Rapid Advice

Updated National Guidelines for the Use of Antiretroviral Therapy in Adults and Children Lao PDR

Ministry of Health and World Health Organization, Lao PDR **2016**

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Forward

The first edition of the National Guidelines for the Use of Antiretroviral Therapy in Adults and Children, Lao PDR was published in 2005.

In 2006, the World Health Organization (WHO) revised the guidelines for the use of antiretroviral therapy (ART) in adults and children in resource limited settings; the second edition was revised in 2008.

In 2010, WHO revised the recommendations for a public health approach on Antiretroviral Therapy for HIV Infection in Adults, Adolescents, Infants, and for prevention of mother-to-child transmission (PMTCT). The third edition of the National Guidelines for the Use of Antiretroviral Therapy in Adults and Children, Lao PDR, was revised in 2011.

In 2015, WHO revised Consolidated Guidelines on the Use of Antiretroviral Drugs for Treatment and Preventing HIV Infection. Then, the fourth edition of National guidelines on the Use of Antiretroviral Therapy has been revised in 2015.

New recommendations support ART initiation in all adults, adolescents, and children with regardless of CD4 cell count or clinical stage. (1)

This rapid advice updates to support the implementation of national guidelines on the use of antiretroviral therapy 2016.

Abbreviation and acronyms

/r	/ritronavir
3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine
CD4	T-lymphocyte cell bearing CD4 receptor
CrAg	cryptococcal antigen
CSF	Cerebrospinal fluid
DNA	deoxyribonucleic acid
EFV	efavirenz
HIV	human immunodeficiency virus
INH	isoniazid
IPT	isoniazid preventive therapy
LPV	lopinavir
LA	latex agglutination
LFA	lateral flow assay
NVP	nevirapine
PCR	polymerase chain reaction
PI	protease inhibitor
PMTCT	prevention of mother to child transmission of HIV
RTV	ritonavir
TB	tuberculosis
TDF	tenofovir
VL	viralload
NRTI	nucleoside reverse-transcriptase inhibitor
WHO	world health organization

HIV diagnosis and testing

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.(2)

- Retesting all people previously diagnosed HIV-positive before they enroll in care and initiate antiretroviral therapy (ART).(2)
- Retesting is recommended in all HIV negative pregnant women in the third trimester, postpartum and during labour in low prevalence settings. (3)
- Retesting is recommended in discordant couple or partners who have known ongoing HIV risk. (3)
- 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. (3)
- 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.(3)
- 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.(1)
- 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.(4)

When to initiate ART

Early treatment initiation is associated with clinical and prevention benefits, improving survival and reducing HIV infectionsin the community. Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of person's readiness. (3)

When to start ART (1)	
When to start ART in adults (>19 years old)	• ART should be initiated in all adults and children living with HIV regardless of WHO clinical stage and at any CD4 cell count
When to start ART in adolescents (10-19 years old)	
When to start ART in children younger than 10 years of age	
TB/HIV coinfection	• Begin treatment for TB first, followed by ART as soon as possible within the first 8 weeks of TB treatment • The HIV-positive TB patients with profound immunosuppression (such as CD4 counts less than 50 cells/ mm3) should receive ART immediately within the first 2 weeks of initiating TB treatment
Pregnant women	• ART should be initiated in all pregnant women and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continue lifelong

What to start first-lineregimen (1;3)

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first line regimen. Therefore, a once-daily fixed dose combination of TDF +3TC+EFV is recommended as first-lineregimen in all adults living with HIV including pregnant and breastfeeding women including women in the first trimester of pregnancy andchildbearing age. For children younger than 3 years, a PI-based regimen is recommended.

Recommended first-lineregimen in adults

Preferred and alternative first line-regimen	
Preferred first line-regimen	TDF +3TC+EFV
Alternative first-line	AZT +3TC+EFV AZT+3TC+NVP TDF+3TC+NVP

Recommended first-lineregimen in children and adolescents (1;3)

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

[c]for infants and children infected with HIV younger than 3 years, ABC+3TC+AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

[d]increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.

[e]ensure that the dose of NVP is 200mg/m2

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

Drug dosing of liquid formulations for twice-daily dosing for infants younger than 4 weeks of age

Drug	Strength of oral liquid (mg/ml)	2-3 kg	3-4 kg	4-5 kg
AZT	10 mg/ml	1 ml	1.5 ml	2 ml
NVP	10 mg/ml	1.5 ml	2 ml	3 ml
3TC	10 mg/ml	0.5 ml	0.8 ml	1 ml
LPV/r	80/20 mg/ml	0.6 ml	0.8 ml	1 ml

LPV/r solution should not be given to infants aged < 2weeks; LPV/r solution should not be given in preterm infants until they have reached 42 weeks of gestational age. LPV/r pellets should not be used for infants younger than 3 months. (4)

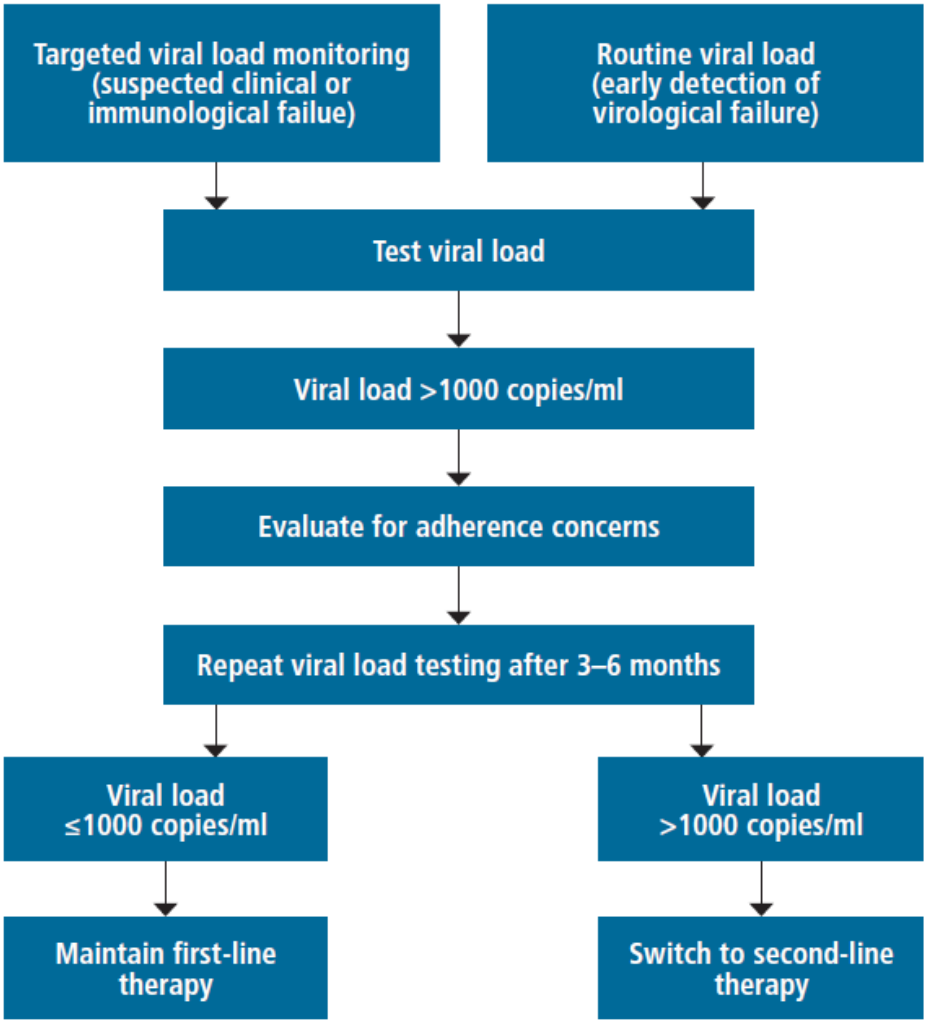
When to switch to second line drugs(3)

WHO definitions of treatment failure

Failure	Definition	Comments
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 syndromeoccurring 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/mm3 following clinical failure Or Persistent CD4 levels below 100 cells/mm3	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(5)
	Children 1) Younger than 5 years Persistent CD4 levels below 200 cells/mm3 2) Older than 5 years Persistent CD4 levels below 100 cells/mm3	
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

Algorithm of viral load testing (3)



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 testing may recommend for switching drugs or regimen.

Second-lineregimen in adults (1; 3)

First Line Regimen	Second Line Regimen	
	NRTI Component	PI Component
TDF + 3TC + EFV TDF + 3TC+ NVP	AZT + 3TC	ATV/r or LPV/r*
AZT +3TC + EFV AZT + 3TC + NVP	TDF + 3TC	

* LPV/r is recommended in TB/HIV coinfection who receives Rifampicine in TB regimen.LPV/r may be used by doubling the daily dose (i.e. LPV/r 800mg/200mg twice daily) or with an adjusted, super- boosted dose of RTV (i.e. LPV/r 400mg/400mg twice daily)

Second-lineregimen in children (1; 3)

Group/Age/ at Initiation	If first-line regimen	Change to second-line regimen
Children <3 years	ABC+ 3TC+LPV/r	No change or continue
	AZT+3TC+LPV/r	No change or continue
Children ≥ 3years and <10 years	AZT+3TC+EFV	ABC+3TC+LPV/r
	AZT+3TC+NVP	
	ABC+3TC+EFV	AZT+3TC+LPV/r
	ABC+3TC+NVP	
Children with TB/HIV coinfection<3 years of age	ABC+3TC+AZT	AZT+3TC+LPV/r *
Children with TB/HIV coinfection ≥ 3 years of age	AZT+3TC+EFV	ABC+3TC+LPV/r*
	ABC+3TC+AZT	AZT+3TC+LPV/r*
Adolescents > 10 years and > 35 kg	TDF+3TC+EFV	AZT+3TC+ATV/r/LPV/r
	TDF+3TC+NVP	
	AZT+3TC+EFV	TDF+3TC+ATV/r/LPV/r
	AZT+3TC+NVP	

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

Infant prophylaxis (1; 3)

<table>
<tr><th>Scenario</th><th>Maternal ARV prophylaxis</th><th>Infant ARV prophylaxis</th><th>Duration</th></tr>
<tr><td>Mother diagnosed with HIV before or during pregnancy and those who are receiving ART >4 weeks</td><td>Continue ART (TDF+3TC+EFV)</td><td>Daily NVP</td><td>6 weeks</td></tr>
<tr><td>Mother diagnosed with HIV for the first time during labour or postpartum</td><td rowspan="5">Initiate TDF+3TC+EFV</td><td rowspan="5">1) Breast feeding:
Daily AZT+NVPin the first 6 weeks;
and
continue only NVP for additional 6 weeks
2) Formula milk feeding: Daily AZT+NVP for 6 weeks only</td><td rowspan="5">6-12 weeks</td></tr>
<tr><td>Infants were born to women with established HIV infection who have received less than four weeks of ART at the time of delivery</td></tr>
<tr><td>Infants were born to women with established HIV infection with VL>1000 copies/ml in the four weeks before delivery, if VL available,</td></tr>
<tr><td>Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing)</td></tr>
<tr><td>Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)</td></tr>
</table>

National or subnational health authorities should decide whether health services will principally counsel and support mothers known to be HIV infected to either breastfeed and receive ARV or avoid all breastfeed. (4)

Primary prophylaxis and post-exposure prophylaxis(4; 5)

All eligible individuals for post-exposure prophylaxis are recommended to initiate 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.

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

* TDF is only approved for use for children 2 years and older. Target dose: 8mg/kg or 200mg/m2 (maximum 300mg). TDF should not be used in young children weighted less than 14 kg. (4)

** NVP is not recommended in children less than 2 years old

Dose of ARV drugs for HIV post-exposure prophylaxis for adults and adolescents (1)

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
Efavirenz (EFV)	200 mg once daily
Nevirapine (NVP)	200 mg twice daily

Criteria for initiating and discontinuing co-trimoxazole (4)

Population	Recommendations	
	Criteria for initiating co-trimoxazole prophylaxis	Criteria for discontinuing co-trimoxazole prophylaxis
Adults (including pregnant women) with HIV	Initiate everyone with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count of ≤350 cells/mm^3	May be discontinued for those who are clinicallystablea, with evidence of immune recovery and/or viral suppression on ART

Children and adolescents with HIV	Initiate for everyone regardless clinical stage and CD4 cell count. Priority should be given to all children less 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 CD4 ≤350 cells/mm3	May be discontinued for those older than 5 years who are clinicallystable, with evidence of immune recovery and/or viral suppression on ART
HIV-exposed infants	Initiate everyone starting at 4-6 weeks after birth	Until the risk of transmission ends and HIV infectionis excluded
People living with HIV and TB	Initiate everyone with active TB regardless of CD4 cell count	Until adults or children criteria for discontinuation are met

a Clinically stable adults are defined as individuals receiving ART for at least 1 year without any new WHO clinical stage 2,3 or 4 events.

Dosing adults (3)

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).

Isoniazid preventive therapy (3)

Adults and adolescents living with HIV should be screened with a clinical algorithm; those whodo not report any one of the symptoms of current cough, fever, weight loss or night sweatsare unlikely to have active TB and should be offered IPT.

Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test(TST) status and are unlikely to have active TB should receive at least 6 months of IPT as partof a comprehensive package of HIV care. IPT should be given to such individuals regardless ofthe degree of immunosuppression and also to those on ART, those who have previously beentreated for TB and pregnant women

Adults and adolescents living with HIV who have an unknown or positive tuberculin skin teststatus and among whom active TB disease has been safely ruled out should receive

at least 36 months of IPT. IPT should be given to such individuals regardless of whether or not theyare 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 unlikelyto have active TB. Children living with HIV who have poor weight gain, fever or current coughor contact history with a TB case may have TB and should be evaluated for TB and otherconditions. If the evaluation shows no TB, they should be offered IPT preventive therapy regardless of their age;

Children living with HIV who are more than 12 months of age and who are unlikely to haveactive TB on symptom-based screening and have no contact with a TB case should receive 6months 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 contactwith a TB case and who are evaluated for TB (using investigations) should receive 6 months ofIPT 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 6 months;

Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy (8)

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-trimox-azole + 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.

References

1. WHO. C*onsolidateed guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva : World Health Organization, 2015.

2. *Consolidated guidelines on HIV testing services*. Geneva : World Health Organization, 2015.

3. Organization, World Health.*Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach* . Geneva : s.n., 2016. 9789241549684.

4. WHO.*Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva : World Health Organization, 2013.

5. living, Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people.

6. WHO.*Consolidateed guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva : World Health Organization, 2015. ISBN 9789241509893.

7. *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for public health approach*. . Geneva, Switzerland : World Health Organization , 2014. ISBN 978924150813.

8. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.