if you take it as prescribed. If you forget to take a tablet, take it as soon as you remember. Significant levels of efficacy will be achieved if daily adherence is high (i.e. PrEP provides high levels of protection in people who take PrEP medicines regularly); PrEP reaches protection after 7 doses for vaginal sex and 4 doses for anal sex.

Additional HIV prevention measures should be taken for seven days after starting PrEP. Time is needed to build up protective levels of the drug in the blood and other tissues. PrEP is safe and effective even if you are taking hormonal contraceptives, sex hormones or non-prescription medications. (5) (6) (7) (8) (9)

Criteria for PrEP

- HIV-negative (Ensuring HIV-negative status before initiation and during use of PrEP is important to minimize the development of resistance among those who become infected while taking anti retrovirals for PrEP).
- No suspicion (acute viral syndrome: consider re-testing in 1 month before PrEP initiation)
- Substantial risk of HIV infection
- No contraindications to TDF/3TC
- Sexual partner with HIV who is not virally supressed or untreated
- Willingness to use PrEP as prescribed, including periodic HIV testing

Contraindications:

- HIV-infection
- Estimated creatinine clearance <60ml/min
- Signs/symptoms of acute HIV infection, probable recent exposure to HIV
- Allergy or contraindication to any medicine in the PrEP regimen.

Discontinuation for PrEP

PrEP can be discontinued when an individual is no longer at risk and when this situation is likely to be sustained. PrEP is only likely to be needed during periods of risk rather than for

life. PrEP maybe discontinued 28 days after the last potential exposure to HIV if an individual does not have continuing substantial risk for acquiring HIV.
For individuals with HBV, who are initiated on PrEP, TDF is an effective treatment for HBV as well; however, stopping PrEP might lead to severe hepatic flares. Therefore in cases of chronic HBV infection PrEP should be taken daily and continued for >1 year if resources to treat HBV are not available.

Laboratory requirement
HIV testing (following the national testing algorithm), Creatinine, and HBV are required before PrEP is offered and should be conducted regularly every three months for HIV and STI screening (e.g. syphilis, gonorrhoea, chlamydia) and every 6 months for Creatinine while PrEP is taken. If HBsAg negative: consider vaccination; if HBsAg positive: assess HBV treatment indications; consider risk of flare if PrEP stopped.
Using quality-assured HIV testing is important and ensuring the use of a more sensitive test as the A1 assay has multiple advantages, including more accurate HIV diagnosis and treatment, better counselling for people with acute HIV infection and minimizing the risk of drug resistance during PrEP. This will help avoid initiation of PrEP during the early period of seroconversion because tests with higher sensitivity support higher accuracy in results and reduce potential of false negativity.

Linking PrEP with other health services
Adherence counselling, safety monitoring and HIV retesting every three months, in addition to other existing HIV prevention options, including condoms, should be offered.

Side effects (4)

- 1 in 10 PrEP users may have side-effects such as nausea, abdominal cramps, headache; these are usually mild and resolve over the first month of taking PrEP.
- 1 in 200 may have creatinine elevation (typically reversible if PrEP is discontinued).
- 1% average loss of bone mineral density (recovers after stopping PrEP).

Operational guidance
Further information about PrEP implementation will be made available by CHAS during the roll-out.

Post- Exposure Prophylaxis

Everyone possibly exposed to HIV should be assessed by a trained health care worker. Essential components of the clinical pathway include assessing the mechanism of exposure and assessing eligibility for post-exposure prophylaxis, examination of the wound and initial first-aid treatment.

Figure 1: Care pathway for people exposed to HIV (10)

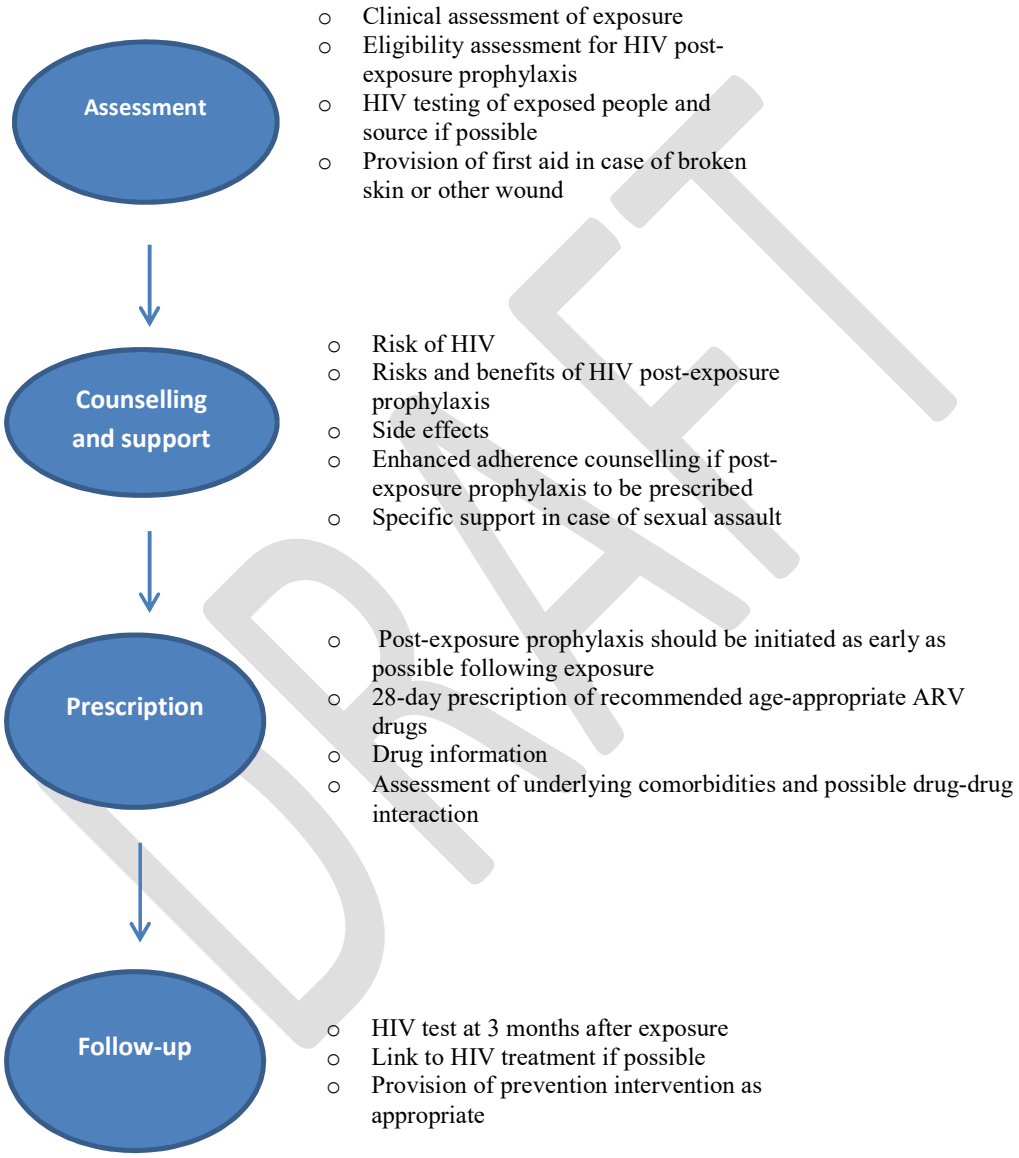


Table 1: Assessment of Risk of HIV by Exposure risk (11)

Exposure	High Risk	Low Risk	No Risk
Body fluids	• Blood • Semen, vaginal secretions • Cerebro-spinal fluid • Human breast milk • Fluid from burns or skin lesions • Other body fluids (synovial, peritoneal, pleural, pericardial) contaminated with visible blood	• Saliva • Urine	• Contact with skin

Type of exposure	• Per cutaneous exposure
	  ○ Injury with contaminated hollow needle or sharp object.
	• Muco-cutaneuos exposure
	  ○ Direct contact between contaminatedbody-fluid and eye or mucous membrane		

Table 2: Risk of Transmission and Post-Exposure Prophylaxis (11)

Disease	Transmission rate	Management
HIV	Per-cutaneous: 0.3% Muco-cutaneous: 0.03-0.09%	PEP (see below)
HBV	Per-cutaneous: 10-30%	Vaccination
HCV	Per-cutaneous: 0-10%	None

Table 3: Assessment of Source Patient

Source Patient	Management
HIV-status unknown	Counseling and HIV-testing as soon as possible
HIV negative	PEP not needed
HIV positive	PEP according to exposure risk Higher risk of transmission if advanced HIV disease, high viral load, no ART

Recommended Eligibility Criteria for Post-Exposure Prophylaxis in Occupational Settings

1. Less than 72 hours has elapsed since exposure; and
2. The exposed individual is not known to be HIV-infected; and
3. The person who is the source of exposure is living with HIV or has unknown HIV status; and
4. Exposure was to blood, body tissues, visibly blood-stained fluid, concentrated virus, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid or amniotic fluid; and
5. Exposure penetrated the skin with spontaneous bleeding or deep puncture or splash of significant amount of fluid to mucous membrane or prolonged contact of risk substance with non-intact skin; and
6. If the skin was penetrated, exposure was from a recently used hollow bore needle or other sharp object visibly contaminated with blood.

Exposed that does not require PEP

1. when the exposed individual is already HIV positive;
2. when the source is established to be HIV negative; and
3. exposed to bodily fluids that does not pose a significant risk: tears, non-blood-stained saliva, urine and sweat

Management after Exposure

A. Immediately after Exposure

Clean the Exposure Site

***A. If the skin is broken following an injury with a used needle or sharp instrument*:**

Wash the site immediately using soap or a mild disinfectant solution.

- o If running water is not available, clean the site with a gel or hand-rub solution.
- o Do not use any strong solutions, such as alcohol, bleach or iodine, as these may irritate the wound and make the injury worse.

B. After a splash of blood or body fluids:

- To unbroken skin:
  -Wash the area immediately.
  -If running water is not available, clean the area with a gel or hand-rub solution.
- To the eye:
  -Wash the exposed eye immediately with water.
  -If you are wearing contact lenses, leave them in place while washing the eye, as they form a barrier over the eye and will help protect it. Once the eye has been cleaned, remove the contact lenses and clean them in the usual way. This will make them safe to wear again.
  - Do not use soap or disinfectant on the eye.

- **To the mouth:**

-Spit the fluid out immediately.
-Do not use soap or disinfectant in the mouth.
-Rinse the mouth thoroughly and spit out again. Repeat this process several times.

B. Contact health provider in-charge

Responsibilities of the Clinical Officer or Medical Officer

- Determine if the exposure is potentially high risk based on the information`

- If exposure is considered high risk: refer to the nearest VCT centre IMMEDIATELY and arrange for shortened version of pre-test counseling and HIV rapid test for exposed employee. If this is likely to take longer than 1 hour, give first dose of PEP before referring.
- Explain that all HIV testing is CONFIDENTIAL
- Ensure the exposed employee also has a CBC and liver test (ALT/AST) done
- Arrange post-test counseling
- Counsel regarding post-exposure prophylaxis (PEP): risks and benefits
- Complete the Report Form describing the details surrounding the exposure
- Determine the need for PEP based on the nature of the exposure and the risks and benefits of taking (or not taking) antiretroviral medications. *PEP should be started preferably within 1-2 hours of the exposure*. If not started within 72 hours of the exposure, PEP will not be provided, as it is not likely to be effective after this time period.

  - Do not give PEP to employees who test positive
  - If employee tests positive, refer to ARV clinic after adequate counselling.
  - Observe confidentiality

Documentation of the incident

- Record date and time of exposure, exposure source, details of the event
- Details of PEP treatment if given
- Follow up

Assessment and Counseling of Exposed Person

Counseling

1) Give health care worker pre- test counseling
2) Test the health care worker (baseline tests)
   - HIV
   - Creatinine
   - Hepatitis B and hepatitis C
   - Hemoglobin, ALT
3) Inform HCW that PEP is not 100% effective.
4) Counsel HCW that they must not give blood and must practice safer sex and safer injecting practices until outcome are known.
5) Review HCW (post- test counseling) and give baseline results.
6) Offer hepatitis B vaccination if HBsAg negative and HBsAb negative.
7) Provide counseling on further HIV transmission including condom use, avoiding pregnancy and breast feeding and not donating blood until the person is tested HIV negative three months after the exposure.

More recent national guidelines have shifted towards recommending a three-drug regimen for everyone, given the availability of less toxic and better tolerated medications, the difficulty in evaluating the risk of drug resistance and need to simplify prescribing

Prescribing frequency

All eligible individuals for post-exposure prophylaxis are recommended to initiate start ARV regimen as soon as possible after exposure, ideally within 72 hours. A 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment.

Table 4: Antiretroviral for PEP (3)

Population	Preferred regimen	Alternative regimen
Adults (including pregnant women) with HIV	TDF+3TC+ATV/r	TDF+3TC+LPV/r
Children ≤ 10 years old	AZT+3TC+LPV/r	ABC+3TC+LPV/r TDF+3TC +LPV/r

Although post-exposure prophylaxis is ideally provided within 24 hours of exposure, people may not be able to access services within this time. Providers should consider to range of other essential interventions and referrals that should be offered to clients presenting after the 72 hours.

Table 5: Doses of ARV drugs for HIV post-exposure prophylaxis for adults and adolescents

Generic name	Dose

Tenofovir (TDF)	300 mg once daily
Zidovudine (AZT)	300 mg twice daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Atazanavir/ritonavir (ATV/r)	300 mg + 100 mg once daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily or 800 mg/200mg once daily

Table 6: Doses of ARV drugs for HIV post-exposure prophylaxis for children (10)

Drug	Strength of tablets	Number of tablets by weight band morning (AM) and evening (PM)									
		3.0-5.9kg		6.0-9.9kg		10.0-13.9kg		14-19.9kg		20-24.9kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Solid formulations											
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3
3TC	Tablet (dispersible) 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3
LPV/r	Tablet (heat stable) 100 mg/25mg	-	-	-	-	2	1	2	2	2	2
Liquid formulations											
AZT	10mg/ml	6ml	6ml	9ml	9ml	12ml	12ml	-	-	-	-
3TC	10mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-
LPV/r*	80/20mg/ml	1ml	1ml	1.5ml	1.5ml	2ml	2ml	2.5ml	2.5ml	3ml	3ml

*LPV/r syrup should not be used for premature babies or infants younger than 2 weeks of age. NVP should be used instead at the following dose: 5ml twice daily (3.0-5.9 kg), 8ml twice daily (6.0-9.9 kg) and 10ml twice daily (10.0-13.9 kg) if syrup available; 1 tablet twice daily (3.0-5.9 kg), 1.5 tablets twice daily (6.0-9.9 kg) and 2 tablets twice daily (10.0-13.9 kg) if dispersible 50mg tablets are available.

Non Occupational Post-Exposure Prophylaxis (nPEP)

Non occupational post-exposure prophylaxis is defined as prophylaxis for any exposure happing outside occupational matters. The regimen is the same between nPEP and PEP by using TDF+3TC+ATV/r for adults and AZT+3TC+LPV/r for children less than 10 years old.

Situations where PEP may be provided

- Unprotected sexual exposure including rape, etc.

Situations where PEP should not be provided

- In situation of nPEP where PEP should not be provided in cases of persistent potential exposure to HIV such as discordant sex partners who rarely use condoms, repeated unprotected sex with sex workers or other non-regular partners, injecting drug users who often share injection equipment.
- Person who engage in frequent, recurrent risk exposure behavior should be counseled and provided with appropriate risk-reduction intervention

Management of providing PEP in nPEP

Table 7: Clinical Management of Unprotected Sexual Exposure (11)

Evaluation	Recommendation
The initial post-visit	• Provide initial crisis intervention (such as emotional support) and first aid. • Explanation for health examination* • Conduct a general health examination, including overall status and recording injuries. • Assess the risk of HIV transmission**. • If appropriate, offer the initial dose of PEP medicine*** • If rapid testing is available, offer HIV pre-and post-test counseling. • Provide clinical management and collect forensic evidence, including pregnancy • Assessment and presumptive treatment of sexually transmitted infections
Establishing eligibility for PEP	• See Recommended PEP above
Informed consent for PEP after sexual assault	• Separate consent should be obtained for the collection of forensic specimens for HIV testing and blood examination • Consent may be given verbally • Consent may be obtained from a parent or guardian
Pregnancy testing and emergency contraception	• All women of childbearing age • If initial pregnancy test is negative, a second pregnancy test may be required in one month later • Emergency contraception is needed, if the pregnancy test is negative • Emergency contraception can be given up to 120 hours (five days) after sexual assault. • Pregnant women at the time of presentation can be offered PEP
Care of children after sexual assault	• The reporting of cases of sexual assault of children should be in accordance with national laws
Follow-up	• Side effects from the PEP medicine: feel sick or tired when taking medicine • Adherence of PEP medicine • Mental health needs or referral to other services • Clinical signs and symptoms of sexually transmitted infections • Repeat HIV testing and counseling at 2-4 months after exposure and again at 4-6 months

* The person should be informed about the general process involved for both the general and, if also conducted at this location, the forensic examination.

** The estimated risk of HIV transmission via sexual exposure ranges from 4 per 10 000 exposure incidents for insertive penile-vaginal intercourse to 138 per 10 000 for receptive anal intercourse. (12)

*** HIV testing or, if rapid testing results are available, within an hour or two immediately to obtain the test results. If forensic evidence is to be collected, it should first be confirmed whether oral sex was performed, as in this case an oral swab should be obtained before taking any medicine.

Counseling

- Assess extent of risk exposure, frequency of exposure and timing
- Try to ascertain the HIV status if the source (often unknown)
- Evaluate for sexually transmitted infections
- Assess the need for emergency contraception ("morning after pill")
- Give HIV pre-test counseling
- Test the individual (baseline tests)
    1. HIV
    2. Creatinine
    3. Hepatitis B and hepatitis C
    4. Swabs and cultures for gonorrhea and Chlamydia if available
    5. Rapid syphilis test (see Annex 21)
    6. Pregnancy test (if available) following appropriate counseling
- Counsel individuals that they must not give blood and must practice safer sex and safer injecting practices and not breast feed until outcome is known
- Review and give baseline results
- Offer hepatitis B vaccination if HBsAg negative

Recommended PEP Eligibility Criteria among Unprotected Sexual Exposure including Rape

1. Less than 72 hours has elapsed since exposure; or
2. The exposed individual is not known to be HIV-infected; or
3. The person who is the source of exposure is living with HIV or has unknown HIV status; or
4. A defined risk of exposure, such as: receptive vaginal or anal intercourse without a condom or with a condom that broke or slipped; or
5. Contact between the perpetrator's blood or ejaculate and mucous membrane or on-intact skin during the assault; or
6. Receptive oral sex with ejaculation; or
7. The person who was sexually assaulted was drugged or otherwise unconscious at time of the alleged assault and is uncertain about the nature of the potential exposure; or
8. The person was gang raped.

Service delivery

1) Differentiated care

Broadly, four groups of patients with specific needs can be identified. First, people who present when well, potentially with higher CD4 cell counts, may require additional and targeted adherence and retention support in order to commit to lifelong ART. Second, people presenting to care with advanced disease require a fast-tracked clinical and care package to initiate ART and prevent death and reduce ill health. A third group of individuals are those who are already on ART but need careful monitoring to ensure timely action as required; this may include clinical care, additional adherence support and timely switch to second-line ART regimens in the case of treatment failure. A final group of stable individuals are likely to represent the majority of people on ART and they can safely reduce the frequency of clinic visits, potentially receiving ART in community settings.

Such an approach can relieve overburdened health-care settings and enable more attention to be paid to patients with more complex conditions who require prompt diagnosis and treatment of opportunistic infections, enhanced adherence support, viral load testing and potential changes of regimen, HIV drug resistance testing or other specialized care. Receiving care closer to their home can also reduce direct and indirect costs related to transport and long facility waiting time for patient**.**

Diversity of care needs for people living with HIV

People presenting when well	Adherence and retention support
People with advanced disease	Clinical package to reduce mortality and morbidity
Stable individuals	Reduced frequency of clinic visits and community ART delivery models
Unstable individuals	Adherence support, viral load testing, switch to second-line ART if indicated, monitoring for HIV drug resistance (HIV-DR)

People with advanced disease are defined as those presenting to care with a CD4 count below 200 cells/mm^3 or WHO disease stages 3 and 4. The package of care for these people should include the following:

- rapid initiation of ART (once the risk of immune reconstitution inflammatory syndrome is ruled out);
- systematic screening for Cryptococcus antigen;
- screening and treatment for tuberculosis or isoniazid preventive treatment as indicated;
- screening for toxoplasmosis and co-trimoxazole prophylaxis; and
- intensive follow-up.

Stable individuals are defined as those who have received ART for at least one year and have no adverse drug reactions that require regular monitoring, no current illnesses or pregnancy, are not currently breastfeeding and have good understanding of lifelong adherence and evidence of treatment success (i.e. two consecutive viral load measurements below 1000 copies/mL, see figure 2). In the absence of viral load monitoring, rising CD4 cell counts or CD4 counts above 200 cells/mm^3, an objective adherence measure, can be used to indicate treatment success. The package of care for stable individuals can include the following:

- less frequent (3–6-monthly) clinic visits;
- less frequent (3–6-monthly) medication pickup;
- community-based care; and
- cessation of CD4 count monitoring if viral load testing is available.

While less frequent clinic visits are recommended for stable individuals, rapidly growing children (0–5 years old) and adolescents will need to be monitored more frequently for treatment dosing/weight changes and adherence support.

2) Linkage from HIV testing to enrollment in care

Following an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV. The following interventions have demonstrated benefit in improving linkage to care following an HIV diagnosis:

- Integrated services, where HIV testing, HIV prevention, treatment and care, TB and sexually transmitted infection screening and other relevant services are provided together at a single facility or site
- Providing on-site or immediate testing for creatinine, CD4 cell count with same-day results
- Decentralized ART provision and community-based distribution of ART
- Using communication technologies, such as mobile phones and text messaging, which may help with disclosure, adherence and retention, particularly for adolescents and young people
- Promoting partner testing may increase rates of HIV testing and linkage to care, as may approaches that encourage male involvement in prevention of mother-to child transmission settings
- Intimate partner notification by the provider, with permission, is feasible in some settings; it identifies more HIV-positive people and promotes their early referral to care
- Support and involvement of trained lay providers who are peers and act as peer navigators, expert patients/clients and community outreach workers to provide support, and identify and reach people lost to follow-up
- quality improvement approaches using data to improve

3) Retention in care

Community support for people living with HIV can improve retention in HIV. The following community-level interventions have demonstrated benefit in improving retention in care:

- package of community-based interventions
- adherence clubs

Package of community-based interventions

Community-based interventions identified with beneficial impact on retention in HIV care included: support centred on the needs of the individual, counselling and psychosocial support by lay adherence counsellors or patient advocates and family and peer support. The lay counsellors or patient advocates assisted patients by linking health facilities with communities, providing counselling and patient-centred support and visiting patients in their home environment. Bringing services closer to communities through decentralization has also improved retention in HIV care.

Adherence clubs

The systematic review identified one retrospective cohort study (13) evaluating the impact of facility-based adherence clubs on loss to follow-up or death at 40 months, with a significant reduction compared to standard care. No studies were identified in the review evaluating the impact of adherence clubs on outcomes for adolescents or children.

Population considerations

1) Pregnant women

Many programmes are implementing community-based interventions: peer support such as mothers-to-mothers programmes and peer adolescent support groups for adolescent pregnant women living

with HIV. Structured counselling sessions and telephone reminders may also have thepotential to support the process of transition from MNCH-based services to HIV care clinics. This transition period is often a critical point in which a substantial number of women and their infants discontinue care.

2) Caregivers

Caregivers are responsible for understanding the importance of retaining children in care, especially
younger children. Disclosure to children typically occurs late, making it challenging to discuss the importance of follow-up. WHO recommends age-appropriate disclosure to children (14). Solutions include:

- supporting caregivers to attend for regular follow-up; and
- reinforcing to caregivers the importance of the process of disclosing to the child, which
- can begin early with age-appropriate messaging and tools.

3) Adolescents

Frequent clinic visits, time spent waiting for services and having to miss school discourages adolescents' engagement in care. Negative attitudes of health workers, concerns regarding privacy and confidentiality and limited opportunity to discuss their concerns also act as barriers to retention for younger people. Distance to facilities and out-of-pocket expenses may restrict their engagement. Service delivery models beyond the facility, which support adolescents to engage in care, such as peer-based interventions and community-based services, should be considered. Peer interventions
are highly valued by young people.

- providing adolescent services at specific times or in separate areas with flexible
- appointment systems that accommodate school hours;
- comprehensive services that address multiple needs, including psychosocial support and
- sexual and reproductive health (SRH); and
- close monitoring of adolescents' engagement in care, rapid proactive follow-up and
- implementation of strategies for re-engagement.

4) Men

A systematic review (15) identified 69 studies demonstrating that men had a 37% increased risk of death while on ART compared to women, after adjusting for baseline characteristics. This is partly explained by the fact that men tend to be diagnosed later and are more likely to start ART late. In several settings, initiatives to improve men's engagement in care have focused on engaging them in services for PMTCT. Innovative service delivery models are essential to improve men's access to HIV care services and ART initiation. Programmes need to routinely disaggregate data by sex in order to better monitor access to and outcomes of treatment for both men and women

4) Frequency of clinic visits and medication pickup

Less frequent clinical visits (3–6 months) are recommended for people stable on ART. Less frequent medication pickup (3–6 months) is recommended for people stable on ART.

Population considerations

1) Pregnant and breastfeeding women

Pregnant or breastfeeding women on ART may require closer follow-up and more frequent visits than other populations. Psychosocial support and counselling requirements may need to be considered, especially with regard to infant feeding and postpartum care. Differential care models should be used from the beginning of pregnancy until the end of the breastfeeding period.

2) Children

The needs of the children evolve as they grow, especially during rapid phases of growth and development, early adolescence and around the time of disclosure. Differential care models should be modified to the child's needs. Growth monitoring is an important component of paediatric HIV care and is necessary for dose adjustment of ART. This should be emphasized within the differential care model.

3) Adolescents

Rapid development may impact on adherence, retention and support requirements for adolescents. The evolving capacities and emerging independence of adolescents need to be recognized as well as the involvement of caregivers. Busy and changing daily routines and competing priorities can make frequent visits challenging for adolescents. Close monitoring of adolescents' engagement in care, rapid and proactive follow up and implementation of strategies for re-engagement are critical. Facilitating independence and self-management can support differential care for adolescents. Peers and other community-based services can also facilitate early identification of adolescents requiring
additional support and follow-up.

5) Decentralization

Decentralization of HIV treatment and care should be considered as a way to increase access to and improve retention in care:

- initiation of ART in hospitals with maintenance of ART in peripheral health
- facilities
- initiation and maintenance of ART in peripheral health facilities ; and
- initiation of ART at peripheral health facilities with maintenance at the community level

6) Integrating and linking services

Chronic care requires integrating and linking related services to ensure comprehensive and consistent patient management over time, including provision of related services in the same settings, systems to share information and effective referrals across settings and providers. Integrating and linking services are likely to reduce missed opportunities for initiating ART, enhance adherence support and optimize retention in care.

In generalized epidemic settings, ART should be initiated and maintained in eligible pregnant and postpartum women and in infants at maternal and child health-care settings, with linkage and referral to ongoing HIV care and ART, where appropriate (strong recommendation, very low-quality evidence. Sexually transmitted infection and family planning services can be integrated within HIV care settings.

7) Delivering HIV services to adolescents

Adolescent-friendly health services should be implemented in HIV services to ensure engagement and improved outcomes.

- Community-based approaches can improve treatment adherence and retention in care of adolescents living with HIV

- Training of health-care workers can contribute to treatment adherence and improvement in retention in care of adolescents living with HIV
- Adolescents should be counselled about the potential benefits and risks of disclosure of their HIV status to others and empowered and supported to determine if, when, how and to whom to disclose

8) Adherence to antiretroviral therapy

Adherence support interventions should be provided to people on ART. The following interventions have demonstrated benefit in improving adherence and viral suppression:

- peer counsellors
- mobile phone text messages
- reminder devices
- cognitive-behavioural therapy
- behavioural skills training and medication adherence training
- fixed-dose combinations and once-daily regimens

The benefits significantly outweigh any potential harm for all interventions identified. Peer counsellors are generally considered to be a low-cost intervention and, in some settings, have been highly cost-effective. Interventions such as cognitive-behavioural therapy and behavioural skills training require initial increased investment for training and resources. Reminder devices, telephone interventions and mobile phone text messages are low cost in the majority of low- and middle-income countries. Cost–effectiveness will vary depending on the setting and epidemic context.

Population considerations

Pregnant and postpartum women

The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence. It is estimated that around a quarter of pregnant women have inadequate ART adherence, and this is higher during the postpartum period (16). Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Other individual factors include suboptimal understanding of HIV, ART and PMTCT, lack of partner disclosure and support, and fear of stigma and discrimination. Service delivery barriers include poor-quality clinical practices, gaps in provider knowledge and training, poor access to services and health worker attitudes.

Adolescents

It is estimated that over one third (38%) of adolescents globally are suboptimally adherent to ART, with substantial regional variation (17). In addition to common challenges to adherence, adolescents face specific challenges, including psychosocial issues such as peer pressure, the perceived need to conform and inconsistent daily routine. Adolescents are often left out of decisions and have limited opportunities to discuss their concerns, and there is limited availability of adolescent-specific treatment literacy and adherence counselling tools. For adolescents who are transitioning from paediatric to adolescent care, additional challenges may include assuming increased responsibility for their own care, issues relating to disclosure to peers or partners, difficulties in navigating the health-care system, lack of links between adult and paediatric services and inadequately skilled health workers.

Infants and young children

Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of children living with HIV may themselves be living with HIV, and suboptimal HIV care and treatment for family members could result in suboptimal care for the child. Other challenges include lack of nutrition support, limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements and difficulties in swallowing tablets.

People with mental health conditions and substance use

People with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate medical therapies for people with mental disorders can help to improve adherence. WHO recommends that assessment and management of depression should be included in care services for all people living with HIV. Use of alcohol and other substances may also contribute to poor adherence to ART. Alcohol and substance use can lead to forgetfulness, poor organization and diversion of monetary resources. Treatment of depression and management of substance use
disorders can improve HIV treatment outcomes. WHO recommends treatment of depression and substance use disorders regardless of HIV status. Other key services for people with HIV who use drugs, such as needle and syringe programmes and drug substitution therapy, provide further opportunities to support adherence.

Key populations

In many settings, key populations face multiple challenges related to stigma and discrimination that can affect access to health services, all of which may impact negatively on adherence.

Adherence information and counseling

Pharmacy refill records

- Pharmacy refill records provide information on when people pick up their ARV drugs. Pharmacy records are more reliable than self-reporting and are already a part of national monitoring and evaluation frameworks in many settings.

Self-reporting

- Self-reported data are easy to collect and can be a useful adjunct to estimating nonadherence
- but are subject to recall bias (18). Counselling on the importance of remembering ART doses and an environment that promotes and enables honest reporting of non-adherence are critical components of monitoring adherence to ART in routine care settings.

Pill counts

- Counting the remaining pills in bottles may help to assess adherence. Pill counts usually take place at routine health-care visits. However, some people discard tablets prior to health-care visits, leading to overestimated adherence. Counting pills also requires health-care personnel to invest significant time and may not be feasible in routine care settings. Pill count has been found to perform better when combined with self-reported adherence (19).

The process of offering information, counseling and adherence support must be carried out by staffs (counselor and/or PLHIV) who understand problems concerning PLHIV. There are 3 steps in this process.

Step 1 – Giving information

Clients are given basic information enabling them to understand the need for a high level of

commitment to treatment and adherence. Information can be provided to a group of PLHIV if the facilitator has some understanding of group dynamics and is able to stimulate group discussion**.**

Step 2 – Counseling – in one or more individual sessions

Help the client explore his/her feelings. Many clients will be preoccupied with problems related to family, job, relationships etc, and cannot focus on strict adherence until they have released negative feelings about these problems

Many will have no private place to store their medicines and will not be able to take them in secret. Not wanting others to know their HIV status is by far the commonest reason that providers come across for poor adherence. The client needs to be realistic about who needs to know their HIV status and how to tell them.

Step 3 – Solving practical problems and creating a treatment plan

Where will the ARV drugs be stored? At what time will they be taken? Who will remind the clients to take them if he or she forgets? What will the client do if her or his normal routine is interrupted? A time should be arranged to meet or telephone the client within a few days in order to discuss any problems.

Intervention strategies for increasing adherence

Adherence is a dynamic process that is determined by a matrix of inter-related factors that shift over time. It is influenced by multiple factors; no factor stands alone and requires a combination of promotion strategies;

1. Requires integrated multidisciplinary team efforts (eg, physicians, nurses, counselors and pharmacists).
2. Promote positive relationship between the patients and health care provider team.
3. Prepare patient with verbal and visual instructional materials geared to the patient's level of knowledge/understanding (eg, how to take medications, why adherence is essential).
4. Pretreatment adherence counseling and patient assessment.
5. Pay special attention and understanding to every aspect of the patients that would be obstacle to adherence (eg. language, literacy, psychological, stress, depression, stigma, active substance abuse, living condition, work environment and economic barriers).
6. Repeat instructions and provide practice in detail (eg, pretreatment simulation trial and practical problem solving).
7. Tailor treatment selection to patient preferences, use simple and low pill burden regimen. However, do not assume that treatment simplification will solve all problems with adherence.
8. Discuss the follow up plan and the adherence promoting strategies to be used for the patient.
9. Measure adherence every visit.
10. In case of non-adherence, explore reasons for prior failures and establish readiness to start antiretroviral therapy.

Promotion of ARV Adherence

The most common reason for ART failure is poor adherence. Adherence should be assessed at every clinic visit. A high degree of adherence to ARV drugs (100%) is necessary for optimal virological suppression. A patient who is 95% adherent will have treatment success in 80%. A patient is considered to non-adherent if missed 3 or more out of 60 drug doses over a 1 month period (95%).

Checklist to assess treatment adherence

- Number of doses missed in the last 3 days
    - Missed doses should be taken any time as soon as recall except the recall is within 1 hour before next dose. The miss dose should be skipped
    - If a patient does not remember whether the ARVs were taken, suggest pill count for re-check

- Number of doses missed since last visit
- To check the time of pill taking. Correct time is critical (e.g. drugs taken twice daily must be taken every 12 hours +/- 30 minutes.
- To check the correct dose of pill taking

Adherence Measurement Method

There are several methods to measure adherence. Every method has different benefits and limitations. The providers' consideration to tailor an appropriate method depends on each patient to get accurate measurement. However, adherence measurement should be used more than 1 method due to different limitations.

To assess adherence, it would be estimated from taking all doses, the time of pill taking and the missing dose measured by pill count and self-report. The missing dose should be given within 30 minutes irrespective of the long or short half-life of pills.

$$\% \text{ adherence} = \frac{\text{Number of doses taken that the patient reports during a specific time.}}{\text{Number of total pills dispensed to the patient during a specific time}}$$

Clinical manifestations suggestive of HIV infection

- Weight loss > 10% of base line body weight
- Fever (continuous or intermittent) more than one month
- Diarrhea (continuous or intermittent) more than one month
- Persistent Generalized lymphadenopathy (PGL) is defined as palpable lymph nodes > 1 cm in 2 or more extra inguinal sites, present for more than 3 months.
- Skin conditions
  1. Fungal infections:
     - Oral candidiasis (thrush)
     - Vaginal candidiasis (recurrent)
  2. Viral infections:
     - Herpes zoster (shingles) recurrent or involving more than one dermatome
     - Genital herpes (recurrent)
     - Molluscum contagiosum
     - Condyloma (genital warts)
     - Oral hairy leukoplegia (OHL)
  3. Bacterial infections:
  4. Other skin conditions:
     - Seborrheic dermatitis
     - Pruritic papular eruption (PPE)
     - Psoriasis
- Respiratory manifestations
  - Cough more than one month
  - Dyspnea
  - Recurrent pneumonia
  - Chronic or recurrent sinus disease
- Neurological manifestations
  - Worsening headache (continuous and unexplained)
  - Febrile convulsion
  - Declining cognitive function
  - Hemiparesis, hemiplegia
- Eye manifestation
  - Blurr vision
- Presence with AIDS defining illness e.g.
  - Tuberculosis
  - Cryptococcosis/Penicilliosis
  - Toxoplasmosis
  - PCP
  - Salmonellosis
  - CMV retinitis

Medical History and Symptoms Check List

The following checklist is a guide to key information to ask the patient at the initial (and subsequent) visits. The information will guide in deciding the need for laboratory requirement, prevention and treatment of opportunistic infection, other health care requirement and follow up plan.

Table 8: History check list Invalid source specified.

HIV Testing	HIV Risk and Behavioral risk
Ever tested for HIV in the past? Date and place of the first HIV test Reason for the HIV test First known HIV-positive status (date/year) Documentation of the result Date of any negative HIV test Prior CD4+ cell counts (if available)	Behavioral risk and mode of transmission (heterosexual, MTCT, MSM, IDU) Unprotected sexual contact Injection drug use Occupational exposure Perinatal transmission Recipient of blood products Unknown
System Review	**Past history of HIV-Related Illnesses**
Unexplained weight loss Swollen lymph nodes Night sweats and fever Unusual headaches or poor concentration Changes in appetite Skin rashes Sores or white spots in mouth Painful swallowing Chest pain, cough or shortness of breath Stomach pain or Vomiting or Diarrhea Numbness or tingling in hands or feet Muscle weakness and changes in vision	Oral candidiasis or *Candida* esophagitis Persistent diarrhea Varicella zoster (shingles) Oral hairy leukoplakia Pneumocystis *jiroveci* pneumonia (PCP) Recurrent bacterial pneumonia Cryptococcal meningitis Toxoplasmosis Kaposi's sarcoma Disseminated Mycobacterium *avium complex* Cytomegalovirus (CMV) infection Tuberculosis Invasive cervical cancer
Tuberculosis History	**General Medical History**
Last chest X-ray Last Gene-Xpert History of past TB History of exposure to TB Treatment given (drugs and duration) BCG and PPD skin test and result	Any other past medical condition such as diabetes, hypertension, cardiovascular disease, Hepatitis B, Hepatitis C
Gynecologic History	**Sexually Transmitted Infections**
Last PAP smear Menstrual irregularities Last menstrual period Pelvic pain or discharge	Genital ulcer or other lesion Genital discharge
Pregnancy and Contraception history	**Vaccination History**
Previous pregnancies and terminations Living children and HIV status of children Exposure to ARV during pregnancy Drugs and duration of ART Contraception used	BCG Hepatitis B vaccine
Medication	**Allergies**

Past drugs and reasons for taking them Past ART Current drugs and reasons for taking them Opioid substitution therapy Concurrent use of herbal/ alternative medicines (possible drug interaction, ADR)	Known allergies to drugs or other substances or materials
ART History	**Psycho Social History**
Current and past exposure to ART Which drugs taken and for how long Understanding and readiness to commence ART if never taken	Family history, e.g. other immediate family member with known HIV infection Social history, e.g. education, occupation, source of income. Financial and family support status Disclosure status, readiness to disclose
Substance use	**Functional status**
Life style (alcohol, substances) Alcohol, stimulant, opiate and other drug use, smoking history	Able to work, go to school, do housework Ambulatory but not able to work Amount of day to day care needed
Financial status	**Marital status**
Financial status/occupation To determine follow up ability	Marital status. e.g condom, safe sex, partner testing

When to start antiretroviral therapy (3)

ART initiation is often seen as a non-emergency intervention, and various approaches are used to help prepare people to begin treatment. However, there is increasing recognition of the benefits of accelerated ART initiation, for example, in pregnant women, in order to avoid unacceptably high rates of loss to follow-up after HIV diagnosis. However, concerns remain that accelerated initiation of ART may lead people to start before they are ready, with adverse consequences for adherence and treatment outcomes. Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness. Rapid initiation of ART is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation. Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment. In the 2017 WHO guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy strongly recommends that ART should be offered on the same day to people who are ready to start. (21)

1) Adults

Antiretroviral therapy should be initiated in all adults living with HIV, regardless WHO clinical stage and any CD4 cell count. As a priority, ART should be initiated in the HIV-positive partner in serodiscordant couple and all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤ 350 cells/mm^3.

2) Pregnant women and breastfeeding women

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (option B+). A

once-daily fixed-dose combination of TDF+3TC+EFV is recommended as first-line ART in pregnant women and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age.

3) Infants and children younger than 10 years of age.

ART should be initiated in all children living with HIV, regardless WHO clinical stage and any CD4 cell count. As a priority, ART should be initiated in all infants diagnosed in the first year of life, and children living with HIV one year old to less than 10 years old. As a priority, ART should be initiated in all children ≤2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count≤750 cells /mm³ or CD4 percentage <25% , and children 5 years of age and older with WHO HIV clinical stage 3 or 4 disease or CD4 count ≤350 cells /mm³ (strong recommendation, moderate-quality evidence).

4) Timing of ART for adults and children with TB

ART should be started in all TB patients living with HIV, regardless of CD4 cell counts. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. HIV-positive TB patients with profound immunosuppression (e.g CD4 counts less than 50 cell/mm^3) should receive ART within the first two weeks of initiating TB treatment.

ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of anti-tuberculosis treatment regardless of the CD4 cell count and WHO clinical stage.

Preparing people living with HIV for ART (3)

Before people start antiretroviral therapy (ART), health-care providers should initiate a detailed discussion about

- willingness and readiness of patients to initiate ART
- antiretroviral (ARV) drug regimen
- dosing
- scheduling
- likely benefits
- possible adverse effects, and
- required follow-up and monitoring visits.

In the case of children with HIV, this conversation should directly involve the caregiver (person directly responsible for giving the child the medicine) and include discussion about disclosing their HIV status. Retesting all people living with HIV before initiating ART is recommended to ensure a correct diagnosis of HIV infection. Initiation of ART should always consider nutritional status, any comorbidity and other medications being taken to assess for possible interactions, contraindications and dose adjustment.

The choice to accept or decline ART ultimately lies with the person or his or her caregiver, and if they choose to defer initiation, ART can be offered again at subsequent visits. If the person faces mental health or substance use issues or other potential barriers to ART initiation or adherence, appropriate support should be provided and readiness to initiate ART should be reassessed at regular intervals. Community and peer support can help a person to prepare and make the decision to start therapy.

People starting treatment and carergivers should be informed that the first ART regimen offers the best opportunity for effective viral suppression, immune recovery and

consequently clinical benefit and that successful ART requires all medications to be taken as prescribed. It is important to acknowledge that there are situations where delays in starting ART can have negative consequences, particularly for people with tuberculosis (TB) or advanced immunosuppression, who are at high risk of death. People should be advised that many adverse effects are temporary or may be treated, and that substitutions can often be made for the ARV drugs associated with adverse effects. In preparation for treatment initiation, it is important to assess the need for psychosocial support to optimize adherence. People receiving ART and caregivers should also be asked regularly about any other medications that are being taken, including herbal remedies and nutritional supplements.

People commencing ART should be given advice on safer sex, including condom use and avoidance of other high-risk activities such as sharing of injecting equipment, to prevent transmitting HIV to other people.

Managing Opportunistic Infections before Starting Antiretroviral Therapy

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 cell counts. At the same time, long-term safety profile of ART and the implications of earlier treatment initiation on drug resistance, toxicity, adherence and retention needed to be monitored.

The following opportunistic infections and HIV-related illnesses need treatment or stabilization before commencing ART.

Table 9: OIs and ART initiation

If patient has this condition	Do This
- Tuberculosis (TB)	• Initiate treatment for TB first • Start ART see TB/HIV co-infection section
- Pneumocystis pneumonia (PCP) Bacterial pneumonia - Cryptococcal meningitis - Toxoplasmosis - Talaromycosis - Invasive fungal diseases - Significant diarrhea which may reduce absorption of ART (e.g. more than 5 loose stools per day)	• Initiate treatment for these illnesses first • Start ART when the treatment of OI clinical stable or consideration of clinician's decision (Not necessary to wait until treatment for OI is completed)
- Esophageal candidiasis	• Initiate treatment for esophageal candidiasis first • Start ART as soon as the patient can swallow comfortably
- Any undiagnosed active infection with fever and patient is unwell	• Diagnosis and treatment should be initiated first • Start ART when stable
- Drug reaction	• Do not start ART during an acute reaction
- Elevated ALT 3-5 times higher than normal limit	• Look for cause and treat if possible (Hepatitis B and C)
- Anemia: Hemoglobin (Hb) < 9.5 g/dl	• Look for treatable cause (blood loss, MAC). If no treatable cause, commence ART with non-AZT contained-regimen (HIV is often the cause of the anemia)

Table 10: HIV/AIDS Management

WHO Clinical Stage and CD4	Management
Stage 2 (CD4 ≥350 cell/mm^3)	- On ART - Check for any symptom of opportunistic infections (TB symptom screening, e.g.) - Symptom directed laboratory evaluation (see Table:16) - Screen for STI and STI management - **No Co- trimoxazole prophylaxis** - IPT should be given if it is determined that there is no active TB - Frequency of follow up visit every 3-6 months are recommended for people stable on ART
Stage 3 and 4 CD4 <350 cell/mm^3)	- On ART - Check for any symptom of opportunistic infections (TB symptom screening, e.g.) - Screen for STI and STI management - Symptom directed laboratory evaluation (please see Table:16) - Start primary opportunistic infections (OI) prophylaxis as in stage 2 above o Cotrimoxazole prophylaxis: primary OI prophylaxis for PCP and toxoplasmosis prophylaxis o Fluconazole for cryptococcal prophylaxis (CD4<100 cells/mm^3). Diagnosis will refer to OI guidelines. - IPT should be given if it is determined that there is no active TB - Frequency of follow up visit (3-6 months) are recommended for people stable on ART

What to start first-line-ART

1. **First line ART regimen for adults, pregnant or breastfeeding women, adolescents and children** (3)

First line ART for adults and adolescents should consist of two NRTIs plus an NNRTI or an INSTI. TDF+3TC+DTG is recommended for first line regimen in adults and adolescents living with HIV (see annex 20). Safety and efficacy data on EFV400 and DTG for pregnant and breastfeeding women and TB coinfection are still emerging. Using simplified, less toxic and more convenient regimens as fixed-dose combination and once daily regimen is recommended for first line regimen; a once-daily fixed dose combination of TDF +3TC+EFV is therefore recommended as first-line regimen in all adults living with HIV who have TB co-infection including pregnant and breastfeeding women, and women in the first trimester of pregnancy and childbearing age.

For children younger than 3 years, a PI-based regimen is recommended. Studies of LPV/r

versus NVP in young children show a substantial efficacy advantage for LPV/r. Failure rates for NVP in young children are nearly twice as high, with close to 60% of children receiving NVP experiencing treatment failure after 2 years according to the IMPAACT P1060 study results. (22) Utilization of LPV/r has been low because of problems with the formulations available for children. Crushing or splitting the tablet LPV/r formulation leads to erratic and much lower absorption of the medicine. The syrup formulation has a very unpleasant taste and has a cold chain requirement that is difficult implement in rural areas. A heat-stable formulation of oral "pellets" has been developed as an alternative to syrup for infants. Each capsule containing the pellets must be opened and sprinkled on food or in a spoon containing breast milk or formula. These pellets have been shown to be a safe and effective method for delivering LPV/r to infants older than 3 months of age until they are able to swallow the tablet formulation whole.

Table 11: Recommended first-line regimen in adults (3)

Preferred and alternative first line-regimen	
Preferred first line-regimen	TDF+3TC+DTG TDF +3TC+EFV_{600}
Alternative first-line	TDF+3TC+EFV_{400} or TDF+3TC+NVP or AZT+3TC+EFV or AZT+3TC+NVP

Notes:

- TDF+3TC+DTG fixed dose combination will be available in Lao PDR starting Q4 2018. CHAS will distribute transition plan guidance to ART sites ahead of the product being introduced in country (see Annex 20). The product is recommended for:
  - All newly initiating ART patients who are not currently pregnant and are not currently co-infected with TB.
  - Current patients taking TDF/3TC/EFV who are suffering EFV-related side effects (such as dizziness, headaches, nightmares, depression)
  - Current patients taking TDF/3TC + Nevirapine (NVP) due to EFV-related side effects (such as dizziness, headaches, nightmares, depression).
- TDF is recommended in hepatitis B and C coinfection with HIV patients
- EFV_{400} is substituted for EFV_{600} if side effects and drug toxicity are reported. However, efficacy data for EFV at a lower dose of 400mg/day in the case of pregnant and breastfeeding women and TB coinfection are still emerging
- EFV is preferred in women with CD4 >250. If NVP is used, it should be used with caution, close clinical monitoring, monitoring of liver function and in women with CD4 > 250
- EFV_{600} is substituted for NVP intolerance and if patients are receiving rifampicin
- EFV can be used in pregnant women in the first trimester of pregnancy and women of childbearing age.
- All patients must receive a triple combination regimen. ATV/r or LPV/r can be considered in the case of toxicity with NNRTIs.

Table 12 : Recommended first-line regimen in children and adolescents > 10 years of age (3)

Group/Age/ at Initiation	Preferred regimen	Alternative regimen
Children < 3 years	ABC+ 3TC+LPV/r[a;b]	AZT+3TC+LPV/r or ABC+3TC+NVP or AZT+3TC+NVP
Children ≥ 3 years and <10 years	ABC+3TC+EFV	ABC+3TC+NVP or AZT+3TC+EFV/NVP
Adolescents > 10 years and > 35 kg	TDF+3TC+EFV	TDF+3TC+NVP or AZT+3TC+EFV or AZT+3TC+NVP

[a] LPV/r is not recommended in premature or in full-term babies younger than 14 days. Dosages of LPV/r for children younger than 6 weeks should be calculate based on body surface area. If initiating ART in an infant less than two weeks of age, a regimen of AZT+3TC+NVP should be started. NVP substituted with LPV/r at the earliest opportunity, preferably at 2 weeks of age, when LPV/r syrup can be used.
[b] where viral load monitoring is available, consideration can be given to substituting LPV/r with EFV at 3 years of age after viral suppression is sustained

Note: If the patients are doing well with the current regimen, there is no need to switch to the new regimen.

Recommended ART prophylaxis in infants (3)

All exposed infants should be given ARV during postpartum period or at any time they present at the ARV clinic during six week after birth especially in high risk infants whose mothers did not receive ARV or breastfed infants, (see Table 13). At the same time, HIV-exposed newborn infants should be tested with nucleic acid test for early infant diagnosis with ARV initiation if they are HIV positive. (see Annex 2).

- HIV-exposed infants who are at high risk of acquiring HIV should receive AZT+NVP as soon as possible after birth for six weeks and continue daily NVP for additional six weeks.
- Infants of mothers who are receiving ART and are not breastfeeding should be given daily NVP as soon as possible after birth for 6 weeks of infant prophylaxis.

High-risk infants are defined as those:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery, or
- born to women with established HIV infection with VL>1000 copies/ml in the four weeks before delivery, if VL available, or
- born to women with incident HIV infection during pregnancy or breastfeeding, or
- identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Table 13: ARV prophylaxis in exposed infants

Scenario	Maternal ARV prophylaxis	Infant ARV prophylaxis	Duration
Mother diagnosed with HIV before or during pregnancy and who have received ART >4 weeks	Continue ART TDF+3TC+EFV or TDF+3TC+DTG*	1) **Breast feeding**: Daily AZT+NVP in the first 6 weeks; and continue only NVP for additional 6 weeks 2) **Formula milk feeding**: Daily NVP for 6 weeks only	6-12 weeks
Mother diagnosed with HIV for the first time during labour or postpartum Infants born to women with established HIV infection who have received less than four weeks of ART at the time of delivery Infants born to women with established HIV infection with VL>1000 copies/ml in the four weeks before delivery, if VL available, Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Initiate TDF+3TC+EFV or TDF+3TC+DTG	1) **Breast feeding**: Daily AZT+NVP in the first 6 weeks; and continue only NVP for additional 6 weeks 2) **Formula milk feeding**: Daily AZT+NVP for 6 weeks only	6-12 weeks

* For the use of DTG in pregnant women (see annex 20)

Table 14: NVP dosing for infant prophylaxis (3)

Infant age	Dosing of NVP	Dosing of AZT
Birth to 6 weeks		
Birthweight 2000−2499ga	10 mg once daily (1ml of syrup once daily)	10 mg twice daily (1ml of syrup twice daily)
Birthweight ≥2500g	15 mg once daily (1.5 ml of syrup once daily)	15 mg twice daily (1.5 ml of syrup twice daily)
>6 weeks to 12 weeks		
	20 mg once daily (2ml of syrup once daily or half a 50 mg tablet once daily)	No dose established for prophylaxis; use treatment dose 60 mg twice daily (6 ml of syrup twice daily or a 60 mg tablet twice daily)

[a] Infants weighing <2000g and above 35 weeks gestational age the suggested doses are: NVP 2mg/kg per dose once daily and AZT 4 mg/kg per dose twice daily. Premature infants younger than 35 weeks of gestational age should be dosed using expert guidance.

Table 15: Recommended ART regimen in adults and children who have TB/HIV coinfection

Group/Age/ at Initiation	Preferred regimen	Alternative regimen
Children with TB/HIV coinfection<3 years of age	AZT+3TC+ABC[a]	ABC+3TC+LPV/r[b] AZT+3TC+LPV/r[b] AZT+3TC+NVP[c] ABC+3TC+NVP
Children with TB/HIV coinfection ≥ 3 years of age and < 10 years	ABC+3TC+EFV	AZT+3TC+ABC[a] AZT+3TC+EFV

[a] Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI or NNRTI based regimen should be restarted when rifampicin-based ends.
[b] LPV/r syrup should not be used for premature babies or infants younger than 2 weeks of age. Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.
[c] NVP should be used instead at the following dose: 5ml twice daily (3.0-5.9 kg), 8ml twice daily (6.0-9.9 kg) and 10ml twice daily (10.0-13.9 kg) if syrup available; 1 tablet twice daily (3.0-5.9 kg), 1.5 tablets twice daily (6.0-9.9 kg) and 2 tablets twice daily (10.0-13.9 kg) if dispersible 50mg tablets are available.

What to expect in the first months of ART

Although ART is a lifelong commitment, the first months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but opportunistic infections (OIs) and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of treatment. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are most common when the people starting ART already have advanced HIV disease with severe immunodeficiency and existing coinfections and/or comorbidities, severely low haemoglobin, low body mass index and very low CD4 cell counts or are severely malnourished. Poor adherence in this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load.

The follow-up serves several purposes

1) Drugs and adherence. Does the patient take the drugs regularly? Does the patient need more counselling and support?
2) Side effects. Do the drugs cause any side effects? Can the patient tolerate them? Should ART regimen be changed?
3) Assessment for signs and symptoms of Immune reconstitution Inflammatory Syndrome
4) Assessment of disease progression and signs and symptoms of first line failure

Monitoring the response to ART in adults

Clinical assessment and laboratory tests play a key role in assessing individuals following a positive diagnosis of HIV. Viral load is the preferred monitoring approach to diagnose and confirm treatment failure.

WHO has recommended VL as the preferred monitoring test and recommend routine viral load testing to be carried out at six and 12 months after initiating ART, and if the patient is stable on ART, every 12 months thereafter. More frequent testing may be necessary in unstable patients (described below).

Lao PDR will switch from targeted viral load testing to routine VL testing for monitoring PLHIV on ART. It is recommended that the following schedule of CD4 and VL testing be followed:

- 1st year when patient is initiated on treatment:
  - CD4 test conducted at initiation for base line and at 6 months (note: ART should not be delayed awaiting CD4 result)
  - Viral Load test at 6 and 12 months
- Following years:
  - If patient is stable[1]:
    - Consider no further routine CD4 testing if access to routine VL testing is possible
    - Viral Load test every 12 months

[1] Stable patients according to WHO are defined as individuals on ART ≥ 1 year, with no current illnesses, no pregnancy and evidence of treatment success (two consecutive VL < 1000 copies/ml).

- If patient is not stable (unstable definition: OIs, detectable VL, CD4 > 200, on current ART regimen ≤ 12 months):
  - CD4 test every 6 months, until stable
  - Viral Load test every 12 months (if VL<1000ml copies)*

* If VL>1000ml copies, refer to section on diagnosis of treatment failure

Monitoring the response to ART in children
Assessment of infants and children receiving ARV
Clinical assessment

- In addition to the clinical assessments recommended in adults, clinical monitoring of ART in children should include:
- Nutrition
- Weight and height growth, Developmental milestones
- Neurological symptoms
- Systematic treatment of intestinal helminthes infection is recommended for HIV-exposed and HIV-infected children >1 year of age before ART initiation and annually.
- Important clinical signs of response to ART in children include
  - Improvement in growth in children who are failing to grow
  - Improvement in neurological symptoms and development in children who are demonstrating delay in developmental milestones or encephalopathy
  - Decrease frequency of infections (bacterial infections, oral thrush, and/or other opportunistic infections).

Table 16: Clinical and laboratory Monitoring of ART (3)

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	• Serology for adults and children 18 months or older; EID for children younger than 18 months)	
ART initiation	• Baseline CD4 cell count • Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child • TB symptom screening • Serum creatinine and estimated glomerular filtration rate (eGFR)[a] or starting TDF • Haemoglobin test for starting AZT[b] • HBV (HBsAg) serology[c] • HCV serology • Cryptococcus antigen if CD4 cell count ≤ 100 cells/mm^3 • Screening for STIs especially Syphilis	• Alanine aminotransferase for NVP[d]
Receiving ART	• HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter)	• Serum creatinine and eGFR for TDF • Pregnancy test,

	• CD4 cell count (once a year until patients are stable on ART) • Screening for STIs especially Syphilis	especially for women of childbearing age not receiving family planning and on treatment DTG or low-dose EFV • Pap smear
Suspected treatment failure	• HIV viral load • Serum creatinine and eGFR for TDF • Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment DTG or low-dose EFV • Screening for STIs especially Syphilis	• HBV (HBsAg) serology[e] (before switching ART regimen if this testing was not done

- [a] Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension, and concomitant use of a boosted PI or potential nephrotoxic drugs. Do not initiate TDF when the estimated glomerular filtration rate is <60 ml/min or in long term diabetes, uncontrolled hypertension, and renal failure. If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating TDF regimen (23)

Cockcroft-Gault formula for calculation of CrCl

$$\text{Male: } \frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CrCl (mL/min)}$$

$$\text{Female: } \frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = \text{CrCl (mL/min)}$$

[b] Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI)

[c] If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART

[d] Among people with a high risk of adverse events associated with NVP, such as being ART naïve, women with HIV with a CD4 count >250 cell/mm^3 and hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity

[e] for HIV/HBV coinfected individuals who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second-line regimen

Immune Reconstitution Inflammatory Syndrome

Table 17: Immune Reconstitution Inflammatory Syndrome (IRIS) (24)

Definition	A reaction against a foreign antigen (alive or dead) soon after starting ART in a patient who has undergone a reconstitution of their immune responses against this antigen.
Frequency	• 10% of all patients initiating ART • Up to 25% among patients initiating ART with a CD4 cell count < 50 cells/mm^3
Timing	• Typically within 2-12 weeks of initiation of ART • Up to 30% of IRIS can present beyond the first 3 months of ART
Signs and symptoms	• Unexpected deterioration of clinical status soon after commencing ART • Unmasking of subclinical infections such as TB, which present as new active disease • Worsening of co-existing infections such a flare of hepatitis B or C
Most common IRIS events	• 60% of IRIS events are M. Tuberculosis, MAC or cryptococcal disease
Management	• May be mild and resolve without treatment. Continue ART if possible • Treat unmasked active OI, such as TB • Temporary interruption of ART may be needed until the patient is stable on TB drugs, then reintroduction of ART • Steroids: Prednisone 0.5mg/kg/day for 5-10 days in moderate to severe cases of IRIS with tapering of prednisolone dose when stable

Common IRIS conditions and management

Table 18: Management of common IRIS (24)

IRIS condition	Clinical presentation	Onset after starting ART	Management
TB	fever, worsening respiratory status, increase in size and inflammation of lymph nodes or new lymphadenopathy, expanding CNS lesions, radiologic worsening of pulmonary infiltrations, and increasing pleural effusions	1-6 weeks	Resolves with ART/TB Give steroids
MAC	fever, weight loss, anaemia, lymphadenitis, lung infiltrates	1-12 weeks	Resolves with ART/MAC Give steroids
Cryptococcal meningitis	headache, nausea, vomiting, or visual disturbance	1week-8 months	Resolves with ART and antifungal treatment
CMV	Retinitis, vitritis, uveitis	1-8 weeks	Resolves with ART
HSV and VZV	Typical attack	1-12 weeks	Resolves with acyclovir
Penicillosis	fever, anaemia, umbilical papules, hepatosplenomegaly	1week-8 months	Resolves with ART and antifungal treatment
Hyper-thyroidism	progressive weight loss, asthenia, tachycardia, tremor, anxiety, and hypertension	14-22 months	Methimazole or Propythiouracil

Stop ART or not

Emphasize continue ART unless severely ill or bed ridden patients, educate patients about IRIS to prevent self-stopping ART

Monitoring the response to ART and diagnosis of treatment failure

Defining Failure:

Failure of the first line ART is diagnosed when patient who has been on ART for at least six months and who has demonstrated good in adherence to ART presents with any of the virological, immunological or clinical criteria indicative of failure (See table 21 for WHO definitions of treatment failure).. Viral load is the more sensitive and specific indictor of ART failure.

ART failure should not be diagnosed in the first 6 months on ART as it may take this long for a patient to achieve good adherence and viral suppression. Patients with virological or immunological criteria suggestive of failure (VL not suppressed or poor/no CD4 cell response) in the first six months of ART may have poor adherence. Reasons for poor adherence need to be explored and a plan developed to overcome issues which are causing

the adherence problem. Clinical events that occur before the first 6 months of therapy (such as IRIS) do not indicate failure. IRIS is a clinical consequence of having immune recovery following ART initiation in some patients. Individuals with TB /crypto often have advanced disease, suppressed immune systems and thus may be at increased risk for IRIS.

It is recommended that the full regimen be changed from a first to a second line combination regimen in the case of treatment failure. The backbone of all second line ART is a ritonavir boosted protease inhibitor. The new second line regimen should ideally include at least two new drugs, with one from at least one new class, in order to increase the likelihood of treatment success and minimize the risk of cross resistance.
Patients suspected of clinical or immunological failure should be prioritized for viral load testing and upon virological confirmation of failure, ART switching should be considered.

Table 19: WHO definitions of clinical, immumological, viral logical failure for decision to switch ART regimens.

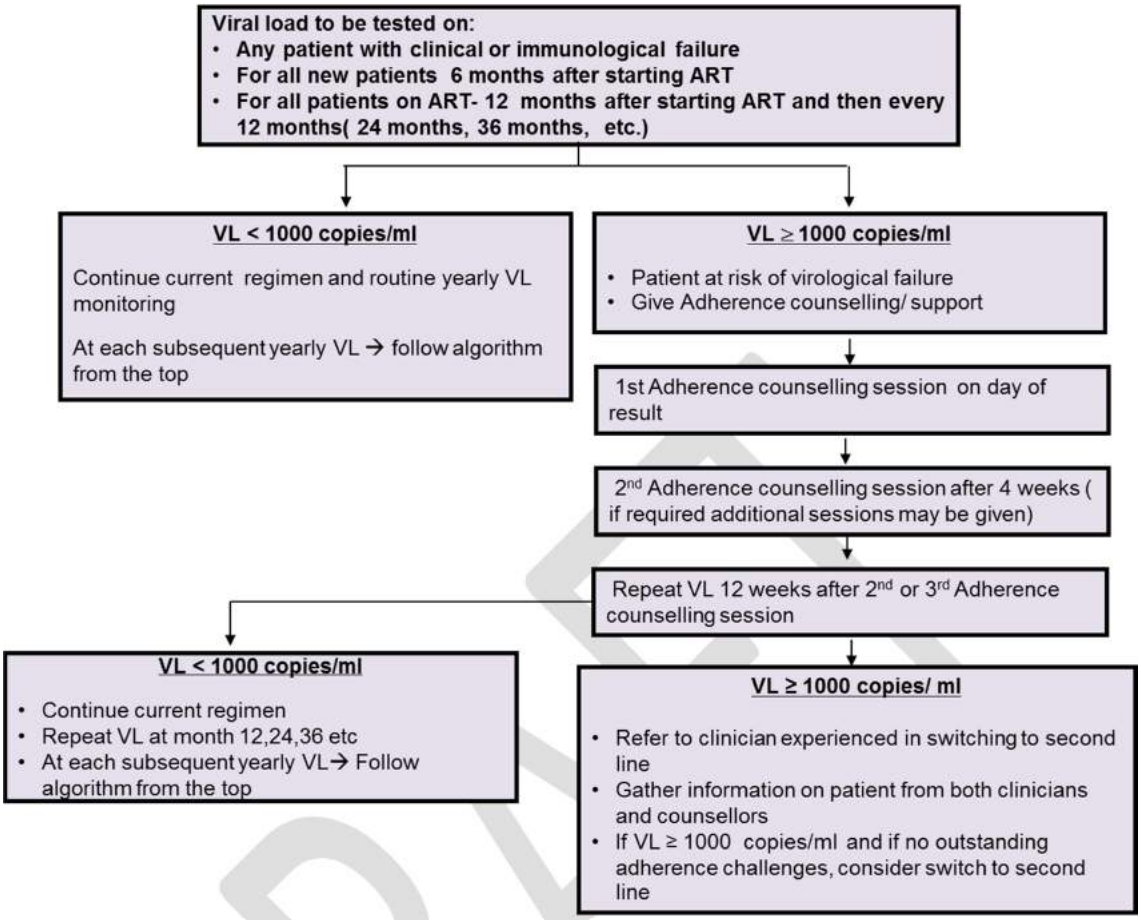
Failure	Definition	Comment
Clinical failure	Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment Children New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure
Immunological failure	Adults and adolescents CD4 count at or below 250 cells/mm^3 following clinical failure Or Persistent CD4 levels below 100 cells/mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
	Children 1) Younger than 5 years Persistent CD4 levels below 200 cells/mm^3 2) Older than 5 years Persistent CD4 levels below 100 cells/mm^3	
Virological failure	Viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support following the first viral load test	An individual mush be taking ART for at least 6 months before it can be determined that a regimen has failed

Recommendations for diagnosis of treatment failure

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, otherwise virological confirmation should be obtained. A threshold of 1000 copies /mL can be used to determine viral failure when using dried blood spot samples, as defined for testing in plasma. Second clinical and epidemiological studies show that the risk of HIV transmission and disease progression is very low when the viral load is lower than 1000 copies/ml.

Viral failure is defined by a persistently detectable viral load exceeding 1000 copies /mL (that is, two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen. The aim of providing enhanced adherence support is to ensure that the health care providers have confidence the patient is adherent to treatment between the period of the 1st and 2nd follow up viral load. If adherence is not assured in this period then a second viral load test should be delayed till the patient's adherence issues are resolved.

Figure 2: Algorithm of viral load testing



Note:

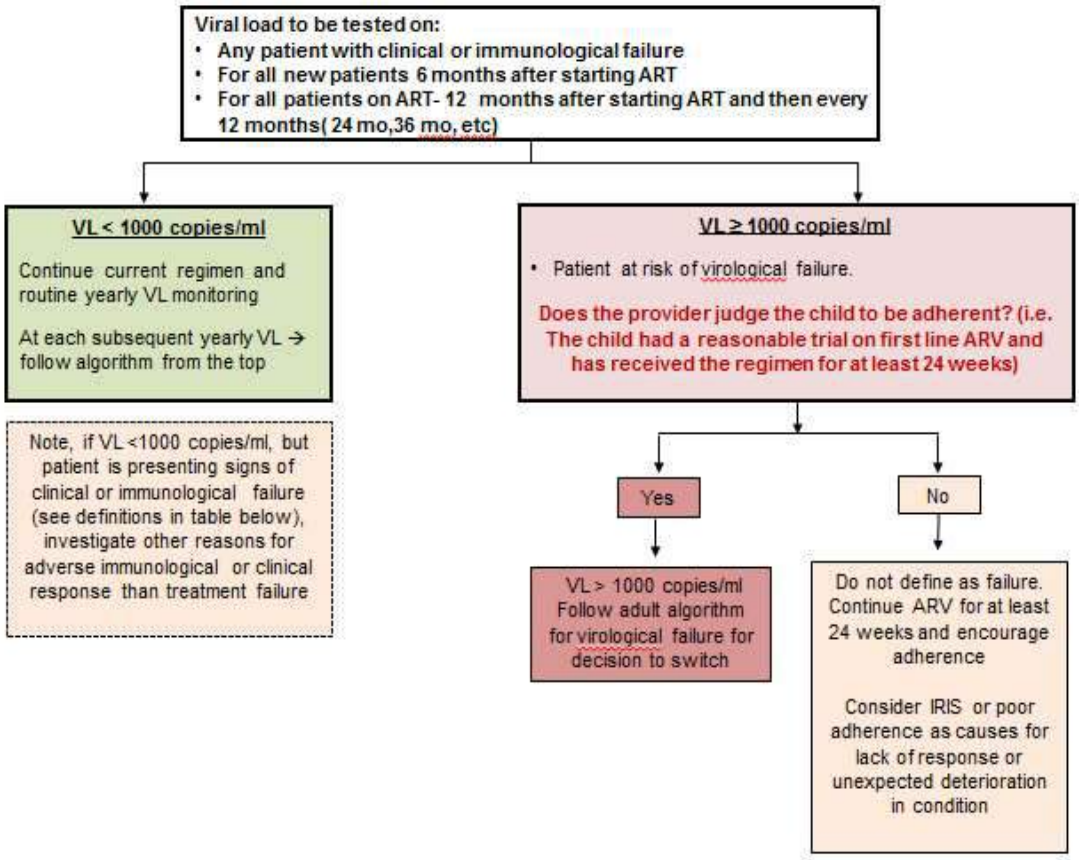
1) If a patient has a detectable viral load close to 1000 copies/ml, this person is at risk of failing and should receive close ongoing follow-up.
2) Resistance testing remains too costly and complex for routine use as part of a public health approach. If the second viral load test result is still around 1000 copies/ml, together with adherence assessment, drug resistance may be the potential cause of virological failure and the patient should be switched to 2nd line treatment. Drug resistance testing (HIV genotyping/sequencing) is the only definitive way to detect whether a patient has drug resistance and may be performed to inform switch decisions if available. However due to limited access of drug resistance testing in Lao PDR, complexity with results interpretation, and limited options of drug availability, the switch to 2nd line should occur for any patient with virological failure and should not be delayed in order to perform drug resistance testing if it is not accessible.

Monitoring of patients on the second line regimen is the same as the first line regimen

When to switch ARV drugs for treatment failure in children

The management of drug toxicity and the principles for changing ARV in children are similar to those in adults.

Figure 3: Switching ARV drugs for treatment failure



Details on defining failure	
Clinical failure*	• Lack of growth among children who show an initial response to treatment • Decline in growth among children who show an initial response to therapy • A loss of neuro-development milestones or the development of encephalopathy • Occurrence of new opportunistic infection or malignancy signifying clinical disease progression. This must be distinguished from immune reconstitution syndrome, which can occur in the first 3 months following the initiation of ARV and dose not signify treatment failure • Recurrence of infections, such as oral candidiasis that is refractory of treatment
Immunological failure**	• Return in CD4 cell percentage (or for children ≥ 5 years of age, absolute CD4 cell count) to pre-therapy baseline or below, absence of other concurrent infection to explain transient CD4 decrease • A rapid CD4 decrease (>30% over six months) also may indicate immunological failure
Virological failure	• Incomplete virological response to therapy: HIV RNA >1000 copies/mL after six months of ART with good adherence • Virological rebound: after virological suppression (viral load , 250 copies/mL), repeated detection of HIV RNA >1000 copies/mL

What to switch to second line regimen

Second-line therapy for children in the event of first-line regimen failure follows the same principles as for adults and includes a change in nucleoside backbone (e.g., from AZT +3TC to ABC + 3TC) plus a protease inhibitor.

Table 20: Preferred second-line regimen (3)

Group/Age/ at Initiation	First line regimen	Second line regimen
Children < 3 years	ABC+3TC+LPV/r	AZT+3TC+LPV/r
Children ≥ 3 years and <10 years	ABC+3TC+EFV	AZT+3TC+LPV/r
Children with TB/HIV coinfection<3 years of age	AZT+3TC+ABC	ABC+3TC+LPV/r* or AZT+3TC+LPV/r*
Children with TB/HIV coinfection ≥ 3 years of age and < 10 years	ABC+3TC+EFV	
Adolescents > 10 years and > 35 kg	TDF+3TC+EFV	AZT+3TC+ATV/r
HIV and HBV coinfection	TDF+3TC+EFV	AZT+TDF+3TC+ATV/r

*increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1

Note:

- If TDF is used in the first line, it is recommended to be continued in second line regimen in addition to AZT in case of HIV-HBV co-infection to reduce the risk of hepatic flares, regardless of the selected second-line regimen, which should be AZT+TDF +3TC +a boosted PI.
- The entire treatment regimen needs to be changed in the setting of treatment failure. Only 3TC will keep in second regimen. Continuation of 3TC should not be taken on an empty stomach in children. Second-line regimens may be considered.
- If genotypic resistance testing is available, adding or substituting at least 2 new drugs that is not resistant to the regimen is recommended.

Monitoring of substitutions for ARV drug toxicities

As in 2013, these guidelines recommend a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. At the same time, several laboratory tests for monitoring ARV toxicity are advised (but not required) for specific high-risk people using certain drugs. Lists the key types of toxicity and associated risk factors for the major ARV drugs, (see Table 21).

Monitoring of drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment outcomes. More data are also needed on whether routine laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all people or only those at risk. In general, in the event of severe and life-threatening toxicity or hypersensitivity, ART should be discontinued until symptoms have resolved and a substitution regimen can be safely initiated.

Table 21: Types of toxicities associated with first-, second- and third-line ARV drugs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 allele	Do not use ABC in the presence of a known HLA-B*5701 allele. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1A1*28 (UGT1A1*28) allele	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors
AZT	Severe anaemia, neutropaenia	CD4 cell count of)200 cells/ mm^3	Substitute with TDF or ABC. Consider use of low-dose zidovudine.
	Lactic acidosis or severe hepatomegaly with	BMI >25 (or body weight >75 kg) Prolonged exposure to	Substitute with TDF or ABC

	steatosis Lipoatrophy Lipodystrophy Myopathy	NRTIs	
DTG	Hepatotoxicity Hypersensitivity reactions, Insomnia	Hepatitis B or C coinfection Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline)	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/ day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	
EFV	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs)
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. If LPV/r is used in second- line ART for adults, and the person has treatment failure

			with NNRTI in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol misuse	
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea		Substitute with ATV/r, DRV/r or integrase inhibitors.
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm^3 in women or >400 cells/mm^3 in men)	Depending on the severity ofhepatotoxicity , consider substitution with EFV, including in children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age BMI <18.5 or low body weight (<50 kg) notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC. Do not initiate TDF at eGFR <60 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.Note that DTG can be associated with a benign elevation in creatinine. When used together with TDF, it could lead to an apparent decline in renal function.
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

Monitoring drug toxicity

Monitoring TDF toxicity

1) Monitoring TDF toxicity in adults

The renal toxicity of TDF is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease, and also with bone mineral density loss. Serum creatinine and glomerular tests may not adequately measure tubular injury. The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory for initiating treatment with TDF. However, it is advisable to detect and limit further progression of renal impairment in high-risk people. The major risks for TDF-related kidney damage are underlying kidney disease; age more than 50 years; low body weight (<50 kg), notably in females; untreated hypertension; and diabetes. Use of TDF with other nephrotoxic drugs, including those sold over the counter, nonsteroidal anti-inflammatory drugs, boosted PIs and ledipasvir, a direct-acting antiviral (DAA) drug to treat hepatitis C infection, leads to a greater initial decline in renal function. This decline may be worse when TDF is given in combination with ATV/r compared to when combined with LPV/r. People with impaired eGFR at baseline (<60 mL/min) should not initiate TDF.

2) Monitoring TDF toxicity in adolescents and children

The systematic review indicated that TDF toxicity among children and adolescents could be similar to that seen in adults. However, data are still lacking, and renal and bone toxicities in growing children and adolescents remain a concern. In the context of lack of paediatric formulations, increasing monitoring for TDF toxicity should be considered, including in young children or adolescents with low body weight who are using split adult tablets.

Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while adolescents and children are receiving TDF. When serum phosphate testing is available, by extrapolation, low serum phosphate should give rise to concern about bone mineral density loss. Increasing dosing accuracy in children and adolescents is extremely important for reducing toxicity (see Annex 12).

Clinical considerations

- Laboratory screening is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring should be used to assess for hypertension.
- If the creatinine test is routinely available, the eGFR at baseline should be used before initiating a TDF-containing regimen.
- TDF should not be initiated when the eGFR is <60 mL/min or in uncontrolled hypertension or diabetes and renal failure.
- Patients should be screened and treated for associated risk factors such as hypertension or diabetes and their treatment monitored.
- Growth should be carefully monitored in children using TDF.

Monitoring the toxicity of integrase inhibitors (3)

DTG may cause generally mild or moderate nausea, headache and diarrhoea that do not limit treatment. Serious adverse effects include abnormal liver function, particularly in patients with HBV or HCV coinfection, and potentially serious hypersensitivity reactions. DTG does not need a boosting agent (such as RTV or COBI), which minimizes drug interaction potential. DTG is reported to affect renal function, with a 10% serum creatinine increase due to inhibition of renal transport protein and consequently an estimated reduction in creatinine clearance, but without any eGFR modification. Small changes in creatinine are expected in a patient initiating DTG and caution is needed in interpreting changes in creatinine in patients receiving TDF and DTG concurrently. Data on the use of INSTIs (DTG) in pregnant or breastfeeding women is emerging.

Safety of dolutegravir (DTG) during pregnancy

There is a lack of data on the safety of INSTIs during pregnancy and breastfeeding. The

safety of DTG in pregnancy in particular is not well established, as there is limited safety or efficacy data on the outcomes of treating women with DTG during pregnancy. Limited data from 2 high-income country registries (the Antiretroviral Pregnancy Registry and European Pregnancy and Paediatric HIV Cohort Collaboration) have not shown poor pregnancy outcomes or increased rates of congenital anomalies among women taking DTG. In addition, from Botswana where DTG has been adopted since May 2016 for all first line patients including pregnant women, data has shown that rates of adverse birth outcomes are similar for DTG-based ART and EFV-based ART initiated during pregnancy. Furthermore, calcium or iron supplements frequently used during pregnancy could significantly reduce DTG drug levels. In the absence of well-controlled studies in pregnant women, DTG should be used only if the perceived benefits outweigh the risk. For practical purposes, in most settings, first-line therapy for pregnant women should continue to be based on drugs for which adequate safety data are available. For these reasons, EFV- based regimens are preferred over DTG-based regimens until more data become available.

Monitoring the toxicity of other ARV drugs in adults, adolescents and children

1) **Monitoring the toxicity of abacavir (3)**

The use of ABC has been limited due to its toxicity profile, including an increased risk of hypersensitivity reaction (HSR) and myocardial infarction in adults. HSR, which is associated with the presence of the HLA-B*-5701 allele, represents a main concern in children. Despite heterogeneity between studies with regard to the incidence of adverse outcomes, the review found no increase in HSRs, treatment discontinuations due to toxicity, grade 3 and 4 reactions or death associated with ABC exposure compared to exposure to other ARV drugs. The estimated incidence of HSR from the systematic review among children exposed to ABC was low (2.2%), as was the number of reported deaths (3.3%), with none of the deaths reported as being associated with ABC toxicity. Among adults, a strong relationship was reported between HSR related to ABC and HLA-B*-5701 allele genotype, but this association has not been studied in children. A hypersensitivity reaction to ABC is no more severe and no more prevalent than a hypersensitivity reaction to NVP, which has been used extensively around the world for nearly 2 decades. Clinicians should be alerted to this possible toxicity and the appropriate management, but fear of it should not limit the use of this drug.

2) **Monitoring the toxicity of efavirenz**

The main type of toxicity of EFV is CNS side-effects, which typically resolve after a few weeks. In some cases, they can persist for months or not resolve at all. A recent systematic review comparing the risk of discontinuation due to adverse drug reactions associated with EFV compared to other ARV drugs in first-line therapy found that EFV was well tolerated, with over 90% of patients remaining on an EFV-based first-line regimen after an average follow-up time of 78 weeks. In children, CNS toxicity will need to be monitored more closely, as younger children may have more difficulty in characterizing symptoms. EFV-associated dizziness is reported between 30 and 50% of patients receiving the drug even if only about 10% discontinue. Continuing to take a drug in the face of ongoing side effects is a risk factor for non-adherence.

Safety of efavirenz and tenofovir during pregnancy

Review of the evidence showed no increased risk in overall congenital anomalies with EFV compared to other ARVs. The risk of neural tube defects associated with EFV remained low (0.05%).

3) Monitoring the toxicity of nevirapine

The laboratory measurement of liver enzymes has very low predictive value for adverse reactions to NVP-containing regimens. However, monitoring hepatic enzymes is recommended where feasible, especially for women with HIV who have CD4 counts above 250 cells/mm^3 and people with HIV who also have HBV or HCV.

Safety of nevirapine during pregnancy

Concerns about a higher risk of severe hepatic and skin reactions with NVP compared with EFV were addressed for the 2013 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. The systematic review conducted at the time suggested that the frequency was increased but no higher than in the general adult population and concluded that NVP needs to be used with caution in pregnant women or women who might become pregnant. The higher risk of hepatic and skin reactions with NVP in pregnancy and at higher CD4 counts led to the 2013 recommendation favouring EFV as a first-line NNRTI.

4) Monitoring the toxicity of zidovudine

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin should be considered before initiating ART, mainly among adults and children with low body weight, low CD4 cell counts and advanced HIV disease. Monitoring severe anaemia at baseline (haemoglobin <6.5 g/dL) and during treatment in adults and children is recommended, notably in those receiving AZT as part of first-line therapy.

Drug substitutions for ARV drug toxicity

Drug regimen or single-agent substitutions may be required to manage drug toxicity and to avoid drug interactions. Delaying substitutions or switches when there are severe adverse drug reactions may cause harm and may affect adherence, leading to drug discontinuation, resistance and treatment failure. When drug interruptions are required, such as for severe and life-threatening adverse reactions, it is important to consider the various half-lives of ARV drugs. For example, when an NNRTI needs to be discontinued, a staggered approach should be followed, in which the use of the NRTI backbone is prolonged for two to three weeks. Alternatively, the NNRTI could be temporarily substituted with a boosted PI.

Key ARV drug interactions

Pharmacological interactions can reduce the efficacy of ART and/or increase ART-related toxicities. Major ARV drug interactions are summarized, (see Table 22; and Annex 14). Providers should be aware of all drugs that people are taking when ART is initiated, including alternative medicine products such as herbal remedies and dietary supplements as well as new drugs that are added during treatment maintenance.

Some drugs in the PI group have been associated with metabolic syndromes, particularly ATV/r,

LPV/r. In addition drug interactions with ritonavir-boosted PIs are important to assess, such as those with Methergine® and ergotism. Methylergomertrine (Methergine)® is the same category with antimigraine agents that contains ergotamine. The effects of these drugs will increase ergot level in peripheral blood vessels. Methergine ® is very common using in pregnant women during intrapartum or postpartum. Methergine ® and antimigraine agents are not recommended in patients who are taking PI especially ritonavir. In severe ergotism, vasodilator drug should be given such as prostaglandin analogue (see Annex 12).

Antituberculosis drugs

WHO Treatment of tuberculosis guidelines include key considerations for managing concomitant TB and HIV therapy. A key contraindicated drug combination is rifampicin with PIs. When people with HIV-related TB are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the boosting dose of RTV. For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered. For patients who are coinfected with HIV and extensively drug-resistant or multidrug-resistant (XDR/MDR) TB, there is limited information on the drug interactions of ARV drugs with new drugs such as bedaquiline and delamanid. As bedaquiline is primarily metabolized by CYP3A4, concomitant use with EFV and PIs can interfere with drug concentrations and should be undertaken with extreme caution and close clinical monitoring; alternative ARV options should be considered. Rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule may be necessary, but there are very few studies and limited clinical experience with this combination, particularly in individuals living with HIV and active TB.

Drugs for hepatitis C (3)

Potential drug interactions should be considered when using ARV drugs and DAAs for HCV infection. Simeprevir and the combination of ombitasvir + paritaprevir + ritionavir plus dasabuvir should not be co-administered with any PI or NNRTI. Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. Ledipasvir and sofosbuvir have shown reduced potential for drug interactions with ARV drugs due to their use of different metabolic pathways. Although access to DAAs is still limited in many settings, ribavirin and pegylated interferon alpha-2a are being less frequently used to treat HCV infection. Administration of both agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfected with HCV and HIV who are using AZT may need to be switched to TDF. A complete list of drug–drug interactions is available at www.hep-druginteractions.org.

Antifungal agents

Itraconazole and ketoconazole are often used to treat fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to subtherapeutic levels. Alternative antifungal agents (such as flucytosine and fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV.

Antimalarial drugs (3)

WHO recommends artemisinin-based combination therapies for treating uncomplicated Plasmodium falciparum malaria. The WHO has recommended a number of artemisinin-based combination therapies including Artemether-Lumefantrine, which is the preferred first line treatment in Laos.

There are limited data on how to manage patients with HIV and malaria and given Lao PDR is a low prevalence- HIV setting and relatively low incidence malaria area, these are likely to be rare occurrences. For HIV positive individuals on EFV and being treated for uncomplicated malaria using Artemether-Lumefantrine, possible drug interactions between EFV and lumefantrine should be considered, and if needed, antimalarial dosing may be adjusted accordingly. While EFV does lower lumefantrine levels, dose adjustments have not been adequately studied. Interactions also exist between antimalarials and NVP, resulting in lower antimalarial levels as well as lower NVP levels, which could lead to NVP resistance. These patients should be monitored for failure of malaria treatment, and if receiving NVP should also be monitored for ART failure. Consideration may also be given to using second line treatment with quinine/doxycycline as an alternative. Although generally not used in children or pregnant women, dental staining is unlikely to occur following a course of therapy of only 1 week and benefits may outweigh these small risks. Switching adult patients to a DTG-based regimen could help address potential drug interactions with antimalarials. In general, HIV positive individuals living in areas with high malaria infection rates should be receiving co-trimoxazole, which can prevent malaria.

Opioid substitution therapy (3)

WHO recommends methadone and buprenorphine for treating opioid dependence. Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People taking methadone and NNRTIs should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose. There is no interaction between methadone, buprenorphrine and DTG.

Hormonal contraceptives (3)

ARV drugs have the potential to either decrease or increase the levels of steroid hormones in hormonal contraceptives. There may be drug interactions between some NNRTIs and RTV-boosted PIs with hormonal contraceptives, which can reduce the effectiveness of both the hormonal contraceptive and the ARV drug. There are generally fewer concerns regarding interactions of hormonal contraceptives with NRTIs and newer NNRTIs (see Annex 14). The contraceptive efficacy of injectable formulations of either intramuscular or subcutaneous depot medroxyprogesterone acetate (DMPA) is unaffected by ARV drugs and can be used without restriction. There is a potential for reduced efficacy of long- acting progestogen-only implants when a women is also on ART containing EFV. If women receiving ART decide to initiate or continue using hormonal contraceptives, consistently using condoms and other contraceptive methods is recommended both to prevent HIV transmission and unintended pregnancy. Importantly, there is no interaction between DTG and hormonal contraceptives. WHO recommendations released in 2014 on the use of hormonal contraception by women receiving ART are available at www.who.int/ reproductive health/publications/ family planning/MEC-5/en.

Antihistamines (3)

Concomitant use of boosted PIs and NNRTIs with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratidine and cetirizine.

Statins (3)

WHO recommends statins for people with a 10-year cardiovascular risk exceeding 30%. Boosted PIs may lead to increased concentrations of lovastatin and simvastatin, which may increase the risk of serious adverse events such as myopathy, including rhabdomyolysis.

Alternative cholesterol-lowering agents should be used to prevent severe toxicity in people with HIV.

Other interactions (3)

DTG should not be simultaneously administered with cation-containing antacids, laxatives and multivitamin or mineral supplements because of the risk of chelation. If combined, DTG should be administered two hours before or six hours after taking medications containing polyvalent cations.

Table 22: Key ARV drug interactions and suggested management

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and pegylated-interferon alpha-2a	Substitute AZT with TDF
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the dose of LPV/r or substitute with three NRTIs
	Halofantrine and	Use an alternative antimalarial agent
	Lovastatin and simvastatin	Use an alternative cholesterol-lowering agent
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
DTG	Carbamazepine, phenobarbital and	Use alternative anticonvulsant agent
	Dofetilide	Use an alternative anti-arrhythmic or ARV
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg- or Zn-multivitamin supplements; mineral
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate or consider using DTG-based regimen
	Hormonal contraceptives	Use alternative or additional contraceptive methods to prevent HIV transmission and unintended pregnancies, as EFV may lower efficacy of some long-acting hormonal contraceptives or consider
	Astemizole and terfenadine	Use an alternative antihistamine agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
NVP	Rifampicin	Substitute NVP with EFV
	Methadone	Adjust the methadone dose as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	Itraconazole and	Use an alternative antifungal agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA

Managing common coinfections and comorbidities

Introduction

Various coinfections, comorbidities and other concomitant health conditions are common among people living with HIV and have implications for their treatment and care, including the timing and choice of ARV drugs. This section provides a brief overview of the most common and important conditions. It summarizes selected key recommendations from existing WHO guidelines and related materials, focusing on the screening, prophylaxis and timing of ART for these conditions; it does not cover their management in detail.

Prevention, screening and management of common coinfections

1. Co-trimoxazole prophylaxis

Co-trimoxazole (CTX) is a fixed-dose combination of two antimicrobial agents (sulfamethoxazole and trimethoprim) used to treat a variety of bacterial, fungal and protozoan infections. CTX prophylaxis is a feasible, well-tolerated and inexpensive intervention to reduce HIV-related morbidity and mortality in people living with HIV. CTX is an off-patent drug and is widely available in resource-limited settings. In recent years, new evidence has emerged showing that with expanded access to ART, there is a broader benefit of CTX prophylaxis beyond the prevention of some AIDS-associated opportunistic diseases (Pneumocystis jirovecii pneumonia [PCP] and toxoplasmosis) and the reduction of HIV-associated mortality in people with low CD4 cell counts. These benefits relate to prevention of malaria and severe bacterial infections (SBIs) in adults and children with HIV.

1.1. Co-trimoxazole prophylaxis for adults

Co-trimoxazole (CTX) prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and /or with a CD4 count ≤350 cells/mm^3;
Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression;
Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count

1.2. Co-trimoxazole prophylaxis for HIV-infected infants, children and adolescents

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and /or those with a CD4 count ≤350 cells /mm^3;

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants 4 to 6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding.

Table23: Criteria for initiation and discontinuation of co-trimoxazole prophylaxis

Population	Recommendation (3)	
	Criteria for initiation of co-trimoxazole prophylaxis	Criteria for discontinuation of co-trimoxazole prophylaxis
Adults (including pregnant women) with HIV	• Initiate in all with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count)350 cells/mm^3[a] • In settings with a high prevalence of malaria and/or severe bacterial infections[b]: initiate in all regardless of WHO clinical stage or CD4 cell count	• May be discontinued in those who are clinically stable[c], with evidence of immune recovery and/or viral suppression on ART[d,e] • In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued
Children and adolescents with HIV	• Initiate in all regardless of WHO clinical stage or CD4 cell count • As a priority: (1) initiate in all less than 5 years of age, regardless of WHO clinical stage or CD4 cell count; (2) initiate in all older than 5 years of age and with severe /advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count) 350 cells/mm^3	• In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued until adulthood • In settings with a low prevalence of both malaria and severe bacterial infections: may be discontinued for those older than 5 years of age who are clinically stable, with evidence of immune recovery[f] and/or viral suppression on ART
HIV-exposed uninfected	• Initiate in all starting at 4–6 weeks after birth	• Until the risk of HIV transmission ends or HIV infection is excluded[g]
People living with HIV and TB	• Initiate in all with active TB regardless of CD4 cell count.	• Until criteria for discontinuation in adults or children are met.

a This group is also prioritized for ART initiation (as recommended for ART in the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection).
b Settings where malaria and/or SBIs are highly prevalent includes low- and middle-income countries with high rates of mortality among children less than 5 years old
c Clinically stable adults are defined as those individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events.
d CD4 count >350 cells/mm^3, with viral load suppression, is considered indicative of immune recovery (some countries may adopt a threshold of CD4 count >500 cells/mm^3).
e WHO recognizes that in settings with a low prevalence of malaria and SBIs where CTX is used primarily as prophylaxis for some AIDS-associated opportunistic infections (PCP and toxoplasmosis), guidelines exist for discontinuing CTX in adults with HIV infection when there is evidence of viral suppression and immune recovery at CD4 cell counts >200 cells/mm^3 and being on ART for at least 1 year.
f Parameter for immune recovery in children when >5 years old: CD4 cell count >350 cells/mm^3, with viral load suppression.
g In settings with a high malaria transmission, consideration may be given to extend CTX prophylaxis in HIV-exposed uninfected infants up to 2 years of age.

Dosing adults (23)
The recommended dose of co-trimoxazole for adults living with HIVis 960 mg daily (800 mg sulfamethoxazole + 160 mg trimethoprim, either as a 960 mg double –strength tablet or two 480-mg-single-strength tablets).

Table 24: Simplified dosing of isoniazid and co-trimoxazole prophylaxis for infants and children who are at least 4 weeks of age.

Drug	Strength of tablet or oral liquid (mg or mg/5ml)	Number of tablets or milliliters by weight band once daily					Strength of adult tablets (mg)	Number of tablets by weight band
		3.0-5.9 kg	6.0-9.9 kg	10.0-13.9 kg	14.0-19.9 kg	20.0-24.9 kg		25.0-34.9 kg
Isoniazid	100 mg	0.5	1	1.5	2	2.5	300 mg	1
Co-trimoxazole	Suspension 200/40 per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	-	-
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	-	-
	Tablets (scored) 400/80 mg	-	0.5	0.5	1	1	400 mg/80 mg	2
	Tablets (scored) 800/160 mg	-	-	-	0.5	0.5	800 mg/160 mg	1
Isoniazid + co-trimoxazole + B6*	Tablets (scored) 300 mg/ 960 mg/25 mg	-	-	-	0.5	0.5	960 mg/300 mg/25 mg	1

*this formulation is currently awaiting regulatory approval, and a scored tablet (480 mg/150 mg/125 mg) is also being developed.

2. Tuberculosis (3)

TB is the most common cause of death in hospitalized adults and children living with HIV, accounting for about a third of all mortality. A systematic review of autopsy studies among adults who had had HIV showed a pooled prevalence of almost 40% in the cadavers, with just under half of the cases previously undetected.
Routine TB symptom screening for people with HIV, using an algorithm containing fever, cough of any duration, weight loss and night sweats, will help to identify people who should either be expedited for TB diagnosis or given preventive TB therapy. The combined use of isoniazid preventive therapy (IPT) and ART has been shown to have both TB prevention and mortality benefits, including in people with a higher CD4 count. The timely initiation of ART and implementation of the "Three I's" for HIV/ TB (increased TB case-finding, IPT and infection control) are critical to prevent TB and mortality from HIV-associated TB.
Diagnosis of HIV-associated TB using smear microscopy, a widely available method, is very challenging in people with HIV, resulting in delayed diagnoses and misdiagnoses. WHO-approved nucleic acid-based molecular tests (e.g. Xpert MTB / RIF) improve the yield and speed of diagnosis, and need to be scaled up in all HIV clinical settings. This section

presents the review of evidence and relevant recommendations on the use of urine lipoarabinomannan (LAM) antigen test for diagnosis and presumptive TB treatment for people living with HIV who are severely immunocompromised.

TB diagnosis and treatment

• Xpert MTB/ RIF should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having multidrug-resistant TB (MDR-TB) or HIV-associated TB
• Xpert MTB/ RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients suspected of having TB meningitis
• Xpert MTB/ RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non- respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB
• Except as specifically described below for people with HIV infection with low CD4 counts or who are seriously ill, a urine lateral flow (LF) -LAM should not be used for the diagnosis of TB

1. LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients living with HIV, with signs and symptoms of TB (pulmonary and /or extrapulmonary), who have a CD4 count less than or equal to 100 cells/mm^3, or people living with HIV who are seriously ill,a regardless of CD4 cell count or with unknown CD4 cell count
2. LF-LAM should not be used as a screening test for active TB

Notes:

- TB patients with known positive HIV status and TB patients living in HIV- prevalent settings should receive at least six months of a rifampicin-containing treatment regimen. The optimal dosing frequency is daily during the intensive and continuation phases.
- "Seriously ill" is defined as four danger signs: respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided.
- This recommendation also applies to adults living with HIV who are outpatients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/mm^3 or who are seriously ill a regardless of CD4 count or with unknown CD4 count, based on the generalization of data from inpatients. This recommendation also applies to children living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalization of data from adults, while acknowledging that data are very limited and that there are concerns regarding low specificity of the LF-LAM assay in children.

Early identification of TB among people with HIV through careful assessment of symptoms and signs, diagnosis using proper investigation (i.e. Xpert MTB / RIF) and prompt initiation of anti-TB treatment is important to improve survival and quality of life as well as reduce transmission of TB in the clinic and the community.
All people living with HIV should be regularly screened for TB using a clinical symptom-based algorithm. Those who report any one of the symptoms may have active TB and should be evaluated for TB and other diseases. Xpert MTB / RIF should be used as the initial diagnostic test in adults and children suspected of having HIV-associated TB. Xpert MTB / RIF should also be used as a preferred initial diagnostic test for cerebrospinal fluid investigation in people with HIV presumed to have TB meningitis.

Extrapulmonary TB in people living with HIV

The risk of extrapulmonary TB is higher in people living with HIV, especially in those with lower CD4 cell counts (30). People living with HIV with extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death. The commonest forms include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body). Pericardial and meningeal TB are less frequent forms of extrapulmonary TB but are more likely to result in fatal outcomes (31).

Timing of ART for adults and children with TB

Early initiation of ART in TB patients living with HIV is critical for reducing mortality. Antiretroviral therapy is recommended for all patients with HIV and drug- resistant TB requiring second-line antituberculosis drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of antituberculosis treatment

Isoniazid preventive therapy (IPT)

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT (INH 300 mg daily).
- Adults and adolescents living with HIV who have an unknown status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals regardless of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.
- Adults and adolescents living with HIV who have an unknown and among whom active TB disease has been safely ruled out should receive at least 6 months of IPT. IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.
- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who have poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age.
- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg /kg /day) as part of a comprehensive package of HIV prevention and care.
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.
- All children living with HIV, after successful completion of treatment for TB, should receive IPT for an additional six months

3. Cryptococcal disease (3)

Cryptococcal meningitis is a common opportunistic infection and a leading cause of death in people with HIV before and after ART is initiated, especially in sub-Saharan Africa and South-East Asia. The main reasons for this high death rate include delayed presentation, together with poor availability and high cost of treatment.

A rapid advice on diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children was published by WHO in 2011. Additionally in

2017 WHO has published advanced disease guidelines, which include recommendations for cryptococcal antigen testing (CrAg) and management of cryptococcal infection. The advice covers diagnosis, screening and prevention of cryptococcal infection; induction, consolidation and maintenance regimens; monitoring and managing toxicities; timing of ART; and discontinuation of maintenance regimens. The 2017 advanced disease guidelines also include recommendations on CrAG testing. These recommendations encourage earlier diagnosis and early treatment with amphotericin B–based regimens as part of a minimum package of toxicity prevention, monitoring and management, prompt management of raised intracranial pressure and systematic evaluation of a clinically deteriorating patient. They also provide guidance on timing of ART initiation and discontinuation of maintenance treatment.

Diagnosis of cryptococcal disease

For HIV positive patients that exhibit signs and symptoms of meningitis, prompt lumbar puncture with measurement of CSF opening pressure and rapid CSF cryptococcal antigen (CrAg) assay is recommended for diagnosing or ruling out cryptococcal meningitis.

If disseminated cryptococcal disease is suspected (i.e. if a patient does not have signs or symptoms of meningitis) a rapid serum CrAg may be done. If this is positive a lumbar puncture and a CSF CrAg should be done. Note that a positive serum CrAG does not always mean meningitis, although usually it done, especially in the presence of illness (see Annex 23).

Prevention of cryptococcal disease

The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells /mm^3 and who are CrAg negative or where CrAg status is unknown is not recommended prior to ART initiation, unless a prolonged delay in ART initiation is likely.
The use of routine serum or plasma CrAg screening in ART-naïve, asymptomatic adults, followed by pre-emptive antifungal therapy if CrAg positive to reduce the development of cryptococcal disease, should be considered prior to ART initiation in:

1) patients with a CD4 count less than 100 cells /mm^3 ; and
2) where this population also has a high prevalence (>3%) a of cryptococcal antigenaemia.

Cryptococcal antigen (a chemical marker that is found in people with active disease) can be detected in the blood weeks to months before the patient develops symptoms of meningitis. Patients who are found to have cryptococcal antigen in their body are much more likely to develop meningitis than those who do not have antigen. The presence of cryptococcal antigen is highly predictive for the development of cryptococcosis.

A patient with a positive cryptococcal antigen test should be contacted urgently to return to the clinic for follow-up, so it is important to keep a detailed record of patients' contact information. The patient should be assessed for symptoms of meningitis and for special situations. If the patient has any symptom of meningitis (headache lasting longer than 24 hours, fever, confusion or coma, blurry vision, or neck stiffness), he or she will need a lumbar puncture.

Induction, consolidation and maintenance antifungal treatment regimens

For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week antifungal regimens are recommended in order of preference.

a) Amphotericin B + flucytosine.

b) Amphotericin B + fluconazole. (If flucytosine is available it is preferred, even with short course according to recent data (ACTA Trial IAS 2017 MOAX0201LB))
c) Amphotericin B short course (5–7 days) + high-dose fluconazole (High dose = 1200mg) (to complete 2 weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full two-week induction period.
d) Fluconazole high dose + flucytosine, when amphotericin B is not available.
e) Fluconazole high dose alone, when amphotericin B is not available.

For the consolidation phase treatment of HIV-infected adults, adolescents and children with cryptococcal meningitis or disseminated non-meningeal disease, the following eight-week antifungal regimen is recommended:

- Fluconazole 400 –800mg /day after a two-week induction with amphotericin B regimen (6 –12 mg /kg /day up to 400 –800 mg /day if below 19 years).
- Fluconazole 800 mg /day after induction treatment with short-course amphotericin B or fluconazole-based induction regimen (fluconazole 12 mg /kg / day up to 800 mg /day if below 19 years).

For maintenance treatment of cryptococcal disease in HIV-infected adults, adolescents and children, oral fluconazole 200 mg daily (6 mg /kg /day up to 200 mg /day if below 19 years) is recommended.

For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded). Fluconazole 800 mg /day (or 12 mg /kg /day if below 19 years) for two weeks, then 400 mg /day (or 6 mg /kg /day up to 400 –800 mg /day if below 19 years) for eight weeks, and continued maintenance with fluconazole 200 mg /day is recommended. The optimal antifungal regimen in this population remains to be determined.

Prevention, monitoring and management of amphotericin B toxicity

In HIV-infected adults receiving amphotericin B– containing regimens for treatment of cryptococcal disease, a minimum package of toxicity prevention, monitoring and management is recommended to minimize the serious amphotericin B–related toxicities of hypokalaemia and nephrotoxicity.

Timing of ART initiation

Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS that may be life threatening.

In HIV-infected adults, adolescents and children with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and after 4 weeks of induction and consolidation treatment with amphotericin B– containing regimens combined with flucytosine or fluconazole, or after 4 – 6 weeks of treatment with a high-dose oral fluconazole induction and consolidation regimen.

Discontinuation of azole maintenance treatment (secondary prophylaxis)

In HIV-infected adults and adolescents with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal maintenance treatment is recommended based on the following criteria:

a. If HIV viral load monitoring is not available
   When patients are clinically stable, adherent to ART, CD4 is above 100 cells and antifungal maintenance therapy for at least one year and
b. If HIV viral load monitoring is available
   Patient stable and adherent to ART and antifungal maintenance treatment for at least one

year and with CD4 count greater than or equal to 100 cells /mm^3 (two measurements six months apart) and a suppressed viral load.

In HIV-infected children aged between 2 and 5 years with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal treatment maintenance is recommended if the child is stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count percentage greater than 25% or absolute count greater than 750 cells /mm^3 (two measurements six months apart).
Maintenance therapy for cryptococcal disease should NOT be discontinued in children less than two years.
Maintenance treatment for cryptococcal disease should be restarted if CD4 count drops to 100 cells /mm^3 or below in HIV-infected adults and adolescents (or CD4 cell count less than or equal to 25% or 750 cells /mm^3 in children aged between two and five years), or if a WHO stage 4 clinical event occurs, irrespective of patient age.

4. Hepatitis B and C (3)

Chronic hepatitis B virus (HBV) infection affects 5–20% of the 36 million people living with HIV worldwide, and hepatitis C virus (HCV) affects 5-15% , rising to 90% among people who inject drugs. The burden of coinfection is highest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for hepatitis B.
Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV in some regions, including among people on ART. A comprehensive approach includes prevention, HBV and HCV testing, hepatitis B vaccination and treatment and care for people with HIV who are coinfected with hepatitis B and /or hepatitis C.

Management of HIV and hepatitis B coinfection

HIV coinfection has a profound impact on the course of HBV infection, including more rapid progression to cirrhosis and hepatocellular carcinoma, higher liver-related mortality and decreased treatment response compared with people who do not have HIV.
Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, spontaneous bacterial peritonitis, variceal haemorrhage and hepatic encephalopathy), sepsis or liver insufficiency (jaundice).
The recommended NRTI drugs for ART – TDF with 3TC or FTC – are active against HBV. However, of these, only TDF is recommended in the WHO HBV guidelines for patients with HBV monoinfection. Furthermore, treatment of HIV-HBV coinfection without the use of TDF in the regimen may lead to flares of hepatitis B due to ART- associated immune reconstitution. Similarly, treatment discontinuation, especially of 3TC, has been associated with HBV reactivation, ALT flares and, in rare cases, hepatic decompensation. If ARV drugs need to be changed because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs.
The risk of HBV infection may be higher in HIV-infected adults. All people newly diagnosed with HIV should therefore be screened for hepatitis B surface antigen (HBsAg) and vaccinated if non-immune.

Management of HIV and hepatitis C coinfection

Hepatitis C virus (HCV) -related liver disease progresses more rapidly in people coinfected with HIV. Treatment of HCV is therefore a priority for people with HIV/ HCV coinfection. The decision to initiate treatment for HCV is more complex than in those with HCV monoinfection, because response rates are lower, the risk of potential toxicities is higher and

treatment is complicated by a high pill burden, overlapping toxicities and interactions between drugs used for treating HCV and HIV. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in people with advanced immunosuppression (CD4 count below 200 cells /mm^3). The newer, all-oral direct-acting antiviral HCV regimens (DAAs) produce similar rates of sustained virological response regardless of HIV status.

Careful consideration of drug–drug interactions is important to avoid toxicity and to ensure the efficacy of regimens used to treat both HIV and HCV. Further information regarding choice of anti-HCV regimen, including potential drug–drug interactions with ARV drugs, is provided in the 2014 WHO Global guidelines for the screening, care and treatment of persons living with hepatitis C infection, HCV treatment using older regimens (pegylated interferon and ribavirin) generally yielded low rates of success among HCV/ HIV coinfected patients, but outcomes for HCV therapy with DA As in people with HIV coinfection are comparable to those with HCV monoinfection. Updated WHO guidelines for the treatment of people with HCV infection, including management of HCV in HIV-coinfected patients, will be released in 2016. The newer all-oral DA As also have fewer drug–drug interactions than earlier interferon-based regimens (see Annex 14).

The decision to start ART among people coinfected with HCV should follow the same principles as in HIV monoinfection. Potential harmful effects of ARV drugs include their hepatotoxic effects. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine, didanosine, nevirapine or full-dose ritonavir (600 mg twice a day). For most HIV/ HCV coinfected people, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury.

5. Malaria (3)

There is significant geographical overlap between HIV and malaria. People living with HIV have increased risk of more frequent and higher-density infection, severe malaria and malaria-related death, depending on the malaria transmission intensity of the area.

Key interventions to control malaria include early diagnosis, prompt and effective treatment with artemisinin-based combination therapies and use of insecticide-treated nets and indoor residual insecticide spraying to control the vector mosquitoes. In areas of stable malaria transmission, people with HIV (as for the general population) should routinely use insecticide-treated bed-nets or have access to indoor residual spraying to reduce their exposure to malaria. Intermittent preventive treatment during pregnancy and seasonal malaria chemoprophylaxis are also recommended in areas of high transmission. Treatment or intermittent preventive treatment with sulfadoxine- pyrimethamine should not be given to patients with HIV or HIV-exposed infants who are taking CTX prophylaxis.

People with HIV who develop malaria should receive prompt, effective antimalarial treatment. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or a rapid diagnostic test. However, absence or delay of parasitological diagnosis should not delay the immediate start of antimalarial treatment.

Some drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa-based drugs) and may have important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and PIs). For this reason, people receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions, and people with HIV receiving AZT or EFV should, if possible, avoid amodiaquine-containing artemisinin-based combination regimens because of the increased risk of neutropaenia in combination with AZT and hepatotoxicity in combination with EFV.

Recommendation

In settings where malaria and /or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.

Notes:

In people who have HIV and uncomplicated P. falciparum malaria, avoid artesunate + sulfadoxine-pyrimethamine if they are being treated with co- trimoxazole and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

Intermittent preventive treatment for malaria in pregnancy should not be provided in addition to CTX prophylaxis.

6. Sexually transmitted infections and cervical cancer (3)

The epidemiological synergy between HIV and sexually transmitted infections (STIs) is well established, and they frequently coexist. Most of these infections are asymptomatic, especially among women. However, even asymptomatic STIs can cause complications, be transmitted to sexual partners and enhance HIV transmission. It has been shown that infection with N. gonorrhoeae substantially increases shedding of HIV-1 from the male genital tract in seminal fluid. It has also been shown that herpes simplex virus (HSV) is associated with increased acquisition and transmission of HIV. HIV infection may also alter the natural history of STIs. HIV infection has been found to change the natural history of HSV infection, resulting in more frequent recurrences in coinfected individuals, many of which are subclinical. In addition, serious clinical manifestations of HSV, human papillomavirus (HPV), syphilis and other STIs are observed among people with advanced HIV disease.

A systematic review showed that the prevalence of STI among people with HIV on ART was as high as people not on ART, suggesting that STI coinfection could undermine efforts to use ART for prevention unless STIs are appropriately treated. It is necessary to appropriately screen, diagnose and treat STIs, especially among the most vulnerable populations and people living with HIV. STI services should be an important part of comprehensive HIV care among adults and adolescents.

WHO guidelines on treatment of specific STIs (gonorrhoea, chlamydial infection, syphilis and HSV) are in the process of being updated. Existing recommendations on STI case management and screening for sex workers and men who have sex with men are given in the resource list below.

Cervical cancer is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer. The risk and persistence of HPV infection increases with low CD4 count and high HIV viral load. Women living with HIV should be followed closely for evidence of precancerous changes in the cervix, regardless of whether they are taking ART or their CD4 count or viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. All women with HIV should therefore be screened for cervical cancer regardless of age. Immediate management for precancerous and cancerous lesions should be provided. WHO guidance covers HPV vaccination and prevention, screening and treatment and palliative care of cervical cancer. To date, concerns about the safety or reduced efficacy among women who may be infected with HIV should not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization.

7. Vaccines for people living with HIV

Immunizations are an important component of the HIV care package in many international guidelines, and people living with HIV should be assessed for eligibility for vaccination at all stages of care. Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression, notably when the

CD4 count is above 200 cells/mm^3. People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines. Inactivated vaccines, although safe, can be less effective in this group and may require supplemental doses or revaccination after ART-induced immune reconstitution. Transient increases in plasma HIV-RNA load have also been reported after the administration of several vaccines. Available evidence indicates that these transient increases do not have clinical significance.

In general, HIV-exposed infants, children and adolescents with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules. In adults living with HIV, immunization against some diseases such as influenza, hepatitis B, pneumococcal disease and tetanus are frequently indicated. Other immunizations may be recommended based on age, risk factors or travel plans.

8. HIV-related skin and oral conditions (3)

HIV infection increases the prevalence and severity of skin and oral diseases, especially when the person's CD4 count declines below 200 cells /mm^3. As a result, skin and oral conditions affect up to 90% of adults and children with HIV in resource-limited settings. Adverse drug reactions of the skin are also 100 times more common in people living with HIV compared to the general population, and their prevalence increases as immunodeficiency worsens. Skin and oral manifestations of HIV infection can aggravate stigma in some societies, as physical signs in the form of skin diseases, such as papular pruritic eruptions, which suggest the possibility of HIV infection, could make the affected person more vulnerable to discrimination.

Certain systemic diseases, such as Kaposi sarcoma, may initially be noted on the skin and may require urgent ART to reduce mortality. Others, while not always a major cause of mortality, can be a source of severe morbidity through, for example, itching that provokes scratching, secondary infections, disfigurement, sleep disturbance and psychological stress. In the case of candidiasis, it can cause pain on swallowing, limiting a person's ability to take ARV drugs.

Due to a lack of services to promptly diagnose and manage skin and oral conditions, many people attempt to conceal the skin disease or avoid social contact. These could affect their health-seeking behaviour, leading to a negative impact on their self-esteem and quality of life. Skin and oral conditions are among the most common management problems faced by health-care workers caring for patients with HIV infection.

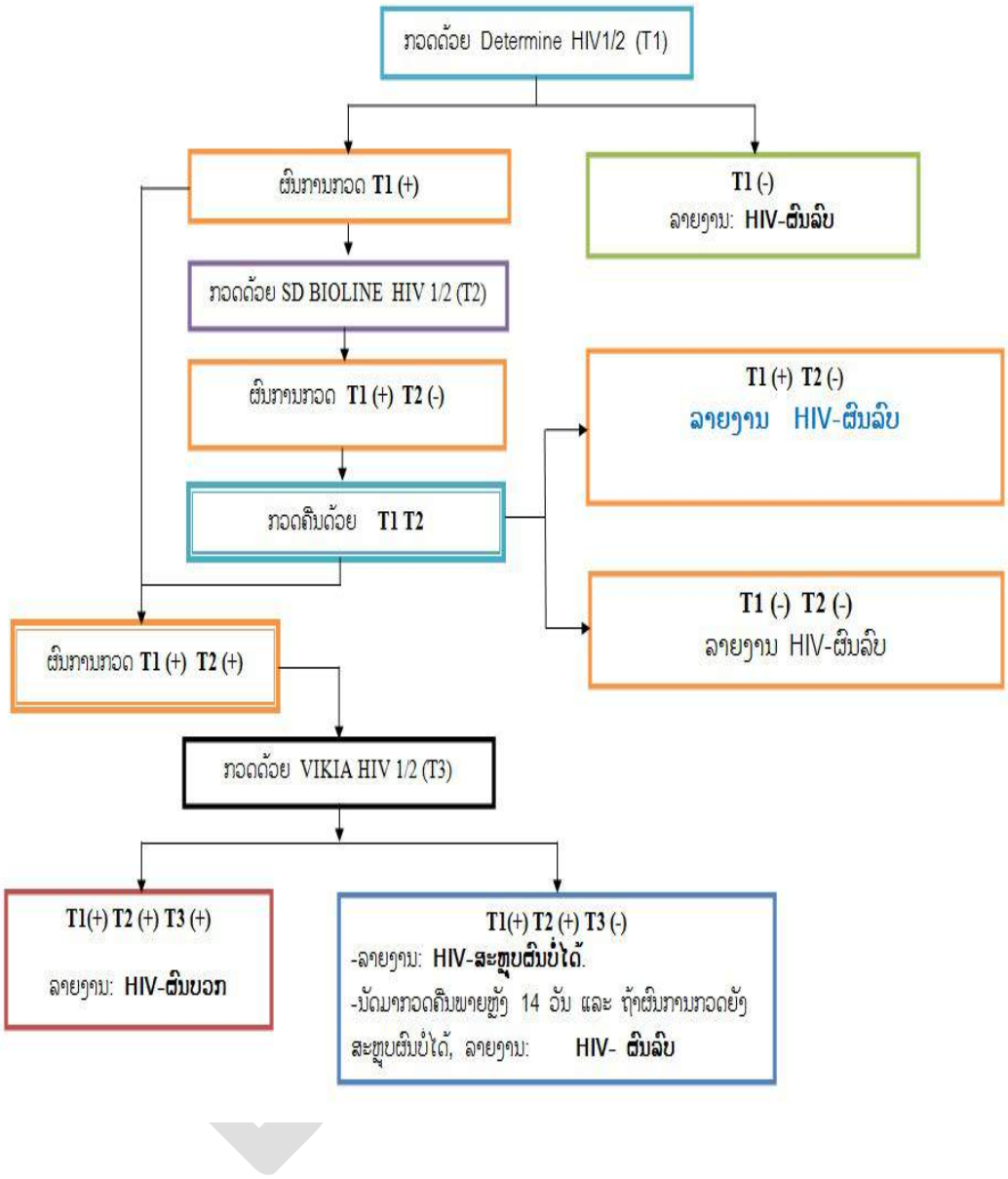
In 2014, WHO released guidelines for the treatment of common HIV-associated skin and oral conditions in low- and middle-income countries. These guidelines are applicable for all adults, pregnant women, adolescents and children living with HIV and recommend HIV testing for all those with unknown HIV status presenting with the discussed skin conditions. If the HIV status is known, they should be evaluated for initiation of ART.

ART is the initial treatment of choice for a number of these conditions (e.g. Kaposi sarcoma, papular pruritic eruption, eosinophilic folliculitis, molluscum contagiosum).

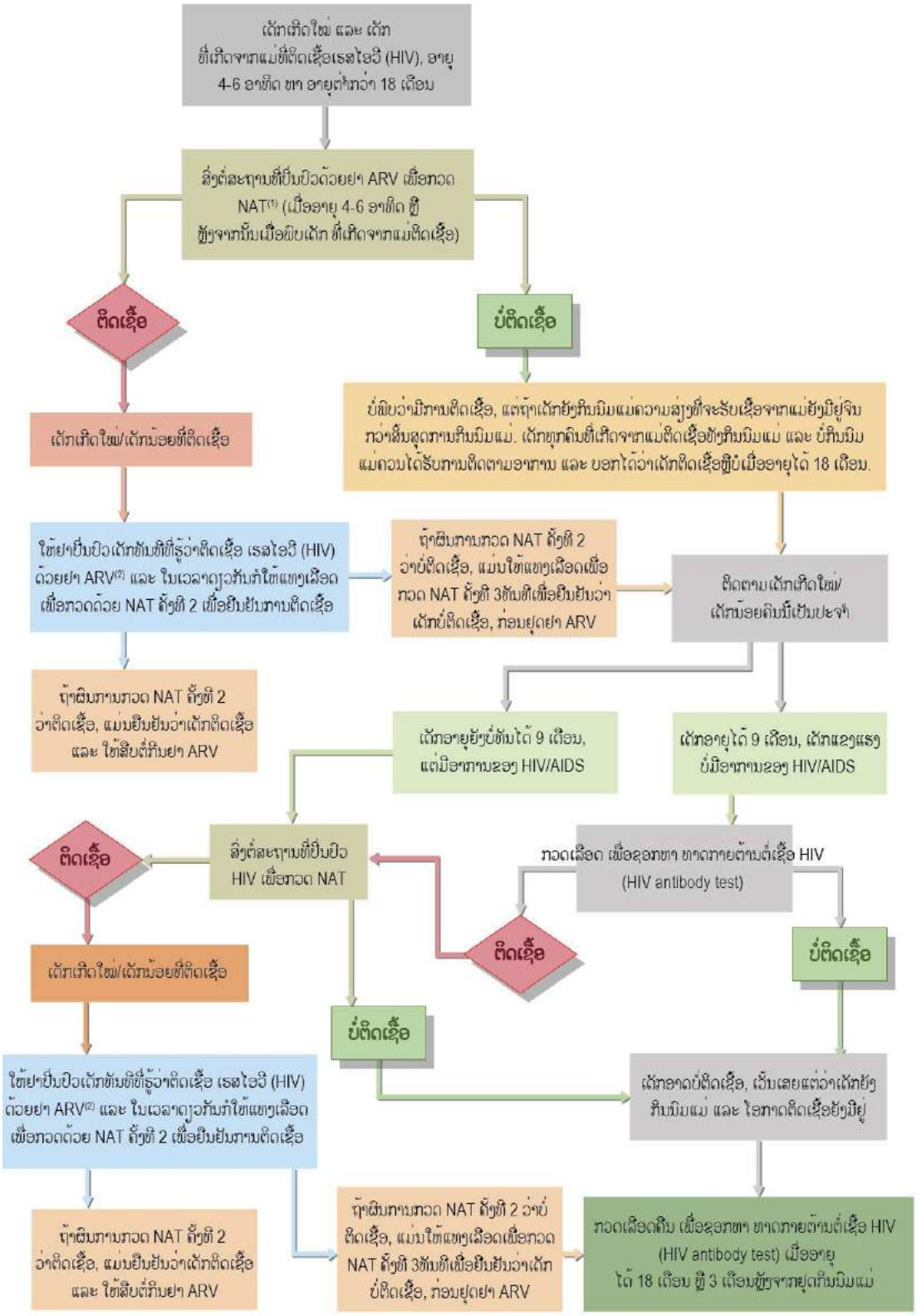
Annexes

Annex 1: HIV testing algorithms

ขั้นตอนการตรวจหาการติดเชื้อ เรสไอวี สำหรับผู้ใหญ่ และ เด็กอายุสูงกว่า 18 เดือน



Annex 2: HIV testing algorithm to diagnose children less than 18 months of age

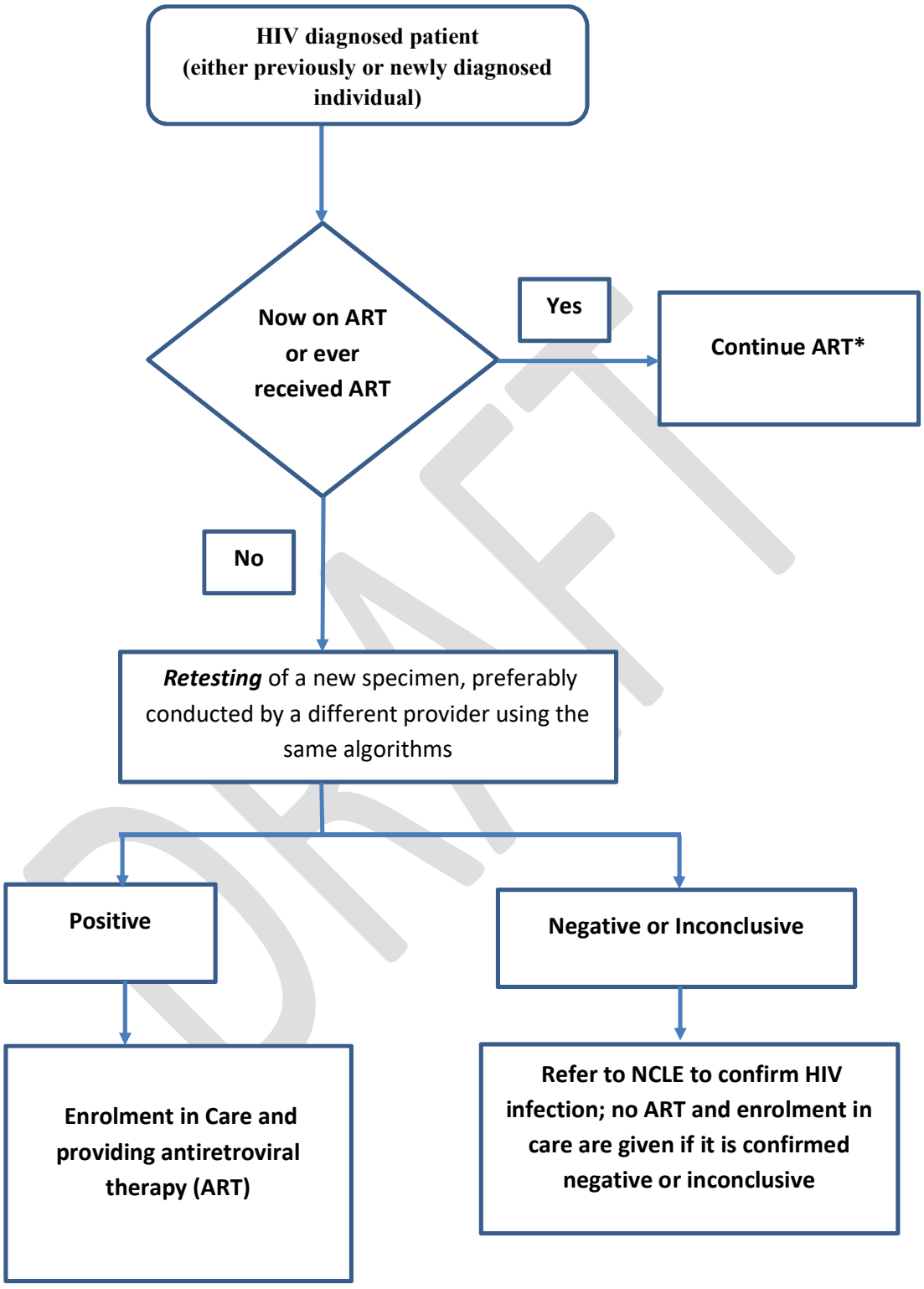


[1] Nucleic acid test (NAT) ເປັນເທັກນິກໂມເລກຸນທີ່ມີຄວາມໄວສູງທີ່ໃຊ້ເພື່ອບົ່ງມະຕິໃນເດັກເກີດໃໝ່ ແລະ ເດັກນ້ອຍລຸ່ມ 18 ເດືອນ. ເພື່ອຢັ້ງຢືນການຕິດເຊື້ອໃນເດັກແມ່ນຕ້ອງກວດ (NAT) ຄືນພື່ອໃຫ້ຜົນບວກ

ສອງຄັ້ງ. ກົງກັນຂ້າມ, ໃນກໍລະນີທີ່ຜົນກວດ (NAT) ເປັນລົບແມ່ນບໍ່ແນະນຳໃຫ້ກວດຄືນເພື່ອຢັ້ງຢືນວ່າເດັກບໍ່ຕິດເຊື້ອ.

(2) ໃນເດັກທີ່ຕິດເຊື້ອ ແມ່ນບໍ່ຄວນຊັກຊ້າໃນການໄດ້ຮັບຢາຕ້ານໄວຣັສ ຫຼື Antiretroviral therapy (ARV) ໃນຊ່ວງເວລາທີ່ລໍຖ້າຜົນກວດ ຢັ້ງຢືນການຕິດເຊື້ອຄັ້ງທີ່ສອງ.

Annex 3: Flowchart of Retesting Prior to Enrolment in Care and Antiretroviral Therapy



* Retesting people on ART is not recommended as there are potential risks of incorrect diagnosis. The effect of ART in suppressing replication may extend to suppression of the immune response and therefore antibody production. Once a person is started on ART, low antibody titres.

Annex 4: WHO clinical staging of HIV disease in adults, adolescents and children

Adults and adolescents	Children
Clinical stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruption • Fungal nail infections • Seborrhoeic dermatitis	• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections • (otitis media, otorrhoea, sinusitis, tonsillitis) • Herpes zoster • Lineal gingival erythema • Recurrent oral ulceration • Papular pruritic eruption • Fungal nail infections • Extensive wart virus infection • Extensive molluscum contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month) • Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × • 109/L) and/or chronic thrombocytopaenia (<50 × 109/L)	• Unexplained moderate malnutritionb 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 one 1 month) • Persistent oral candidiasis (after first six weeks of life) Oral hairy leukoplakia • Lymph node tuberculosis; pulmonary tuberculosis • Severe recurrent bacterial pneumonia • Acute necrotizing ulcerative gingivitis or periodontitis • Unexplained anaemia (<8 g/dL), neutropaenia (<0.5 × 109/L) or chronic thrombocytopaenia (<50 × 109/L) • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis

Clinical stage 4	
• HIV wasting syndrome Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month in duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis • Chronic isosporiasis • Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) • Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or • cardiomyopathy • Recurrent septicaemia (including nontyphoidal • Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Unexplained severe wasting, stunting or severe malnutritiond not responding to standard therapy • Pneumocystis (jirovecii) 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's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at age older than one month) • Central nervous system toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) • Cerebral or B-cell non-Hodgkin lymphoma HIV- associated nephropathy or cardiomyopathy

Annex 5: Continuum of HIV care for people living with HIV

Overview of key elements of general care over the continuum of HIV care for people living with HIV

Service	At HIV diagnosis	At enrolment inti care	At initiation of ART	Stable while receiving ART	At treatment failure and switching ART regimen
General care					
WHO clinical staging	√	√	√		
1) Pregnancy status 2) Family planning and contraception 3) PMTCT	√	√	√	√	√
Support for disclosure and partner notification	√	√	√	√	√
Risk reduction counselling and combination HIV prevention approaches	√	√	√	√	√
Screening for, preventing and managing, comorbidities and non-communicable diseases	√	√	√	√	√
Screening for and managing mental health problems and substance use Psychosocial counselling and support	√	√	√	√	√
Managing pain and symptoms	√	√	√	√	√
Nutritional assessment and counselling	√	√	√	√	√
1) Nutritional, growth and development assessment in children and adolescents 2) infant and child feeding	√	√	√	√	√
Preventing and treating coinfection					
Co-trimoxazole preventive therapy	√	√	√	√	√
Intensified TB case	√	√	√	√	√

finding					
Isoniazid preventive therapy	√	√	√	√	√
Screening for cryptococcal infection and fungal prophylaxis		√	√		
Screening for hepatitis B and C		√	√		√
Screening for sexually transmitted infection	√	√	√	√	√
Prevention of and screening for cervical cancer		√	√	√	√
Assessing for vaccine-preventable diseases	√	√	√	√	√
Preparing people for ART		√	√		
Preparing, assessing, and supporting adherence			√	√	√
Current medications		√	√	√	√

Annex 6: Dosages of ARVs for adults & adolescents

Generic name	Dose	
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Abacavir (ABC)[e]	300 mg twice daily or 600 mg once daily	
Zidovudine (AZT)	300 mg twice daily	
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)		
Tenofovir (TDF)	300 mg once daily	
Non-nucleoside Reverse Transcriptase Inhibitors (nNRTIs)		
Efavirenz (EFV)[f]	400-600 mg once daily	
Nevirapine (NVP)	400mg once daily for those are virally suppressed. (Lead-in NVP dosing should not be used when initiating NNRTI regimen more than two weeks and NNRTI-containing ART with TB treatment)	
Proteases inhibitors		
Atazanavir/ritonavir (ATV/r)[g]	300 mg/100 mg once daily	
Darunavir/ritonavir (DRV/r)	800 mg/100 mg once daily[a] or 600 mg/100 mg twice daily[b]	
Lopinavir/ritonavir (LPV/r)[c]	Tablet (heat stable formulation)[d] Lopinavir 200mg + ritonavir 50mg	Treatment naïve patients Two tablets twice daily irrespective of co-administration with EFV or NVP (400/100 mg twice daily)
		Treatment experienced patients Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
Integrase strand transfer inhibitors (INSTIs)		
Atazanavir/ritonavir (DTG)	50 mg once daily	
Raltegravir (RAL)	400 mg twice daily	

[a] For individuls with no previous use of protease inhibitors.
[b] For individuls with previous use of protease inhibitors.
[c] See TB section for TB-specific dose modifications of Lopinavir/ritonavir
[d] The LPV/r heat stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. The adult 200/50 mg tablet could be used for children 14.0-24.9 kg (1 tablet in the morning and 1 tablet in the evening), and for children 25.0-34.9 kg (2 tablets in the morning and 1 tablet in the evening)
[e] *Screening for HLA-B*5701 may identify those most likely to have hypersensitivity.*
[f] *EFV can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50%. It is not recommended to take amodiaquine with EFV.*
[g] *Should be taken with food.*

Annex 7: Simplified dosing of child-friendly tablets and fixed-dose combination for twice daily dosing for infants and children 4 weeks of age and older[a]. (2)

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets or ml by weight-band morning (AM) and evening (PM)										Strength of adult tablet (mg)	Number of tablets by weight-band	
		3.0 – 5.9 kg		6.0 – 9.9 kg		10.0 – 13.9 kg		14.0 – 19.9 kg		20.0 – 24.9 kg			25.0 – 34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulation														
AZT[e]	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC[f]	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
NVP	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
LPV/r[b]	100 mg/25 mg	NR	NR	NR	NR	2	1	2	2	2	2	100mg/25mg	3	3
LPV/r[c]	Pellets 40mg 10mg	2	2	3	3	4	4	5	5	6	6	100mg/25mg	13	13
Fixed-dose combination (FDC)														
AZT/3TC	Tablet[d] (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/150mg	1	1
AZT/3TC/NVP	Tablet (dispersible) 60mg/30mg/50mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/150mg /200mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/600mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120 mg/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	300mg/600mg	0.5	0.5

[a] For infants younger than 4 weeks of age, see annex 8 for more accurate dosing. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exist on the appropriate dosing of ARV drugs for preterm and low birth weight infants

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

[c] The LPV/r pellets formulations should not be used for infants younger 3 months. More details on the administration of LPV/r pellete is available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf.

[d] *Tablets may be crushed and combined with a small amount of food or water and immediately ingested.*

[e] *No food restrictions. Use with caution in children with anemia due to potential for bone marrow*

[f] *Parents/caregivers must be warned about potential hypersensitivity reaction. ABC should be stopped permanently if hypersensitivity reaction occurs.*

Annex 8: Simplified dosing of child-friendly oral liquid formulations and tablets for twice daily dosing for infants and children 4 weeks of age and older[a]. (2)

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets or ml by weight-band morning (AM) and evening (PM)									
		3.0 – 5.9 kg		6.0 – 9.9 kg		10.0 – 13.9 kg		14.0 – 19.9 kg		20.0 – 24.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
AZT	10 mg/ml; 300 mg	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	0.5	0.5	1	0.5
ABC	20 mg/ml; 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
3TC	10 mg/ml; 150 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
NVP[c,d]	10 mg/ml; 200 mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	0.5	1	0.5
LPV/r[b]	80/20 mg/ml	1 or 1.5 ml[b]	1 or 1.5 ml[b]	1.5 ml	1.5 ml	2 ml	2 ml	2.5ml	2.5ml	3 ml	3 ml

[a] For infants younger than 4 weeks of age, see annex 8 for more accurate dosing. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exist on the appropriate dosing of ARV drugs for preterm and low birth weight infants.

[b] LPV/r liquid should be refrigerated, and requires a cold chain during transport and storage. LPV/r liquid: for 3.0 – 3.9 kg, use 1 ml am. and 1 ml pm.; for 4.0 – 5.9 kg use 1.5 ml am. and 1.5 ml pm. The adult 200/50 mg tablet could be used for children 14.0-24.9 kg (1 tablet in the morning and 1 tablet in the evening), and for children 25.0-34.9 kg (2 tablets in the morning and 1 tablet in the evening). Once-daily dosing is not approved for infants or children.

[c] Bottle of liquid should be used within 6 months of opening. *Parents must be warned about a potential severe, life-threatening rash during the 14-day lead-in period. The once-daily induction dose is used to reduce the frequency of rash. NVP should be permanently discontinued and not restarted in children who develop severe rash.*

[d] Avoid NVP if rifampicin is co-administered; also interacts with ketoconazole.

Annex 9: Simplified dosing of child-friendly solid formulations for once daily dosing for infants and children 4 weeks of age and older[a]. (2)

Drug	Strength of Paediatric tablets (mg)	Number of tablets by weight-band once daily					Strength of adult tablets (mg)	Number of tablets by weight-band once daily
		3.0 – 5.9 kg	6.0 – 9.9 kg	10.0 – 13.9 kg	14.0 – 19.9 kg	20.0– 24.9 kg		25.0 – 34.9 kg
Solid formulations								
EFV[b]	Tablet (Scored) 200 mg	NR	NR	1	1.5	1.5	200 mg	2
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	2	3	4	5	6	600 mg/ 300 mg	1
ABC/3TC	Tablet (dispersible) 120 mg/60 mg	1	1.5	2	2.5	3	600 mg/ 300 mg	1
TDF[c]	Tablets 150 mg or 200mg	NR	NR	NR	1 (150 mg)	1 (200 mg)	300 mg	1 (200mg)[c] or 1 (300mg)

[a] For infants younger than 4 weeks of age, see annex 8 for more accurate dosing. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exist on the appropriate dosing of ARV drugs for preterm and low birth weight infants.

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

[c] TDF is only approved for use for children 2 years and older. Target dose: 8mg/kg or 200mg/m^2 (maximum 300mg). 200mg should be used for weight 25.0-29.9 kg and 300 mg tablets for 30.0-34.9 kg. TDF is the preferred ARV in children with hepatitis B aged more than 12 years.

NR – Not Recommend

Annex 10: Serious acute and chronic toxicities

Caused by ARV drugs, possible requiring therapy modification: clinical presentation, laboratory abnormalities and implications for ART management (25)

Possible clinical manifestations (most common ARV drug(s) Associated with the toxicity)	Possible laboratory abnormalities	Implications for ARV drug treatment
Hypersensitivity reaction (ABC or NVP)		
• ABC: Acute onset of a combination of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhea, abdominal pain, pharyngitis, cough, dyspnea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after within 6-8 weeks • NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	• Raised transaminase levels • Raised eosinophil count	• Immediately discontinue all ARVs until symptoms resolve • NVP or ABC should NOT be re-administered to the patient in future • Once symptoms resolve, restart ART by substituting an alternative ARV for ABC or NVP
Lactic acidosis (NRTI class)		
• Generalized fatigue and weakness • Gastrointestinal features (nausea, vomiting, diarrhea, abdominal pain, anorexia, hepatomegaly, poor weight gain and/or pancreatitis • May have hepatitis or pancreatitis *(see above)* • Respiratory features (tachypnea and dyspnea) • Neurological symptoms (including motor weakness)	• Increased anion gap • Lactic acidosis • Raised aminotransferase levels • Raised CPK level • Raised LDH level	• Discontinue all ARVs until symptoms resolve • Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART • Once symptoms resolve, restart ART by substituting the offending drug with an alternative NRTI that has a lower risk of mitochondrial toxicity (e.g. ABC or AZT)
Severe rash/Stevens-Johnson syndrome (NNRTI class, particularly NVP, less common with EFV)		
• Rash usually occurs during the first 6-8 weeks of treatment • Mild-to-moderate rash: erythematous, maculopapular confluent, most often on the body and arms, with no	• Raised aminotransferase levels	• If mild or moderate rash, ART can be continued without interruption but under close observation • For severe or life-threatening rash, discontinue all ARV's until symptoms resolve

systemic symptoms • Severe rash: extensive rash with moist desquamation, angiodema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis • Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis		• NVP should NOT be re-administered to the patient in the future • Once symptoms resolve, restart ART by substituting an alternative ARV for NVP (note: most experts would not change to another NNRTI drug if the patient had severe or life-threatening Stevens-Johnson syndrome with NVP)
Severe, life-threatening anemia (AZT)		
• Severe pallor, tachycardia • Marked fatigue • Congestive heart failure	• Low hemoglobin	• If refractory to symptomatic treatment (e.g. transfusion), discontinue only AZT and substitute an alternative NRTI
Severe neutropenia (AZT)		
• Sepsis / infection	• Low neutrophil count	• If refractory to symptomatic treatment (e.g, transfusion), discontinue only AZT and substitute an alternative NRTI
Chronic late adverse reactions:		
Lipodystrophy/Metabolic syndrome (PIs)		
• Fat loss and/or fat accumulation in distinct regions of the body: - Fat deposited around the abdomen, buffalo hump, breast hypertrophy - Fat loss from limbs, buttocks and face occurs to a variable extent • Insulin resistance, including diabetes mellitus • Potential risk for development of coronary artery disease	• Hypertriglyceri-demia • Hypercholesterolemia • Low HDL levels • Hyperglycemia	• Substitute ABC or AZT for d4T; may prevent progression of lipoatrophy • Substitute an NNRTI for a PI; may decrease serum lipid abnormalities
Severe peripheral neuropathy (ddl, rarely 3TC)		
• Pain, tingling, numbness of hands or feet, inability to walk • Distal sensory loss • Mild muscle weakness and areflexia can occur	• None	• Stop suspected NRTI only and substitute with a different NRTI that is not associated with neurotoxicity • Symptoms may take several weeks to resolve

Possible clinical manifestations (most common ARV drug (s) associated with the toxicity)	Possible laboratory abnormalities	Implications for ARV drug treatment

Acute serious adverse reactions		
Acute symptomatic hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
• Jaundice • Hepatosplenomegaly • Fatigue, anorexia • May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6-8 weeks • May have accompanying lactic acidosis *(see below)* if secondary to NRTI drug	• Raised transaminase levels • Raised bilirubin level	• Discontinue all ARVs until symptoms resolve • If possible, monitor transaminases, bilirubin • If receiving NVP, NVP should NOT be readministered to the patient in future • Once symptoms resolve, either - restart ART by changing to an alternative ARV (if on NVP regimen, this is required): or - restart current ART regimen under close observation; if symptoms recur, substitute with an alternative ARV
Acute pancreatitis (NRTI class, particularly ddI; rarely 3TC)		
• Severe nausea and vomiting • Severe abdominal pain • May have accompanying lactic acidosis *(see below)*	• Raised pancreatic amylase level • Raised lipase level	• Discontinue all ARVs until symptoms resolve • If possible, monitor serum pancreatic amylase, lipase • Once symptoms resolve, restart ART by substituting the offending drug with an alternative NRTI, preferably one without pancreatic toxicity

Annex 11: ARV and Storage requirements

Generic name	Storage requirements
Nucleoside RTIs	
Abacavir (ABC)	Room temperature
Zidovudine (AZT)	Room temperature
Didanosine (ddl)	Room temperature for tablets and capsules. Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated.
Emtricitabine (FTC)	Room temperature
Lamivudine (3TC)	Room temperature
Zidovudine (AZT)+lamivudine (3TC) + abacavir (ABC)	Room temperature
Non-nucleoside RTIs	
Efavirenz (EFV)	Room temperature
Nevirapine (NVP)	Room temperature
Protease inhibitors	
Atazanavir (ATV)	Room temperature
Indinavir (IDV)	Room temperature
Fos-amprenavir (Fos-APV)	Room temperature
Lopinavir/ritonavir (LPV/r) capsules	Refrigerate for long term storage At room temperature: stable for 30 days
Lopinavir/ritonavir (LPV/r) heat stable tablets	Room temperature
Nelfinavir (NFV)	Room temperature
Ritonavir (RTV)	Refrigerate capsules until dispensed Stable at room temperature for 30 days Room temperature for oral solution (do not refrigerate)
Saquinavir – hard gel caps (SQV_{hgc})	Room temperature
Room temperature is defined as 15-25°C. Refrigeration is defined as 2-8°C	

Annex 12: Key drug-drug interactions for antiretroviral drugs

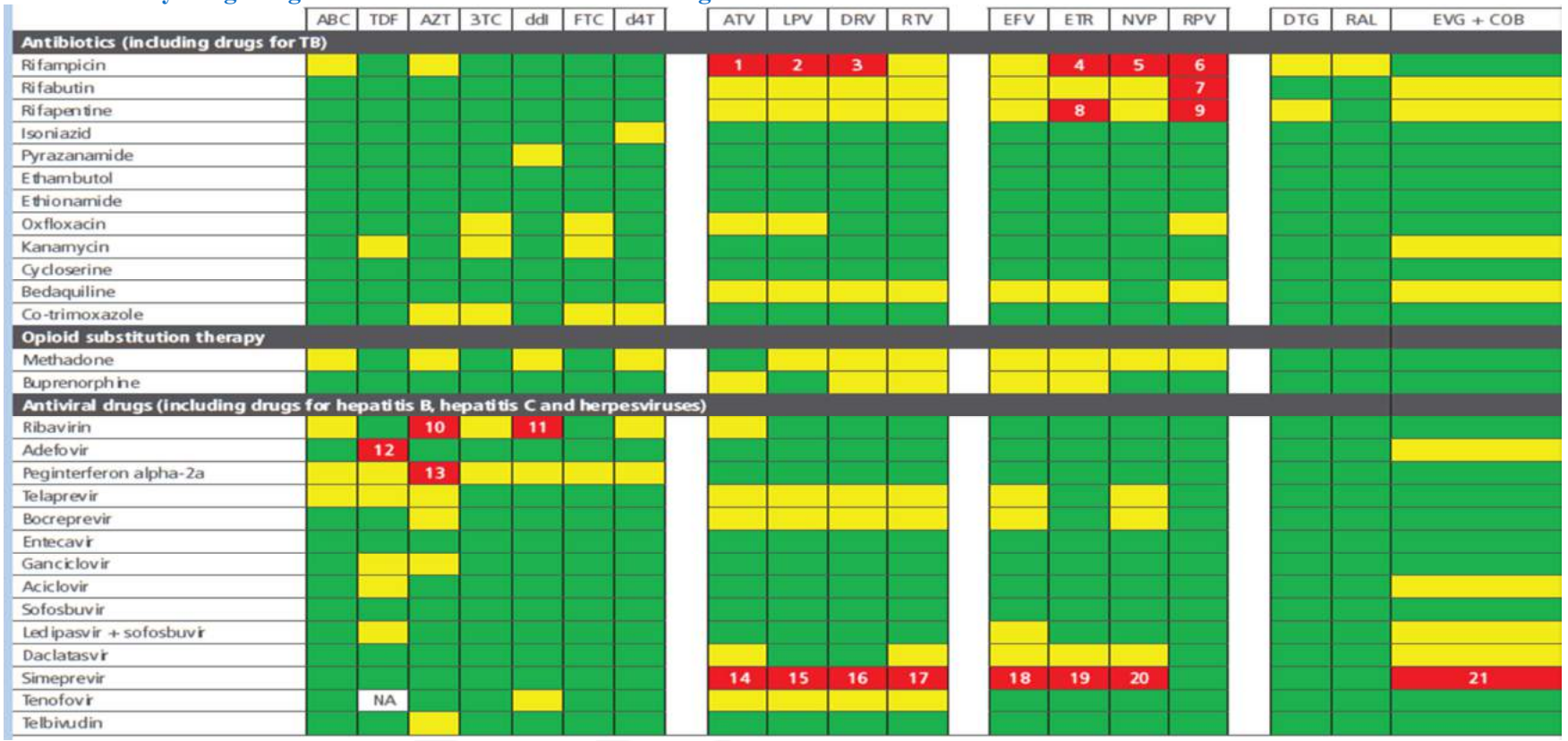


Figure Legend

No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.

Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.

Interaction likely: do not use or use with caution (# indicates cross-reference to interaction explanation).

– No clear data, actual or theoretical, indicate whether an interaction will occur.

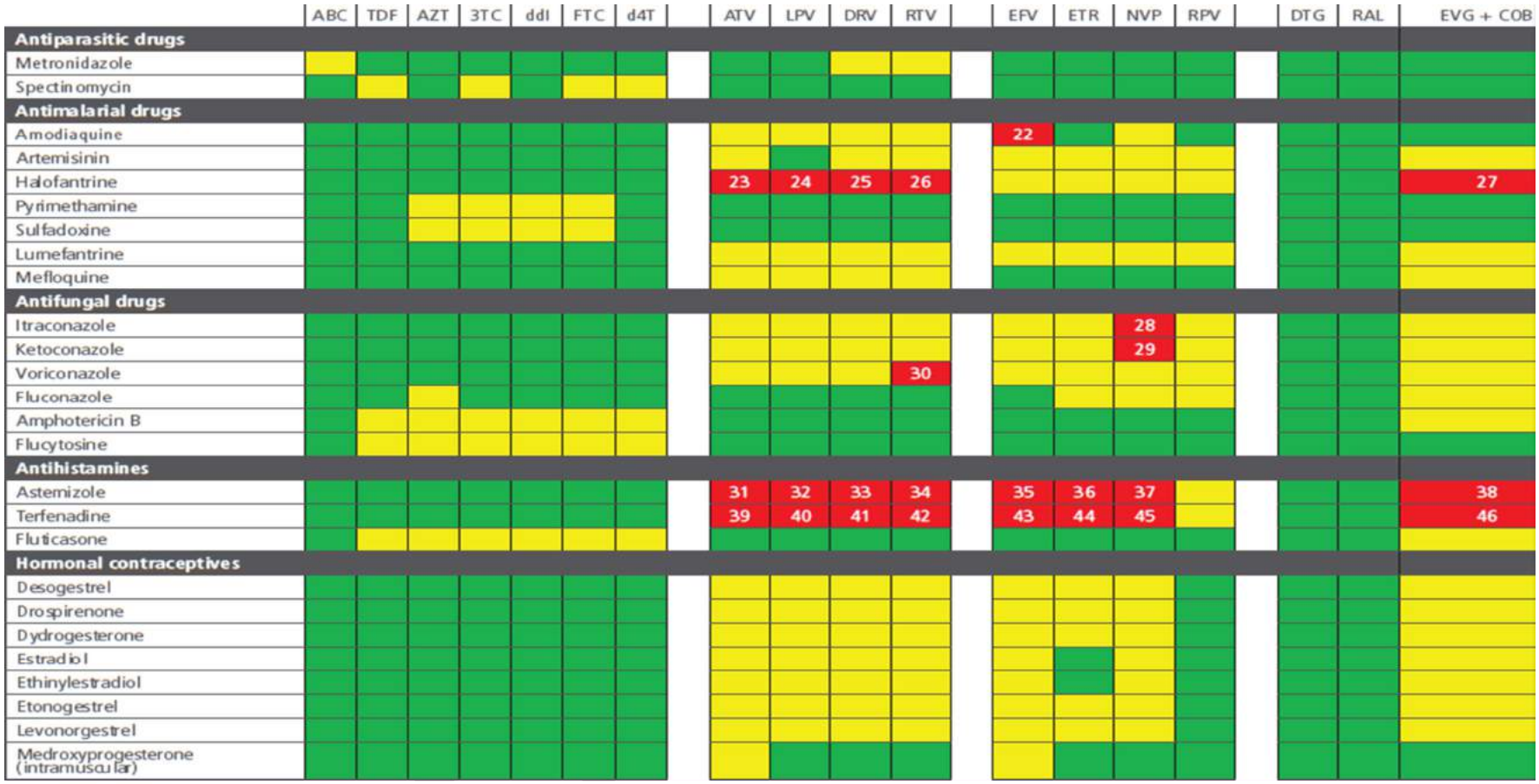


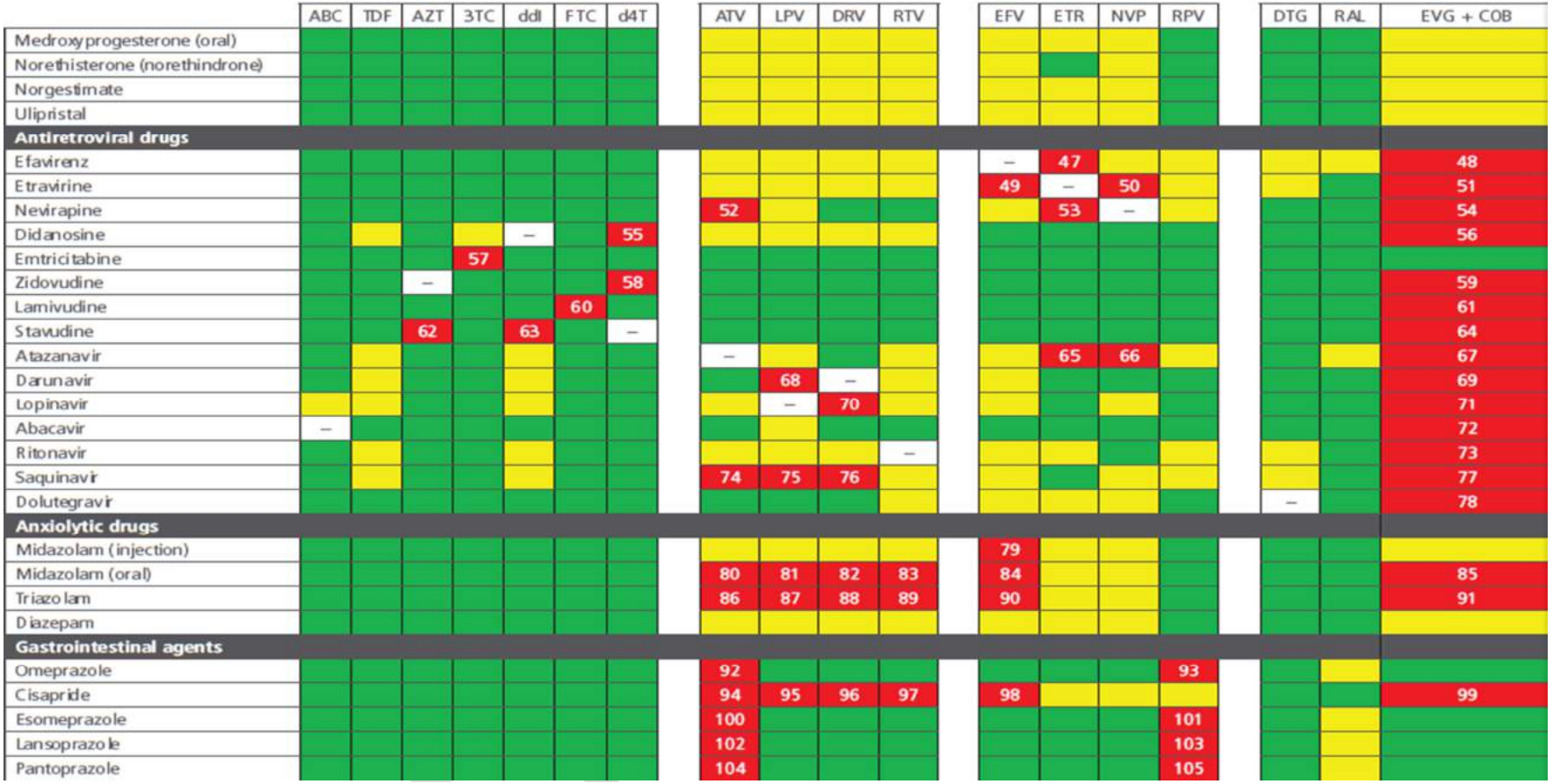
Figure Legend

No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.

Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.

Interaction likely: do not use or use with caution (# indicates cross-reference to interaction explanation).

– No clear data, actual or theoretical, indicate whether an interaction will occur.



	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Medroxyprogesterone (oral)																		
Norethisterone (norethindrone)																		
Norgestimate																		
Ulipristal																		
Antiretroviral drugs																		
Efavirenz												–	47					48
Etravirine												49	–	50				51
Nevirapine								52					53	–				54
Didanosine					–		55											56
Emtricitabine				57														
Zidovudine			–				58											59
Lamivudine						60												61
Stavudine			62		63		–											64
Atazanavir								–					65	66				67
Darunavir									68	–								69
Lopinavir									–	70								71
Abacavir	–																	72
Ritonavir											–							73
Saquinavir								74	75	76								77
Dolutegravir																–		78
Anxiolytic drugs																		
Midazolam (injection)												79						
Midazolam (oral)								80	81	82	83	84						85
Triazolam								86	87	88	89	90						91
Diazepam																		
Gastrointestinal agents																		
Omeprazole								92							93			
Cisapride								94	95	96	97	98						99
Esomeprazole								100							101			
Lansoprazole								102							103			
Pantoprazole								104							105			

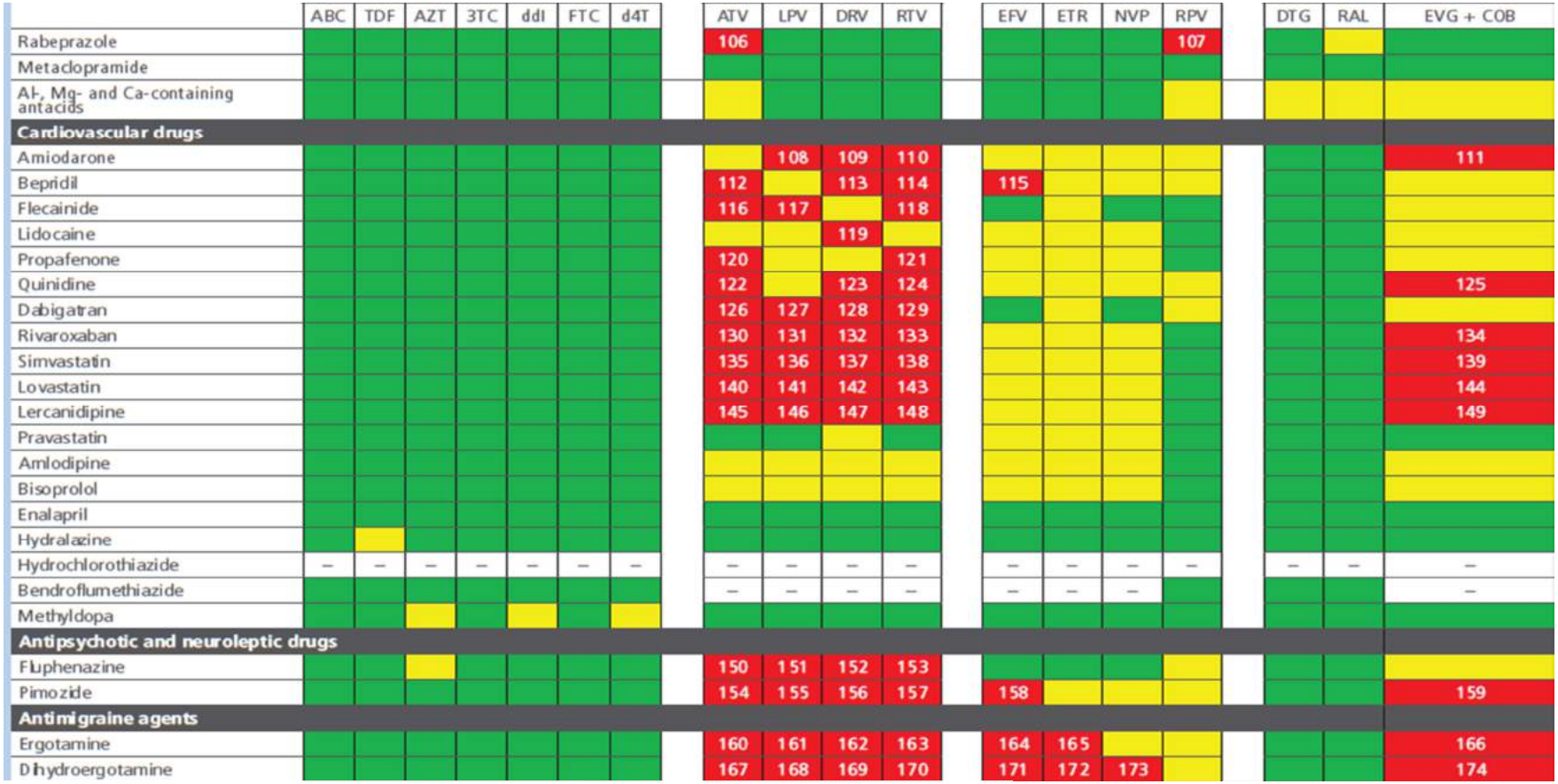
Figure Legend

No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.

Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.

Interaction likely: do not use or use with caution (# indicates cross-reference to interaction explanation).

– No clear data, actual or theoretical, indicate whether an interaction will occur.



	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Rabeprazole								106							107			
Metaclopramide																		
Al-, Mg- and Ca-containing antacids																		
Cardiovascular drugs																		
Amiodarone									108	109	110							111
Bepridil								112		113	114	115						
Flecainide								116	117		118							
Lidocaine										119								
Propafenone								120			121							
Quinidine								122		123	124							125
Dabigatran								126	127	128	129							
Rivaroxaban								130	131	132	133							134
Simvastatin								135	136	137	138							139
Lovastatin								140	141	142	143							144
Lercanidipine								145	146	147	148							149
Pravastatin																		
Amlodipine																		
Bisoprolol																		
Enalapril																		
Hydralazine																		
Hydrochlorothiazide	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Bendroflumethiazide								–	–	–	–	–	–	–				–
Methyldopa																		
Antipsychotic and neuroleptic drugs																		
Fluphenazine								150	151	152	153							
Pimozide								154	155	156	157	158						159
Antimigraine agents																		
Ergotamine								160	161	162	163	164	165					166
Dihydroergotamine								167	168	169	170	171	172	173				174

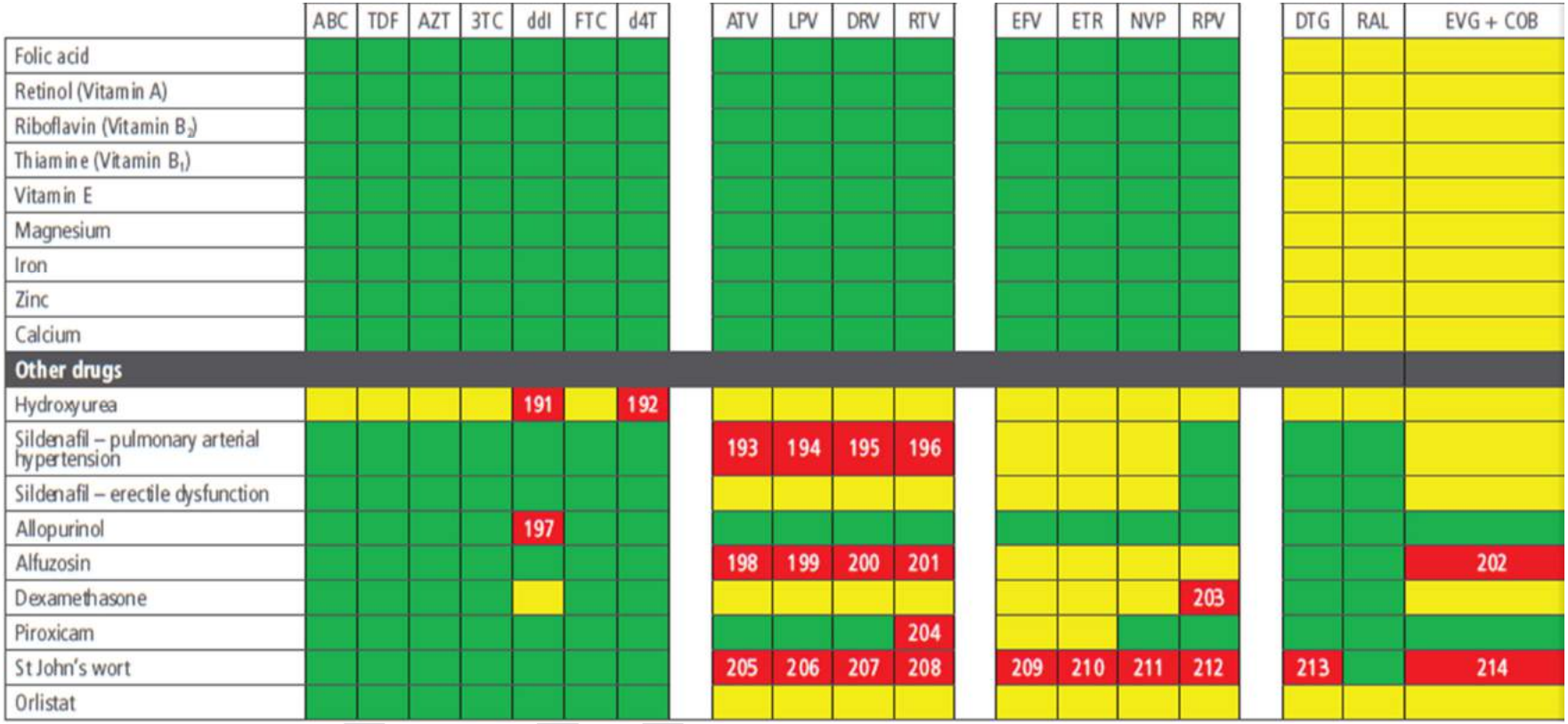
Figure Legend

No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.

Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.

Interaction likely: do not use or use with caution (# indicates cross-reference to interaction explanation).

– No clear data, actual or theoretical, indicate whether an interaction will occur.



	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Folic acid																		
Retinol (Vitamin A)																		
Riboflavin (Vitamin B_2)																		
Thiamine (Vitamin B_1)																		
Vitamin E																		
Magnesium																		
Iron																		
Zinc																		
Calcium																		
Other drugs																		
Hydroxyurea					191		192											
Sildenafil – pulmonary arterial hypertension								193	194	195	196							
Sildenafil – erectile dysfunction																		
Allopurinol					197													
Alfuzosin								198	199	200	201							202
Dexamethasone															203			
Piroxicam											204							
St John's wort								205	206	207	208	209	210	211	212	213		214
Orlistat																		

Figure Legend

- No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.
- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.
- Interaction likely: do not use or use with caution (# indicates cross-reference to interaction explanation).
- – No clear data, actual or theoretical, indicate whether an interaction will occur.

Annex 13: Severity grading of selected clinical and laboratory toxicities most commonly seen with recommended antiretroviral drugs for children (26)

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Severe and potentially life threatening(Grade 4)
General guidance on estimating severity grade				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities:[a] no therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: may require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: requires medical care and possible hospitalization	Symptoms causing inability to perform basic self care functions: [b] requires medical or operative intervention to prevent permanent impairment, persistent disability or death
Hematology[c] Standard international units are listed in italics				
Absolute neutrophil count	750–<1,000/mm^3 0.75 x 10^9– < 1 x 10^9/l	500–749/mm3 0.5 x 10^9–0.749 x 10^9/l	250–500/mm^3 0.25 x 10^9–0.5 x 10^9/l	<250/mm3 <0.250 x 10^9/l
Haemoglobin (child >60 days of age)	8.5–10.0 g/dl 1.32–1.55 mmol/l	7.5–<8.5 g/dl 1.16–<1.32 mmol/l	6.5–<7.5 g/dl 1.01–<1.16 mmol/l	<6.5 g/dl <1.01 mmol/l or severe clinical symptoms attributable to anemia (e.g. cardiac failure), refractory to supportive therapy
Platelets	100,000–<125,000/mm^3 100 x 10^9–125 x 10^9/l	50,000–<100,000/mm^3 50 x 10^9– <100 x 10^9/l	25,000–<50,000/mm^3 25 x 10^9–<50 x10^9/l	<25,000/mm^3 <25 x 10^9/l or bleeding
Gastrointestinal [c]				
ALT (SGPT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	>10.0 x ULN
Bilirubin (>2 weeks of age)	1.1–1.5 x ULN	1.6–2.5 x ULN	2.6–5.0 x ULN	> 5.0 x ULN
Lipase	1.1–1.5 x ULN	1.6–3.0 x ULN	3.1–5.0 x ULN	> 5.0 x ULN

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Severe and potentially life threatening(Grade 4)
Clinical				
Diarrhoea >1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per day	Grossly bloody diarrhoea OR increase of ≥7 stools per day OR intravenous fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hrs OR aggressive rehydration indicated (e.g. IV fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	Not applicable	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Symptomatic AND hospitalization indicated	Life-threatening consequences (e.g. circulatory failure, hemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. IV fluids)	Life-threatening consequences (e.g. hypotensive shock)

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Severe and potentially life threatening(Grade 4)
Allergic/dermatological				
Acute systemic allergic reaction	Localized urticaria (wheals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angioedema	Generalized urticaria OR angio-oedema with medical intervention indicated OR symptomatic mild broncho-spasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal edema
Cutaneous reaction rash	Localized macular rash	Diffuse macular, maculopapular, OR morbilliform rash OR target lesions	Diffuse macular, maculopa-pular, or morbilliform rash with vesicles or limited number of bullae OR superfi-cial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis
Neurological				
Alteration in personality, behavior or mood[b]	Alteration causing no or minimal interference with usual social and functional activities[b]	Alteration causing greater than minimal Interference with usual social and functional activities[b]	Alteration causing inability to perform usual social and functional activities[b] AND intervention indicated	Behaviour potentially harmful to self or others OR life-threatening consequences
Altered mental status	Changes causing no or minimal interference with usual social and functional activities[b]	Mild lethargy or somno-lence causing greater than minimal interference with usual social and functional activities[b]	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities[b]	Onset of delirium, obtundation or coma
Neuromuscular Weakness (including myopathy and neuropathy)	Asymptomatic with decreased strength on examination OR minimal muscle weakness causing no or minimal interference with usual social and functional activities[b]	Muscle weakness causing greater than minimal interference with usual social and functional activities[b]	Muscle weakness causing inability to perform usual social and functional activities[b]	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Severe and potentially life threatening(Grade 4)
Neurological (continue)				
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on examination OR minimal paresthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions[c]
Other laboratory parameters Standard international units are listed in italics				
Cholesterol (fasting, paediatric <18 yearsold	170–<200 mg/dl 4.40–5.15 mmol/l	200–300 mg/dl 5.16–7.77 mmol/l	>300 mg/dl >7.77 mmol/l	Not applicable
Glucose, serum, high: non-fasting	116–<161 mg/dl 6.44–<8.89 mmol/l	161–<251 mg/dl 8.89–<13.89 mmol/l	251–500 mg/dl 13.89–27.75 mmol/l	>500 mg/dl >27.75 mmol/l
Glucose, serum, high: fasting	110–<126 mg/dl 6.11–<6.95 mmol/l	126–<251 mg/dl 6.95–<13.89 mmol/l	251–500 mg/dl 13.89–27.75 mmol/l	>500 mg/dl >27.75 mmol/l
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	Not applicable	500–<751 mg/dl 5.65–<8.49 mmol/l	751–1,200 mg/dl 8.49–13.56 mmol/l	>1,200 mg/dl >13.56 mmol/l

Source: Adapted from Division of AIDS, National Institute of Allergy and Infectious Diseases, Table for grading the severity of adult and paediatric adverse events, Bethesda, Maryland, USA; December 2004.

[a] Usual social and functional activities in young children include those that are appropriate to their age and culture (e.g. social interactions, play activities, learning tasks).

[b] Activities that are appropriate to age and culture (e.g. feeding self with culturally appropriate eating implement, walking or using hands).

[c] Values are provided for children in general except where age groups are specifically noted.

Annex 14: Family planning

Family planning information for HIV-infected women

Providing family planning counselling and services for HIV-infected women to prevent subsequent unintended pregnancy, HIV transmission to child and HIV-uninfected partner are critical. All HIV-infected women should be assessed and counselled for appropriate family planning option. Some HIV-infected women are reluctant to disclose their HIV status with their partners, so they are unable to argue for family planning. Thus, men's involvement in family planning may be a key to preventing subsequent pregnancies among HIV-infected women.

HIV-infected women and partner planning to have children should receive pre-conceptual counselling on mother-to-child HIV transmission risks, their long-term health and possible effects of ARV medication on the fetus. Couples should weight for risks and benefits. Couples who plan to have baby should be referred to specialist for counselling of safe conception and ways to reduce risk for HIV transmission to infants and partners.

HIV-infected women and partner planning not to have children should receive appropriate contraception counselling using "dual method protection" that is consistent condom use plus other birth control options e.g. sterilization, hormonal injection or intrauterine device.

Contraceptive options for HIV-infected women

Women taking any nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) can use all hormonal contraceptive methods without restriction: hormonal contraceptive methods without restriction: oral contraceptive pills, contraceptive injection, implant, and IUD. Only IUD is not recommended in Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) until their illness has improved to asymptomatic or mild HIV clinical disease. Women using ART containing either efavirenz or nevirapine can generally use hormonal contraceptive methods as well without restriction.

Sterilization of females or males

For HIV-infected women who have decided not to have more children, female or male sterilization is a good option.

Condoms

The woman's partner can use condoms for protection against disease and contraception. However, the failure rate of condoms in preventing pregnancy may be as high as 10%. Therefore, dual method protection is recommended.

Annex 15: Infant feeding options

In this guideline recommends two options of infant feeding namely exclusive breastfeeding and formula milk. Exclusive breastfeeding recommend where health services provide and support lifelong antiretroviral treatment including adherence counselling, promote and support breastfeeding among women living with HIV, mother and infant are taking ARV with very good adherence. The duration of breastfeeding should not be restricted. Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (similar to the general population) while being fully supported for ART adherence. (27) Breastfeeding should then stop only once a nutritionally adequate and safe diet without breast milk can be provided.
Formula milk feeding is recommended for mothers or infants, who are not taking ARV drugs or with poor adherence. If the mother decide to feed her baby with formula feeding, AFASS counselling should be provided to avoid child morbidity and mortality by other disease especially diarrhoea. (see infant formula feeding below)

Infant feeding in the context of HIV is complex because of the major influence that feeding practices exerts on child survival. The dilemma is to balance the risk of infants acquiring HIV through breast milk with the higher risk of death from causes other than HIV, in particular malnutrition and serious illnesses such as diarrhoea among non-breastfed infants. Infant feeding options should be discussed with mother during antepartum and postpartum periods. During feeding options discussion, health care providers should ask women specific questions, such as "What will you say when your mother-in-law or neighbour asks you why you are not breast-feeding or why you have stopped breast-feeding?" or "What will you say when your mother-in-law or neighbour asks you why you have to take medication every day". Health care providers should help women prepare to answer questions about her choice. The counselling session may also be an opportunity to further discuss issues that relate to disclosure of the mother's HIV status to the family.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for breastfeeding by mothers living with

HIV while receiving ART includes:

- communicating clearly and effectively to health workers, mothers and the community the effectiveness of ART to reduce the postnatal transmission risks through breastfeeding;
- highlighting the value of breastfeeding for the health, development and survival of mothers living with HIV and their children when the mother is receiving ART;
- implementing and sustaining specific interventions (such as integrated follow up with immunization and other well-child services) to improve postpartum follow up of mother–infant pairs, and supporting breastfeeding practices and ART adherence;
- emphasizing postnatal prophylaxis for infants: infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP, or if they are considered at high risk, enhanced infant prophylaxis using AZT and NVP for 6 weeks followed by either AZT and NVP or NVP alone for an additional 6 weeks (see table:13); and
- linking EID results with appropriate infant-feeding practices: infants who are HIV infected should continue breastfeeding until 24 months or longer.

In addition, there is a need for enhanced monitoring for potential toxicities from prolonged infant exposure to ARV drugs through breast milk and to continue toxicity surveillance, as new drugs are included in maternal ART regimens. In particular, the effects of ARV drugs on neurodevelopmental outcomes, growth and renal and bone health need to be better understood. This could be achieved through sentinel site monitoring of infant cohorts during the first two years of life. For infants who become infected despite interventions to prevent mother-to-child transmission, exposure to drugs through breastfeeding has implications for resistance as well as toxicity, and this may have an impact on the success of ART regimens for the child.

When mother decides to stop breastfeeding

Mothers known to be HIV-infected who decide to stop breastfeeding at any time should stop gradually within one month.

Stopping breastfeeding abruptly is not advisable**.**

What to feed infants when mothers stop breastfeeding

When mothers known to be HIV-infected decide to stop breastfeeding at any time, infants should be provided with safe and adequate replacement feeds to enable normal growth and development.

Alternatives to breastfeeding include:

For infants less than 6 months of age: Commercial infant formula milk (see infant formula feeding below)

For children over 6 months of age: Commercial infant formula milk and/or complementary foods.

When the infant is HIV-infected

If infants and young children are known to be HIV-infected, mothers are strongly encouraged to exclusively breastfeed for the first 6 months of life and continue breastfeeding as per the recommendations for the general population that is up to two years or beyond.

Option 1: Exclusive breastfeeding for 6 months plus ARV in mother and infant

Exclusive breast-feeding
Advantages - Breastmilk is easily digestible and gives infants all the nutrition and water they need. They do not need any other liquid or food for the first six months. - Breastmilk is always available and does not need any special preparation. - Breastmilk protects infants and children from disease, particularly diarrhoea and pneumonia. - Breastfeeding provides close contact that deepens the emotional relationship or bond between mother and child. - Compared to mixed feeding, exclusive breastfeeding for the first few months may lower the risk of passing on HIV. - Transmission risk would be further diminished in presence of ARV interventions in mother and infant.

- Enabling breastfeeding in the presence of ARV interventions to continue to 12 months avoids many of the complexities associated with stopping breastfeeding and providing a safe and adequate diet without breast milk to the infant 6–12 months of age. This was seen as a major advantage.[25]
Disadvantages - Risk of MTCT reduces from ARV intervention but the risk is not zero. - The risk of transmitting HIV through breastfeeding is increased if the mother has a breast infection (e.g. mastitis) or cracked and bleeding nipples. - Family, friends, or neighbours may pressure mothers to give water, other liquids, or foods to the infant. - Although nearly all mothers have sufficient milk to feed their infants, many are concerned that they do not have enough milk to breast-feed exclusively. - Breastfeeding requires feeding on demand at least eight to ten times per day, and working mothers may find it difficult to breast-feed exclusively once they return to work (unless they can privately express milk as required during the workday and can arrange to store milk in a cool place). - Breastfeeding mothers require an additional 500-750 kcal/day to support exclusive breastfeeding during the infant's first six months.

Option2: Formula feeding

Commercial infant formula milk can be given as a replacement feed to their HIV-uninfected infants, when specific conditions are met: (referred to as AFASS – affordable, feasible, acceptable, sustainable and safe) (28)

a. safe water and sanitation are assured at the household level and in the community, and,
b. the mother, or other caregiver can reliably provide sufficient infant formula milk to support normal growth and development of the infant, and,
c. the mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition, and,
d. the mother or caregiver can, in the first six months, exclusively give infant formula milk, and,
e. the family is supportive of this practice, and,
f. the mother or caregiver can access health care that offers comprehensive child health services.

Commercial infant formula
Advantages Commercial formula poses no risk of transmitting HIV to the infant Commercial formulas are made especially for infants Commercial formula includes most of the nutrients that an infant needs Other family members can help feed the infant If the mother is ill, others can feed her infant while she recovers
Disadvantages Commercial formula does not contain antibodies, which protect infants from infection. An infant who is fed commercial formula exclusively is more likely to get sick from diarrhea and pneumonia and may develop malnutrition A continuous, reliable formula supply is required to prevent malnutrition Commercial formula is expensive Families must buy feeding bottles, cups and soap for cleaning utensils used in preparing the formula Safe preparation of commercial formula requires clean water, boiled vigorously for a few

seconds; this also requires fuel Formula should be made fresh for each feeding, according to directions, day and night. The infant needs to drink from a cup or bottle. The mother must stop breast-feeding completely, or she will continue to be at risk of transmitting HIV to her infant. In some settings, family, neighbours or friends may question a mother who does not breast-feed about her HIV status. Formula feeding offers the mother no protection from pregnancy.

Important notes on infant feeding:

- Mix feeding (breastfeeding and formula feeding) is not recommended because of high risk of acquiring HIV virus to her baby. Although exclusive breastfeeding is recommended, practising mixed feeding is not a reason to stop breastfeeding in the presence of antiretroviral (ARV) drugs

Annex 16: Pre-natal, intra-partum and post-natal care

1. Prenatal care

Ideally all pregnant women should be given provider initiative counselling and testing at the first visit of antenatal care. All HIV positive pregnant women should be given ARV drugs for prevention of mother to child transmission and continuing for life (option B+). Partner testing is recommended in all HIV positive pregnant women. If they are in the window period, retesting is recommended as well to exclude HIV infection.

2. Intra-partum care

WHO recommends that elective caesarean section (C-section) should not be routinely recommended to women living with HIV. The use of amniotomy alone for prevention of delay in labour is not recommended. In contrast, the use of amniotomy and oxytocin for treatment of confirmed delay in labour is recommended in women living with HIV and other women.

Vaginal delivery

Invasive procedures e.g. forceps extraction, vacuum extraction, and artificial rupture of the membrane should be avoided unless medically indicated. Women with premature rupture of the membrane >4 hours, labor should be induced to reduce the time to delivery and risk for MTCT.

Elective caesarean section

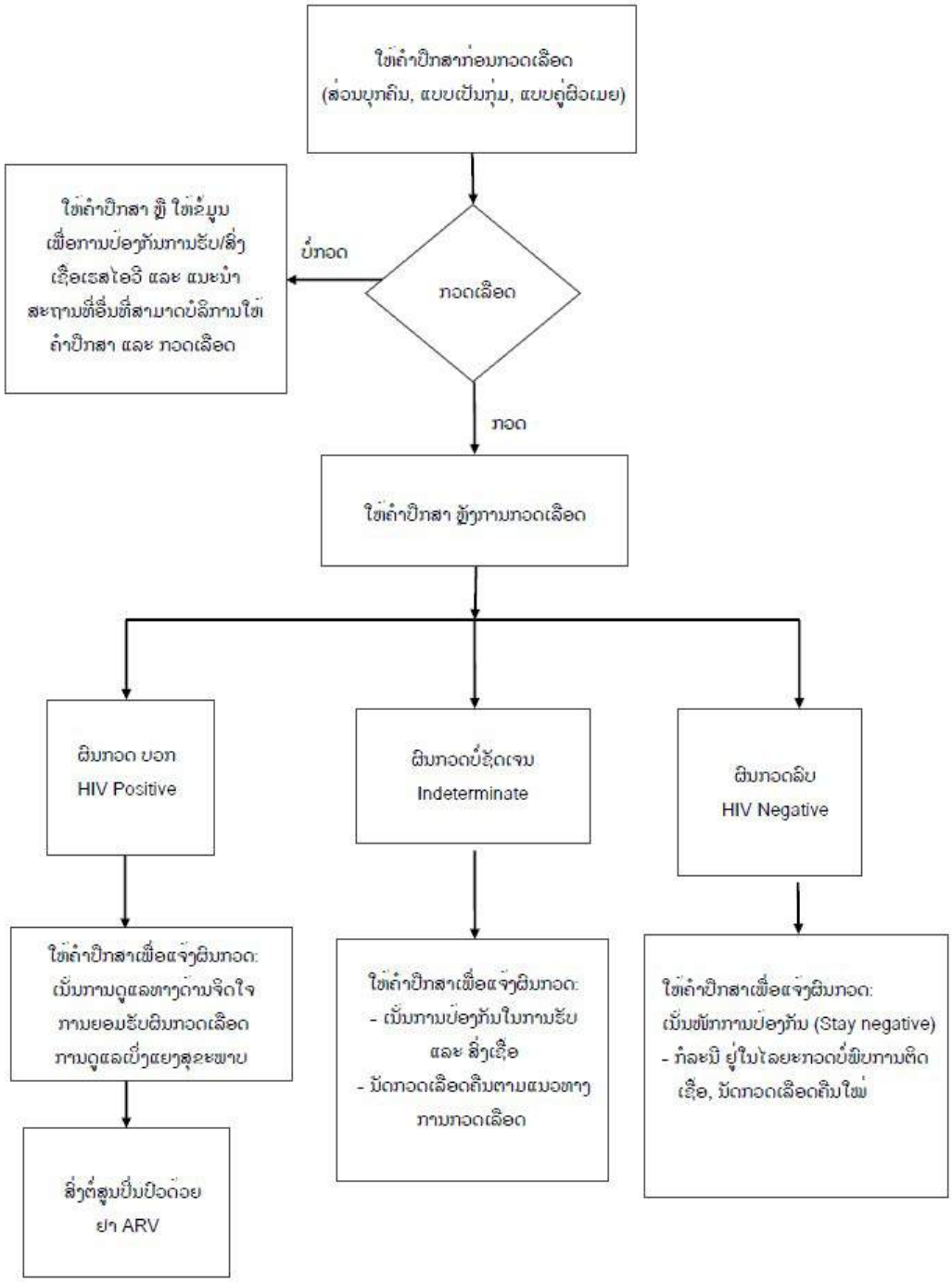
As mentioned above, WHO recommends that elective caesarean section (C-section) should not be routinely recommended to women living with HIV. For women living with HIV, as for all women, the decision on whether or not to have an elective C-section must take into account the range of potential risks as well as benefits for both the mother and the infant. These risks and benefits vary depending on the underlying risk of perinatal transmission during delivery, which is associated with disease stage and ART use, as well as on the underlying risks of C-section compared with vaginal delivery for both the mother and infant. Elective caesarean section before onset of labor and before the rupture of the membrane can reduce risk of MTCT. However, the risk of maternal complication is higher than in normal delivery. In settings that caesarean section is feasible and safe, elective caesarean section should be considered in HIV-infected pregnant women with 38 weeks of gestation who have no ANC or receive ART less than 4 weeks before onset of labor, women with poor ARV adherence, or women with HIV RNA level (if available) at 36 weeks of gestation >1,000 copies/ml.

3. Post-partum care

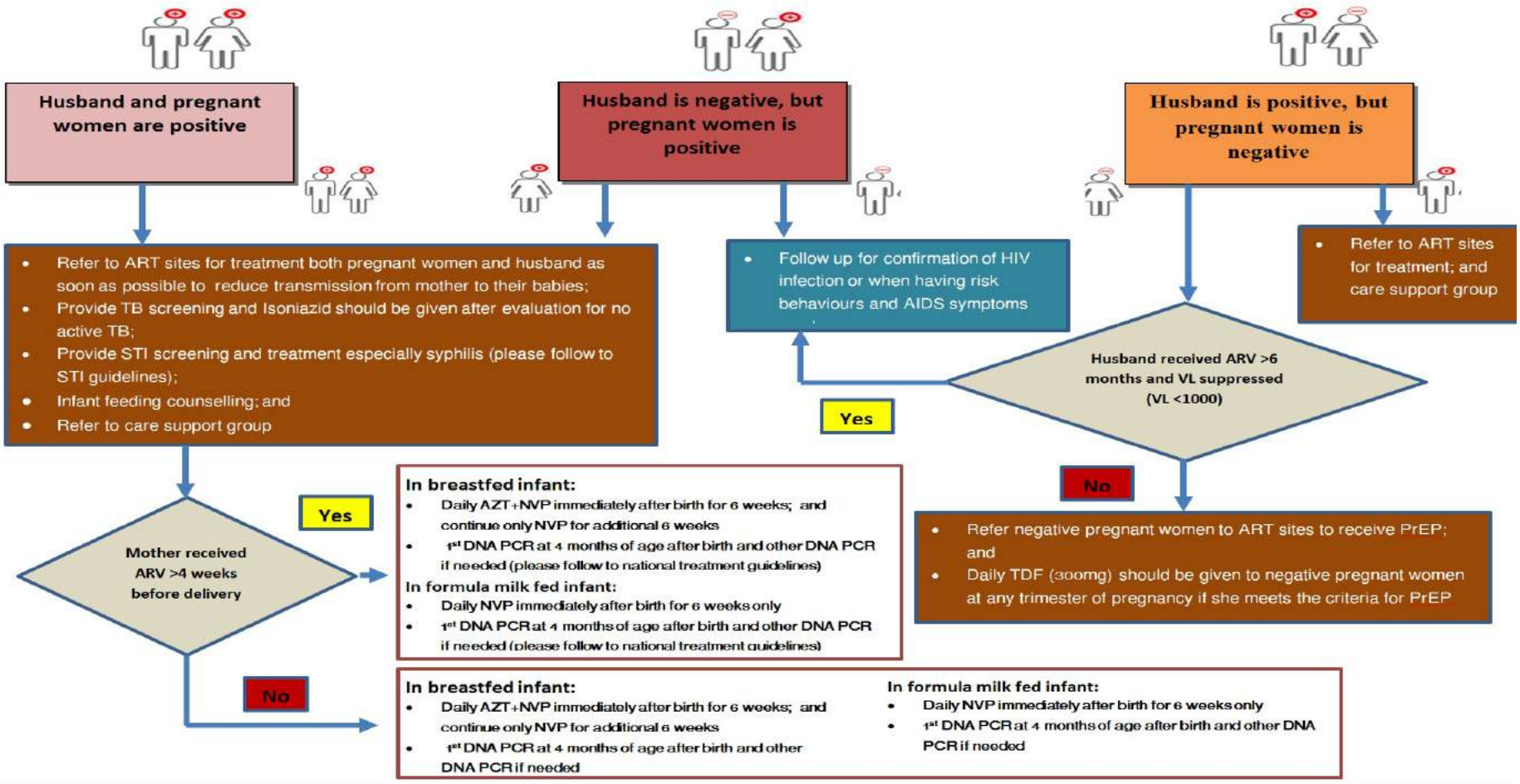
Late cord clamping (performed approximately 1–3 minutes after birth)is recommended even among women living with HIV or women with unknown HIV status. (26) ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count, and continued lifelong. Mothers living with HIV and health-care workers can be reassured that ART reduces the risk of postnatal HIV transmission in the context of mixed feeding. Although exclusive breastfeeding is recommended, practising mixed feeding is not a reason to stop breastfeeding in the presence of antiretroviral (ARV) drugs.

Annex 17: Standard operational procedure on prevention from mother to child transmission

1. Provider initiated counselling and testing in pregnant women

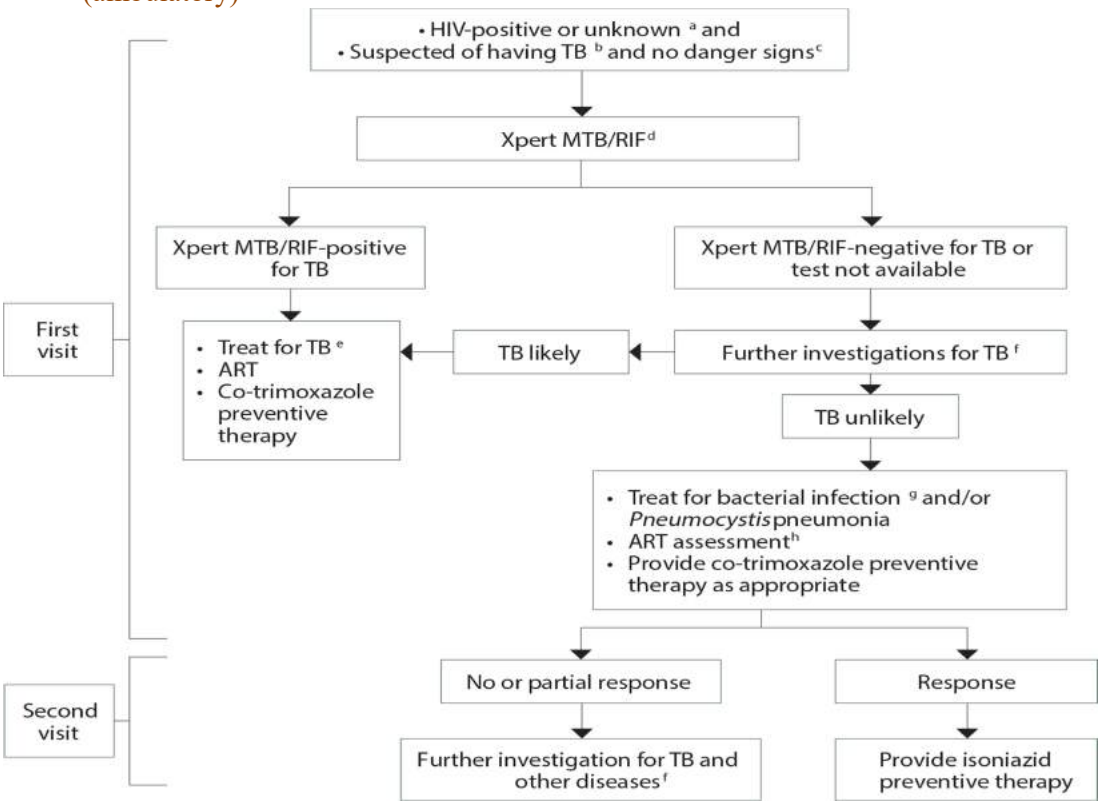


2. Prevention from Mother to Child Transmission



Annex 18: TB/HIV management

1) Algorithm for managing people living with HIV who are suspected of having TB (ambulatory)



a For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

b Suspicion of TB is defined by the presence of any one of the following symptoms.

– For adults and adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.

– For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.

c Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided.

d For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood).

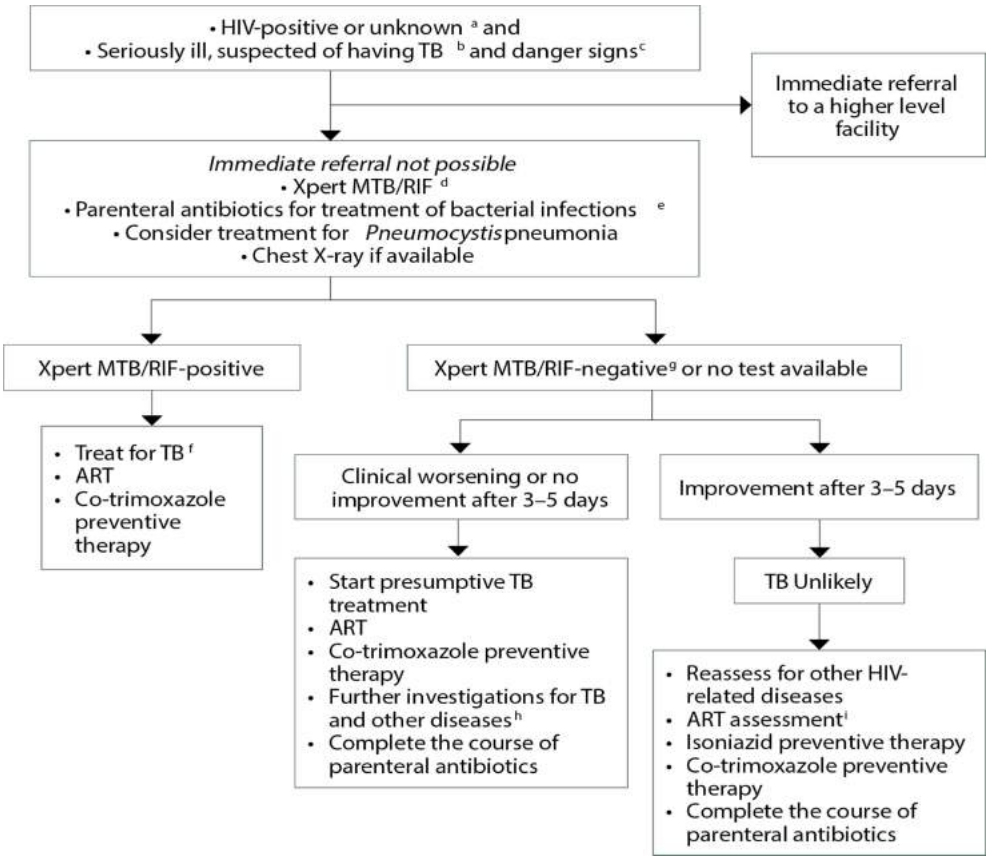
e If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-reistant TB should be initiated. If the person is considered at low
risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.

f Further investigations for TB include chest X-ray, clinical assessment and a repeat Xpert MTB/RIF using a fresh specimen. Refer a sample for TB culture where feasible. If Xpert MTB/RIF is not available, conduct acid-fast bacillus (AFB) microscopy. AFB-positive is defined as at least one positive smear, and AFB-negative as two or more negative smears. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed. These investigations may require additional visits. A urine lateral flow lipoarabinomannan (LF-LAM) assay should not be performed for people with no danger sign.

g Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.

h ART should be given to all adults, regardless of CD4 cell count or clinical stage.

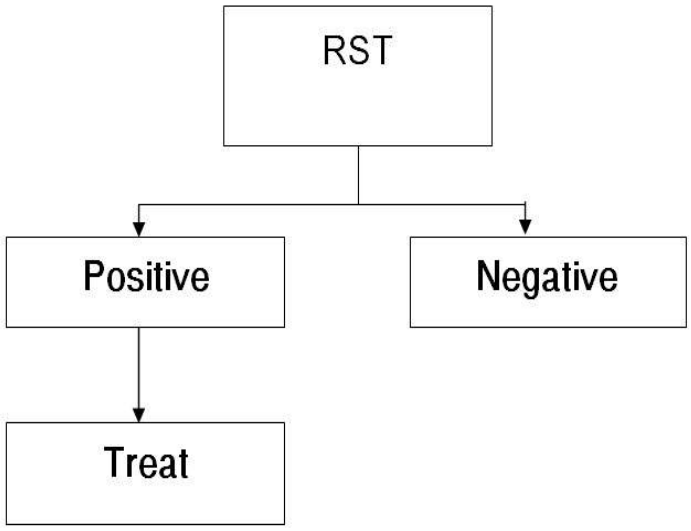
2) Algorithm for managing people living with HIV who are suspected of having TB (seriously ill)



a For all people with unknown HIV status, HIV testing should be performed according to national guidelines.
b Suspicion of TB is defined by the presence of any one of the following symptoms.
– For adults and adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.
– For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.
c Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided.
d For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood).
The urine lateral flow lipoarabinomannan (LF-LAM) assay may be used to assist in diagnosing active TB among seriously ill adults and children living with HIV, regardless of CD4 count.
If Xpert MTB/RIF is not available, conduct AFB microscopy. AFB-positive is defined as at least one positive smear and AFB-negative as two or more negative smears. Refer the specimen for TB culture where feasible.
e Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.
f If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-reistant TB should be initiated. If the person is considered at low
risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.
g If Xpert MTB/RIF shows negative results, the test can be repeated using a fresh specimen.
h Further investigations for TB include chest X-ray, clinical assessment, a repeat Xpert MTB/RIF using a fresh specimen an culture. If extrapulmonary
TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.
i ART should be recommended for all adults, regardless of CD4 cell count or clinical stage.

Annex 19: Syphilis diagnosis

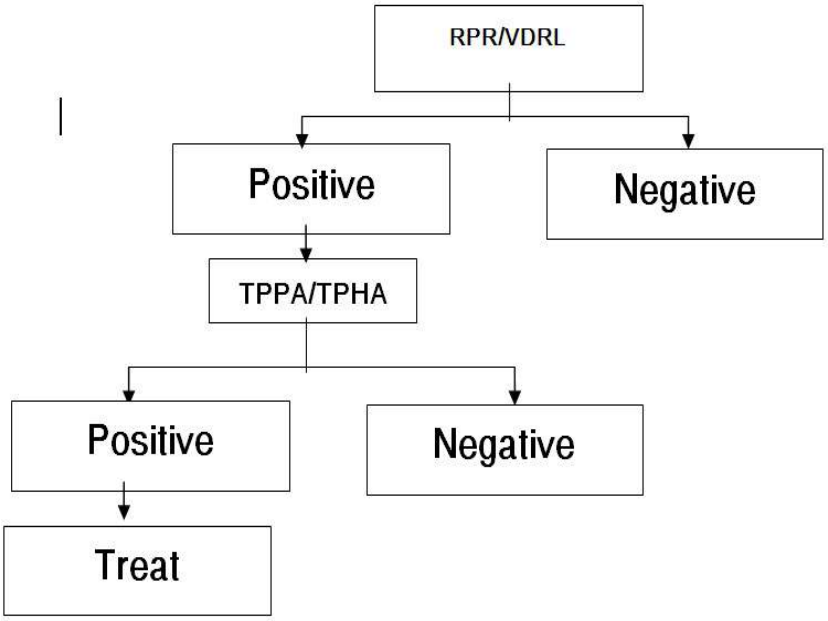
1. Rapid treponemal test



Note:

RST cannot distinguish between active and past treated infection. It can give more benefitsfor pregnant womento be treated and prevent neonatal syphilis.

2. Non-treponemal tests



Annex 20: Operational Guidance on Use of Dolutegravir in Lao PDR

Dolutegravir was first approved by the US Food and Drug Administration in 2013 and has been widely prescribed in the United States and Europe since then. Two suppliers have received stringent regulatory approvals for the generic, fixed-dose combination of Tenofovir + Lamivudine + Dolutegravir ("TLD") in August 2017. One of a newer class of drugs, the integrase strand transfer inhibitors (INSTIs), dolutegravir works by preventing the integration of HIV DNA into the host cell's DNA.

Dolutegravir offers several clinical advantages over efavirenz ("EFV") for use in first-line therapy. It achieves viral suppression faster (on average 4 weeks for DTG vs 12 weeks for EFV) and is more likely to achieve and maintain suppression (e.g. in the SINGLE trial 88% of DTG patients were suppressed at 48 weeks vs 81% of EFV patients). This translates to improved individual patient as well as public health outcomes, as virally suppressed patients are less likely to transmit HIV. (29) Dolutegravir has a high genetic barrier to resistance with no apparent cases of resistance in treatment-naïve clinical trial patients. (29) (30)This reduces the need to switch patients to more expensive and less tolerable second-line regimens. DTG is also a more reliable first-line option, as pre-treatment resistance to EFV continues to rise. Dolutegravir is better tolerated than efavirenz, with lower incidence of side effects and fewer treatment discontinuations. (29) Finally, generic pricing agreements will make dolutegravir-based therapy cheaper than current first line treatment with efavirenz, allowing significant cost savings.

Lao PDR has elected to begin a phased introduction of DTG in first-line therapy. By mid to late 2018 (pending exact confirmation from CHAS regarding delivery dates), clinicians should prescribe TLD for most newly-initiating adolescent and adult patients. ***It is recommended to confirm that patient is virally suppressed before proactively switching from TDF/3TC/EFV to TDF/3TC/DTG. Patient should have a VL < 1000 copies result within the past 12 months. If patient does not have a VL result within the past 12 months, then a new VL test should be done before switching. If the patient is found to have VL > 1000 copies, s/he should be initiated on standard second-line therapy – not switched to TDF/3TC/DTG."***

Special populations who require additional monitoring or alternative therapies include:

- **Pregnant women who are diagnosed HIV+ and initiate ART during the *first or second trimester* of pregnancy (up to 28 weeks of pregnancy).**
    - Such women should be initiated on **TDF+3TC+EFV**. While early programmatic data on the use of DTG in pregnancy has shown no increased risk to the fetus relative to other ARVs, WHO has not yet made a recommendation on the use of DTG in pregnancy.

- **Pregnant women who are diagnosed HIV+ and initiate ART during the *third trimester* of pregnancy (28 weeks and later).**
    - Such women should be initiated on **TDF+3TC+DTG**. An elevated viral load at the time of delivery is the strongest risk factor for mother-to-child transmission of HIV. EFV is estimated to take an average of 12 weeks to achieve viral suppression, as compared to only 4 weeks for DTG. Thus, for women presenting late in pregnancy, the benefits of using DTG to prevent mother-to-child transmission outweigh the potential for risks to the fetus. Fetal

organ development is largely completed in the first trimester and third trimester exposures are not expected to result in fetal malformations. Although fetal growth restriction and premature delivery may still be possible with third trimester DTG use, to date there is no evidence to suggest these adverse events are more likely with DTG compared to other ARVs.

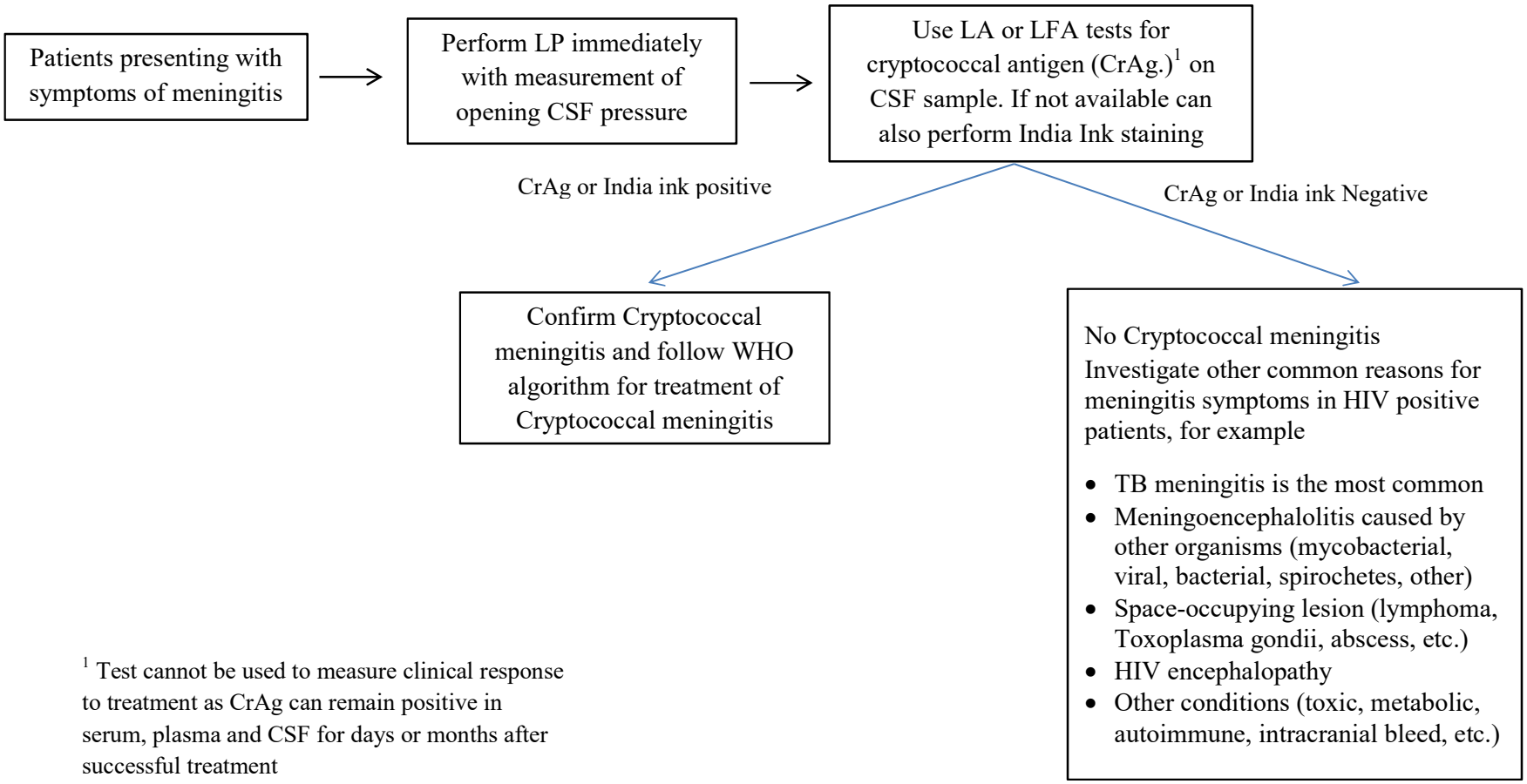
- **Women of reproductive age who wish to become pregnant.**
  - Such women should be initiated on **TDF+3TC+EFV**, in line with current recommendations.
  - Women who do not wish to become pregnant can be initiated on TDF+3TC+DTG and should receive thorough family planning counseling and access to a range of modern family planning methods.

- **Women who become pregnant after initiating DTG.**
  - Because there is currently no documented association between DTG use and fetal abnormalities, and to simplify options for the patient and the program, clinicians are recommended to keep women on **TDF+3TC+DTG** during pregnancy. This is the current recommendation in the United States.

- **Patients initiating ART with CD4 < 100.**
  - DTG and other INSTIs have been associated with an increased risk of Immune Reconstitution Inflammatory Syndrome (IRIS), likely related to the more rapid rate of virologic suppression and immune reconstitution. Clinicians are recommended to use **TDF+3TC+DTG if the patient has access to tuberculosis and cryptococcal disease screening (with TB-LAM and CrAg) and prophylaxis (with IPT and fluconazole)**, to minimize the risk of IRIS. Such patients should be educated about the potential clinical manifestations of IRIS, and should be instructed to return to the clinic if they experience severe symptoms. Symptoms of IRIS are rarely life-threatening, and patients with IRIS should remain on their ART regimen and continue taking their ARVs exactly as prescribed unless their symptoms appear life-threatening.
  - Clinicians also have the option to initiate such patients on TDF/3TC/EFV. It should be noted however that IRIS may still occur in patients initiating EFV-based ART with low CD4 cell counts. All patients initiating ART should be screened for symptoms of opportunistic infections, with appropriate evaluation and treatment according to national protocols.

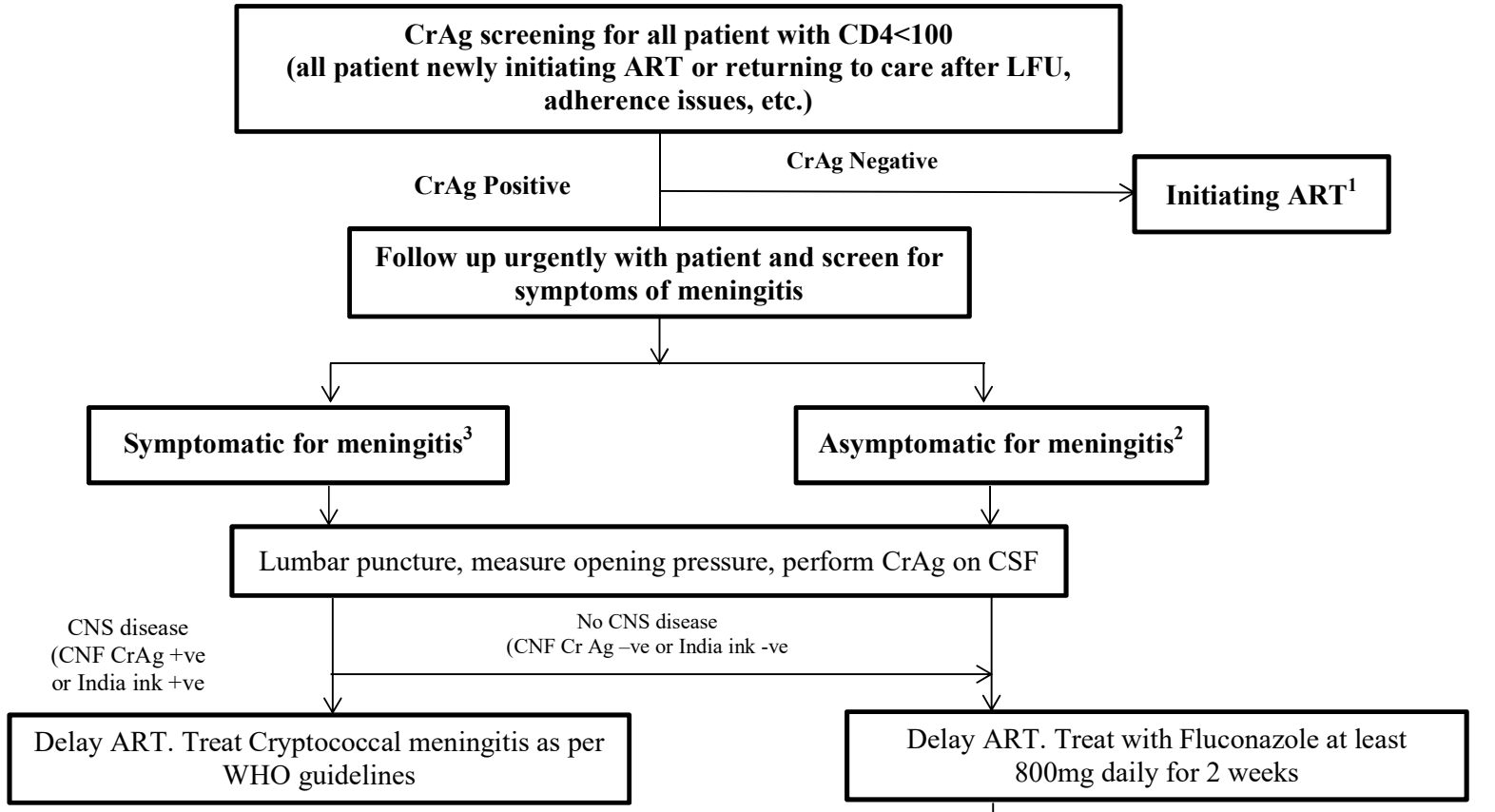
- **Patients who are being treated for TB with rifampicin.**
  - WHO does not currently recommend co-administering DTG with rifampicin. Therefore, patients who are being treated with rifampicine at the time of ART initiation should be started on **TDF/3TC/EFV**.
  - Patients who develop TB while already taking DTG should be **switched to TDF/3TC/EFV** for the duration of their treatment with rifampicin.
  - In both cases, **patients can be switched to TDF/3TC/DTG after their TB treatment is complete.**
  - It should be noted that a 2013 study (31) showed that that double-dosing DTG can overcome reduced concentrations from Rifampicin. As a result of emerging evidence, US FDA has approved DTG double-dosing for TB patients.

Annex 21: Steps to diagnose or rule out active Cryptococcal Meningitis in patients



[1] Test cannot be used to measure clinical response to treatment as CrAg can remain positive in serum, plasma and CSF for days or months after successful treatment

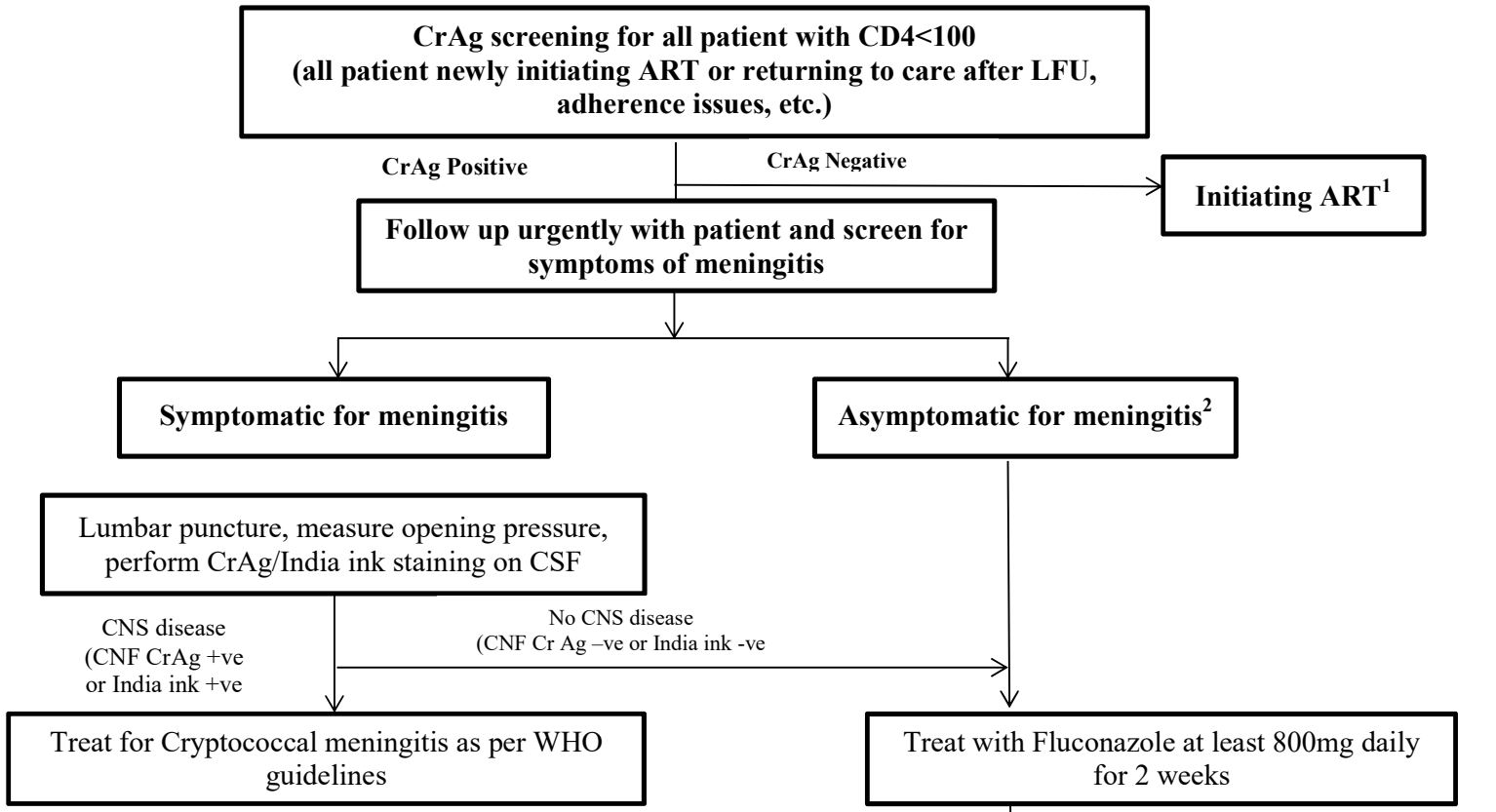
Annex 22: Screening Algorithm for Cryptococcal Antigenemia (scenario 1)



1. Initiate ART if not already started
2. If resources are available, a lumbar puncture should also be offered to asymptomatic patient with appropriate counselling
3. Meningitis symptoms include headache, confusion, vomiting and nausea, blurry vision, sensitivity to light, seizures, papilledema
4. Populations who require special attention include: patients on tuberculosis medications or nevirapine, patients with a previous history of cryptococcal meningitis, pregnant women or breast feeding mothers, patients with liver disease and children.

[T

Annex 23: Screening Algorithm for Cryptococcal Antigenemia (scenario 2)



1. Initiate ART if not already started
2. If resources are available, a lumbar puncture should also be offered to asymptomatic patient with appropriate counselling
3. Populations who require special attention include: patients on tuberculosis medications or nevirapine, patients with a previous history of cryptococcal meningitis, pregnant women or breast feeding mothers, patients with liver disease and children.

Annex 26: Hormone therapy for gender transitioning

1. Estrogen and anti-androgen preparations for use in male to female gender reassignment therapy. (32) (33)

		HIV drugs with no predicted effect	HIV drugs predicted to inhibit metabolism	HIV drugs predicted to induce metabolism
Estrogens		RPV, MVC, DTG, RAL, NRTIs (ABC, ddI, FTC, 3TC, d4T, TAF, TDF, ZDV)	ATV/cobi, DRV/cobi, EVG/cobi	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r, EFV, ETV, NVP
Estradiol oral	*Starting dose*	2 mg/day	1 mg/day	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	4 mg/day	2 mg/day	
	Maximum dose	8 mg/day	4 mg/day	
Estradiol gel (preferred for >40 y and/or smokers)	*Starting dose*	0.75 mg twice daily	0.5 mg twice daily	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	0.75 mg three times daily	0.5 mg three times daily	
	Maximum dose	1.5 mg three times daily	1 mg three times daily	
Estradiol patch (preferred for >40 y and/or smokers)	*Starting dose*	25 µg/day	25 µg/day*	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	50-100 µg/day	37.5-75 µg/day	
	Maximum dose	150 µg/day	100 µg/day	
Conjugated estrogen†	*Starting dose*	1.25-2.5 mg/day	0.625-1.25 mg/day	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	5 mg/day	2.5 mg/day	
	Maximum dose	10 mg/day	5 mg/day	
Ethinylestradiol	*Starting dose*	No interaction expected, but not recommended due to thrombotic risks	Not recommended	Not recommended
	Average dose			
	Maximum dose			
Androgen Blockers		RPV, MVC, DTG, RAL, NRTIs (ABC, ddI, FTC, 3TC, d4T, TAF, TDF, ZDV)	ATV/cobi, ATV/r, DRV/cobi, DRV/r, EVG/cobi, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	EFV, ETV, NVP
Spironolactone	*Starting dose*	50 mg/day	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	150 mg/day		
	Maximum dose	400 mg/day		
Finasteride	*Starting dose*	2.5 mg/day	Finasteride has a large safety margin. No dose adjustment required.	Increase finasteride dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	2.5 mg/day		
	Maximum dose	5 mg day		
Cyproterone acetate	*Starting dose*	50 mg/day	25 mg/day	Increase cyproterone dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	150 mg/day	75 mg/day	
	Maximum dose	150 mg/day	75 mg/day	
Goserelin	*Starting dose*	3.6 mg/month	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	3.6 mg/month		
	Maximum dose	3.6 mg/month		
Leuprorelin acetate	*Starting dose*	3.75 mg/month	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	3.75 mg/month		
	Maximum dose	3.75 mg/month		
Triptorelin	*Starting dose*	3.75 mg/month	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	3.75 mg/month		
	Maximum dose	3.75 mg/month		

† Conjugated estrogen is associated with high thromboembolic risk and therefore should be avoided.

* Matrix type transdermal patch can be cut in order to reduce the amount of hormone delivered/day.

Colour Legend

No clinically significant interaction expected.

Potential interaction which may require dosage adjustment and/or close monitoring.

Coadministration is not recommended.

2. Androgen preparations for use in female to male gender reassignment therapy. (32) (33)

		HIV drugs with no predicted effect	HIV drugs predicted to inhibit metabolism	HIV drugs predicted to induce metabolism
Androgens		RPV, MVC, DTG, RAL, NRTIs (ABC, ddI, FTC, 3TC, d4T, TAF, TDF, ZDV)	ATV/cobi, ATV/r, DRV/cobi, DRV/r, EVG/cobi, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	EFV, ETV, NVP
Testosterone topical gel 1%	*Initial low dose*	12.5-25 mg in the morning	12.5-25 mg in the morning	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.
	Initial average dose	50 mg in the morning	25-50 mg in the morning	
	Maximum dose	100 mg in the morning	50-100 mg in the morning	
Testostereone enanthate or cypionate	*Initial low dose*	Not applicable	Not applicable	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.
	Initial average dose	50-100 mg/week	25-50 mg/week	
	Maximum dose	Not applicable	Not applicable	
Testosterone undecanoate	*Initial low dose*	Not applicable	Not applicable	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.
	Initial average dose	750 mg IM, repeat after 4 weeks and then every 10 weeks	375-500 mg IM, repeat after 4 weeks and then every 10 weeks	
	Maximum dose	Not applicable	Not applicable	
Mixed Testosterone Esters	*Initial low dose*	Not applicable	Not applicable	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.
	Initial average dose	250 mg/2-3 weeks	125 mg/2-3 weeks	
	Maximum dose	Not applicable	Not applicable	

Colour Legend

No clinically significant interaction expected.

Potential interaction which may require dosage adjustment and/or close monitoring.

Coadministration is not recommended.

Recommendations for dose changes:

- All recommendations for dose changes are empirical and based on doses/formulations available in the UK (additional doses/formulations may be available in other countries).
- Recommendations for dose changes in presence of **inhibitors of estrogen metabolism** are based on the assumption that the magnitude of the drug-drug interaction is expected to be less pronounced for transdermal or topical applications than for oral drug administration as the first-pass metabolism is avoided.
- Recommendations for dose changes in presence of **inhibitors of testosterone metabolism** are based on the assumption that the magnitude of the drug-drug interaction is expected to be less pronounced for topical and intramuscular applications than for oral drug administration as the first-pass metabolism is avoided.
- *Note:* androgen deprivation treatment may prolong the QT interval. Caution should be taken when using with antiretroviral drugs that can potentially prolong the QT interval (i.e., ATV/r, ATV/cobi, LPV/r, SQV/r, EFV, RPV).

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