

CLINICAL GUIDANCE ACROSS THE CONTINUUM OF CARE: ANTIRETROVIRAL THERAPY

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Goal of this chapter

To provide updated, evidence-based clinical recommendations outlining a public health approach to ART in the context of the continuum of HIV care, with a focus on resource and capacity limited settings.

7. CLINICAL GUIDANCE ACROSS THE CONTINUUM OF CARE: ANTIRETROVIRAL THERAPY

7.1 When to start ART

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. The 2013 Guidelines Development Group recommends that national HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm³ or less, giving priority to initiating ART among those with severe/advanced HIV disease (see Annex 1) or a CD4 count of 350 cells/mm³ or less. It is also recommended to initiate ART in people with active TB disease and HBV coinfection with severe liver disease, all pregnant and breastfeeding women with HIV, all children younger than five years living with HIV and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count (Table 7.1).

Table 7.1 Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children

Population	Recommendation
Adults and adolescents (≥10 years)	Initiate ART if CD4 cell count ≤500 cells/mm³ <ul style="list-style-type: none"> As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³
	Initiate ART regardless of WHO clinical stage and CD4 cell count <ul style="list-style-type: none"> Active TB disease HBV coinfection with severe chronic liver disease Pregnant and breastfeeding women with HIV HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk)
Children ≥5 years old	Initiate ART if CD4 cell count ≤500 cells/mm³ <ul style="list-style-type: none"> As a priority, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³
	Initiate ART regardless of CD4 cell count <ul style="list-style-type: none"> WHO clinical stage 3 or 4 Active TB disease
Children 1–5 years old ^a	Initiate ART in all regardless of WHO clinical stage and CD4 cell count <ul style="list-style-type: none"> As a priority, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count ≤750 cells/mm³ or <25%, whichever is lower
Infants <1 year old ^a	Initiate ART in all infants regardless of WHO clinical stage and CD4 cell count

^a Initiate ART in all HIV-infected children below 18 months of age with presumptive clinical diagnosis of HIV infection.

7.1.1 When to start ART in adults and adolescents



New recommendations

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm³ (*strong recommendation, moderate-quality evidence*). NEW
- ART should be initiated in all individuals with HIV with a CD4 count >350 cells and ≤ 500 /mm³ regardless of WHO clinical stage (*strong recommendation, moderate-quality evidence*).^a NEW
- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:
 - Individuals with HIV and active TB disease (*strong recommendation, low-quality evidence*).
 - Individuals coinfectd with HIV and HBV with evidence of severe chronic liver disease^b (*strong recommendation, low-quality evidence*). NEW
 - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (*strong recommendation, high-quality evidence*).
 - Pregnant and breastfeeding women with HIV (see section 7.1.2 for recommendations). NEW

^aThere is insufficient evidence and/or favourable risk–benefit profile to support initiating ART at a CD4 cell count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage in the following situations: individuals with HIV older than 50 years, individuals with HIV-1 infected or coinfectd with HIV-2, individuals with HIV coinfectd with HCV and key populations with HIV with a high risk of transmission (such as people who inject drugs, men who have sex with men, transgender people and sex workers). ART initiation in these populations should therefore follow the same principles and recommendations as for other adults with HIV.

^bThere is insufficient evidence and/or favourable risk–benefit profile to support initiating ART in everyone coinfectd with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is therefore recommended among people with evidence of severe chronic liver disease, who are at greatest risk of progression and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.



Table 7.2. Summary of when to initiate ART in adults and adolescents

When to start ART in adults and adolescents	
Target population	Recommendation
Severe/advanced HIV infection (WHO clinical stage 3 or 4)	Initiate ART in all individuals regardless of CD4 cell count
HIV infection (WHO clinical stage 1 or 2)	Initiate ART if CD4 ≤ 500 cells/mm ³ (CD4 ≤ 350 cells/mm ³ as a priority)
TB disease	Initiate ART in all individuals with active TB disease regardless of CD4 cell count ^a (<i>Unchanged from 2010 recommendations (2)</i>)
Hepatitis B coinfection	Initiate in all individuals with CD4 ≤ 500 cells/mm ³ and regardless of CD4 cell count in the presence of severe chronic liver disease ^b
HIV-serodiscordant couples	Provide ART to all partners infected with HIV regardless of CD4 cell count (to reduce the risk of HIV transmission to the negative partner) (<i>Existing 2012 recommendation (49)</i>)

^a TB treatment should be initiated first, followed by ART as soon as possible afterwards (and within the first eight weeks of initiating TB treatment). For those with a CD4 count less than 50 cells/mm³, ART should be provided within two weeks of starting TB treatment (*see section 8.1.2*).

^b 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, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

Background

Since 2002, WHO guidelines on ART have evolved as the body of evidence to support the earlier initiation of ART has progressively increased (1). The 2010 WHO guidelines for adults and adolescents (2) recommended initiating ART for all individuals (including pregnant women) with a CD4 count ≤ 350 cells/mm³ regardless of WHO clinical stage and for those with severe or advanced HIV disease (WHO clinical stages 3 or 4) regardless of CD4 count. This strong recommendation was based on moderate-quality evidence from randomized controlled trials (3,4) and observational studies (5–8) showing that initiating ART at or below this CD4 threshold reduced mortality, disease progression (including TB), vertical HIV transmission and serious adverse events. Mathematical modelling simulations also suggested that initiating ART earlier could impact on both sexual and vertical HIV transmission if there is high treatment coverage and full adherence (9). For people with active TB disease or HBV coinfection requiring HBV treatment, the 2010 guidelines (2) recommended initiating ART regardless of CD4 cell count.

Global ART coverage for those eligible according to the 2010 recommendations (CD4 ≤ 350 cells/mm³) had reached 54% – or more than 8 million people – by the end of 2011 (10), but coverage varies across regions, ranging from 15% to 68% (11). Only 9 low- and middle-income countries have reported coverage exceeding 80%, and 68 countries have reported coverage of less than 50%. Nevertheless, policy changes in countries have been significant. A recent survey in 92 countries (Web Annex www.who.int/hiv/

pub/guidelines/arv2013/annexes) showed that more than 90% had adopted the CD4 threshold for initiating ART of 350 cells/mm³ or less, and several other countries have moved their CD4 threshold above 350 cells/mm³. The median CD4 count at the time ART is initiated, although increasing, has been far lower than 350 cells/mm³ in almost all settings, including high-income countries (12,13), and late presentation for treatment is associated with high early mortality rates and poor retention in care (6,14). Increasing knowledge of HIV status, strengthening links between testing and care and ensuring optimal long-term retention and adherence remain significant challenges in many settings.

Rationale and supporting evidence

Since 2010, evidence and programmatic experience have continued to shift the risk-benefit ratio towards initiating ART earlier. Increasing evidence also indicates that untreated HIV may be associated with the development of several non-AIDS-defining conditions (including cardiovascular disease, kidney disease, liver disease, several types of cancer and neurocognitive disorders) (15–17) and that initiating ART earlier reduces such events and improves survival. Recent evidence (18) also show that ART substantially reduces sexual transmission in HIV-serodiscordant couples, but not all studies have reported survival benefits. At the same time, more convenient and less toxic regimens have become more widely available, and ARV costs have continued to fall. How early ART should be started is still debated, and the Guidelines Development Group paid close attention to evaluating the potential benefits and harms to the individual and community in developing these new recommendations.

Initiating ART in individuals with symptomatic and asymptomatic HIV disease at a CD4 count ≤ 350 cells/mm³ as a priority

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 counts. The 2013 Guidelines Development Group did not change the strength and quality of evidence for this recommendation established in the 2010 ART guidelines (2). Moderate-quality evidence from two randomized controlled trials and several observational studies shows that initiating ART at CD4 ≤ 350 cells/mm³ significantly reduces mortality, disease progression and the incidence of opportunistic diseases, especially TB and non-AIDS-defining conditions (2).

Initiating ART at a CD4 count between 350 and 500 cells/mm³

The risk-benefit analysis of the rationale for ART initiation between 350 and 500 CD4 cells/mm³ in these guidelines was debated. The Guidelines Development Group agreed that impact on HIV transmission is strongly supported by the evidence. The quality of evidence for clinical benefit of earlier ART initiation was rated as moderate using the GRADE system, as it mostly relies on observational data mainly from high-income countries. The Guidelines Development Group strongly recommended earlier ART as a public health approach. In settings where feasibility of implementation is a concern, the Guidelines Development Group suggested conducting operational research during implementation to assess context-specific factors such as feasibility, linkage to and retention in care, adherence and resource allocation.

The recommendation for initiating ART at CD4 counts between 350 and 500 cells/mm³ is based on a systematic review with GRADE evidence profiles (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) that assessed the quality and strength of the evidence from 21 observational studies (8,19–39) and three randomized controlled trials (3,18,40) reporting morbidity, mortality and immunological and virological outcomes. They showed that initiating ART at a CD4 count >350 cells/mm³ compared with treatment at a CD4 count ≤350 cells/mm³ reduced the risk of progression to AIDS and/or death, TB, development of a non-AIDS-defining illness and increased the likelihood of immune recovery. Although no studies suggest that earlier ART causes individual harm, these studies were of limited duration.

The pooled analysis of the observational studies found a consistent decreased risk of death with earlier initiation of ART in 13 studies (21–23,26,29–31,34–39) and a decreased risk of progression to AIDS or death in 9 studies (21,23,26,27,30,33,34,36,39) and 3 randomized controlled trials (3,18,40), with a low level of heterogeneity, supporting moderate-quality evidence for earlier treatment. A further subgroup analysis showed a reduced risk of mortality with a CD4 threshold for initiating ART of 500 cell/mm³. The impact on immune recovery was inconsistent and rated as low- to very-low-quality evidence (20,24,28). Two studies found no significant difference in the likelihood of viral suppression (<500 copies/ml), risk of virological failure and viral rebound when treatment is initiated at higher or lower CD4 cell counts (20,36).

In the pooled analysis of two randomized controlled trials (3,18) there was low-quality evidence supporting ART initiation at higher CD4 thresholds for reducing mortality, disease progression or the combined outcome of death and/or progression and, in one trial, the risk of non-AIDS-defining illnesses. The risk of severe adverse events did not differ significantly, but the risk of Grade 3 or 4 laboratory abnormalitiesⁱⁱ was increased in one randomized controlled trial (40). Since treatment in the delayed arm of the SMART trial (3) was initiated when the CD4 count fell below 250 cells/mm³ (rather than 350 cells/mm³), the quality of the evidence for clinical benefit was graded as low because of imprecision and indirectness.

A separate systematic review (41) identified one randomized clinical trial (18) and two observational studies (42,43) reporting a decreased risk of TB when individuals initiated ART with CD4 counts exceeding 350 cells/mm³. ART also reduces recurrent TB by about 50% (44). Dynamic models have suggested ART initiation above 350 cells/mm³ could lead to a more substantial reduction in population tuberculosis incidence (45).

Finally, there is high-quality evidence from one randomized controlled trial (18) indicating that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners. This is supported by the secondary outcomes of a trial that also found a 92% reduction in HIV sexual transmission from partners with HIV taking ART (46).

Cost and cost-effectiveness

The Guidelines Development Group reviewed mathematical simulations of the costs and epidemiological benefits of initiating ART at a CD4 count ≤350 cells/mm³, CD4 count ≤500 cells/mm³ and for all adults with HIV regardless of CD4 cell count. These models suggest that expanding the ART eligibility criteria to ≤500 cells/mm³ could lead to substantial health benefits and be cost-effective in both generalized and concentrated epidemic settings; the increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing

ⁱⁱ Grade 3 and 4 laboratory abnormalities are considered as severe drug adverse reactions and usually requires discontinuation of ARV drugs until the patient is stabilized and substitution for an alternative drug (See Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes)

new HIV infections (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). However, these benefits depend on a high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The models also show that, because the greatest costs are associated with full implementation of the 2010 ART guidelines (2) (initiating ART at CD4 count ≤ 350 cells/mm³), the incremental cost of moving the ART initiation criterion from a CD4 count ≤ 350 cells/mm³ to ≤ 500 cells/mm³ is relatively small, especially if countries already have a substantial number of people with HIV with a CD4 cell count less than 350 cells/mm³ already receiving ART. These modelling findings support the recommendation to initiate ART in adults and adolescents with HIV with a CD4 count ≤ 350 cells/mm³ as a priority. However, the cost implications at the regional and country levels should be explored further, since countries have different levels of treatment coverage and local cost considerations depending on their context and resources.

Potential harms

Not all observational studies have consistently demonstrated the beneficial impact of initiating ART earlier on mortality and the incidence of non-AIDS events associated with chronic inflammation and ongoing viral replication, and longer follow-up is needed to evaluate potential harms and benefits. The long-term safety profile of ART and the implications of earlier initiation on drug resistance and toxicity will also need to be closely monitored.

Feasibility

According to cohort and national programme data, the number of people needing treatment could increase by up to 25% if eligibility is based on CD4 counts increasing from ≤ 350 cells/mm³ to ≤ 500 cells/mm³ (47,48) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). However, country experience has also shown that moving to a higher CD4 threshold for ART initiation may not necessarily lead to a significant immediate increase in the numbers of people who actually access treatment in the absence of increased uptake of HIV testing and counselling, stronger linkages to care, adequate treatment monitoring and sustained adherence support.

Implementing the recommendation to initiate ART in individuals with HIV with CD4 counts between 350 and 500 cells/mm³ may involve additional human, infrastructure and financial resources. Chapter 10 discusses these issues in further detail.

Initiating ART regardless of CD4 cell count

HIV-positive partners in HIV-serodiscordant couplesⁱⁱⁱ

The results of the HPTN052 study (18) strongly support the use of ART to prevent HIV transmission among HIV-serodiscordant couples. The Guidelines Development Group therefore endorsed the recommendations established in the 2012 WHO guidance on HIV testing and counselling including ART for treatment and prevention in serodiscordant couples (49) that the sexual partner with HIV in such a couple should be offered ART regardless of CD4 count.

ⁱⁱⁱ An HIV-serodiscordant couple is a couple in which one of the sexual partners is HIV-positive and one is HIV-negative. Although one partner is currently HIV-negative, this does not mean that this partner is immunized or protected against getting HIV in the future.

Treating active TB disease^{iv}

In 2010, WHO recommended starting ART in all people with HIV and active TB regardless of CD4 cell count, and that TB treatment should be started first, followed by ART, as soon as possible afterwards (and within the first eight weeks). The Guidelines Development Group reviewed evidence from three randomized clinical trials that showed for people with TB and severe immunodeficiency (CD4 count ≤ 50 cells/mm³), starting ART before eight weeks has a clinical benefit compared with deferring treatment to later than eight weeks (50–52), and endorsed the 2010 recommendations. Implementation of the recommendations on HIV and TB management may be facilitated by integration of services (Chapter 9).

HIV and HBV coinfection with evidence of severe chronic liver disease^v

HIV coinfection affects almost every aspect of the natural history of HBV infection. The consequences include higher rates of chronicity; less spontaneous HBV clearance; accelerated liver fibrosis progression with increased risk of cirrhosis and hepatocellular carcinoma; higher liver-related mortality and decreased ARV response (53–56). Liver disease has emerged as a leading cause of death in people coinfecting with HIV and HBV (57,58).

The 2010 WHO ART guidelines (2) recommended initiating ART among all individuals coinfecting with HIV and HBV who require treatment for their HBV infection (defined as chronic active hepatitis), regardless of CD4 cell count or WHO clinical stage. However, in the absence of routine screening for HBV, most people are unaware of their HBV status. In addition, there is limited access to costly diagnostic tools for staging liver disease (liver biopsy, transient elastography, HBV-DNA and serum biomarkers) needed to establish the presence of chronic active liver disease and eligibility for HBV treatment.

A meta-analysis (59) and a subgroup analysis of a randomized controlled trial (60) provide low-quality evidence of the overall impact of ART on liver-related morbidity and mortality among individuals coinfecting with HIV and HBV, but these studies did not examine the benefit of initiating ART at higher CD4 counts.

Overall, the Guidelines Development Group considered that there was not sufficient evidence and/or a favourable risk–benefit profile to support initiating ART among all people coinfecting with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 count or stage of liver disease. There are also risks associated with initiating ART earlier (hepatotoxicity, immune reconstitution inflammatory syndrome and hepatic flares).

However, the Guidelines Development Group does recommend providing ART to all people coinfecting with HIV and HBV regardless of CD4 count in people with evidence of severe chronic liver disease, who are at greatest risk of liver disease progression and mortality. The term severe chronic liver disease was used instead of chronic active hepatitis (as in the 2010 guidelines), as this is a term that is more widely understood and applicable using clinical criteria alone. In settings where ART cannot be provided to all individuals with HIV with CD4 counts ≤ 500 cells/mm³, giving priority to diagnosing and treating individuals coinfecting with HIV and HBV should be considered.

As reported in the 2010 WHO ART guidelines (2), data from one randomized controlled trial support the use of at least two agents with activity against HBV (TDF + 3TC or FTC) in terms of improved viral load response and reduced development of HBV drug resistance (61,62).

^{iv} Active TB disease refers to TB infection where the person has symptoms and clinical disease. Latent TB infection refers to TB infection where the person does not have symptoms or clinical disease. Not all persons with latent TB infection will develop TB disease, but the risk of progressing to disease is very high in people with HIV.

^v 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, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

Critical research gaps in this area include the need for more data on the impact of ART on liver-related outcomes in HBV-coinfected people in resource-limited settings and on the relative impact of ART in people with CD4 cell counts >500 cells/mm³ and early-stage liver disease.

Populations for which no specific new recommendation is made

The Guidelines Development Group did not find evidence and/or favourable risk–benefit profiles to support recommendations for initiating ART at CD4 cell count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage in the following populations.

Individuals with HIV who are 50 years of age and older

A pooled analysis of data from 13 cohorts from Europe and North America showed increased risk of death and disease progression in people with HIV older than 50 years of age (26). However, these data were not stratified by CD4 cell count and do not support initiating ART at CD4 counts > 500 cells/mm³ for this group.

Individuals with HIV-2

The lack of randomized treatment studies in individuals with HIV-2 makes it difficult to determine the optimal timing of ART initiation in this population. A systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) evaluated observational data from 15 studies and showed no significant differences between initiating ART at a CD4 count ≤ 350 cells/mm³ and >350 cells/mm³, considering the outcomes of mortality, disease progression, increase in CD4 cell count, virological response and risk of drug resistance. The quality of evidence was rated as low to very low, with serious risk of bias and imprecision (few events) for all these outcomes.

Individuals coinfecting with HIV and HCV

Observational studies have shown that coinfection with HIV and HCV accelerates HCV-related progression of liver fibrosis and leads to a higher rate of end-stage liver disease (63) and mortality (63–65).

There is consistent but low-quality observational data about the overall benefit of ART on mortality and progression of liver disease in individuals coinfecting with HIV and HCV based on evidence from a meta-analysis (66), and a review of nine cohort studies that examined the relationship between ART and hepatic fibrosis showing that ART was associated with a decreased rate of liver fibrosis progression, although this was not evaluated by the level of CD4 count (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The Guidelines Development Group endorsed the special note in the 2010 guidelines (2) that initiating ART among people coinfecting with HCV should follow the same principles as in HIV mono-infection. Initiating ART regardless of CD4 cell count was not recommended because of lack of evidence.

There are challenges in diagnosing and treating active HCV infection in settings with limited access to HCV antibody and RNA assays, diagnostic tools for staging of liver disease (such as biopsy) and HCV therapy and in certain populations such as people who inject drugs. However, limited access to HCV testing or treatment and/or high rates of HCV infection should not be barriers to initiating ART.

WHO hepatitis guidelines forthcoming in 2014 will provide detailed guidance on HCV screening, treatment and care. People coinfecting with HIV and HCV receiving ART and HCV drugs require close monitoring because of potential drug interactions and increased risk for drug toxicity between HCV drugs (such as interferon, ribavirin and newer directly acting agents) and ARV drugs.

Key populations

The scale-up of ARV drugs for preventing HIV infection or reducing HIV incidence in key populations has been evaluated in community-wide and ecological studies and mathematical models (67–79). Some of these studies showed a reduction in the community viral load, with and without an associated decline in HIV incidence, invariably where ART coverage is high or access to ART is expanding rapidly. However, the Guidelines Development Group concluded that there is insufficient evidence to recommend earlier initiation of ART in key populations regardless of CD4 cell count. The initiation of ART in key populations should follow the same general principles and recommendations as in other adults and adolescents with HIV.

Clinical considerations

Section 10.6 (Checklist 10.3) discusses implementation considerations for moving the CD4 threshold from 350 cells/mm³ to 500 cells/mm³ of relevance to programme managers.

Key research gaps

Further research is required to determine more fully the clinical benefits and disadvantages of earlier ART initiation. Two large randomized trials are examining the optimal timing for initiating ART, with results expected in 2014 to 2015. The Strategic Timing of Antiretroviral Therapy (START) trial in ARV-naïve adults aged 18 years and older is comparing immediate ART in those with CD4 cell counts above 500 cells/mm³ to ART deferred until the CD4 count falls below 350 cells/mm³ or an AIDS event develops (80). The TEMPRANO trial (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis against Tuberculosis in HIV-infected Adults – ANRS 12136) is comparing the benefits and risks of initiating ART according to the 2010 WHO guidelines (≤ 350 cells/mm³) (2) to the benefits and risks of initiating ART immediately among adults with CD4 counts >350 cells/mm³ in Côte d'Ivoire (81). These studies will inform future WHO recommendations.

Other research priorities include assessing the incidence of severe adverse events as a result of increased exposure to ART and assessing ART acceptability, uptake, adherence and long-term retention in care for people who initiate ART at higher CD4 counts, and the magnitude of the prevention benefit of immediately initiating ART in key populations.

7.1.2 When to start ART in pregnant and breastfeeding women

New recommendations

NEW

- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (*strong recommendation, moderate-quality evidence*).
- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (*conditional recommendation, low-quality evidence*).
- In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased (*conditional recommendation, low-quality evidence*).

Table 7.3 Programme options for ART for PMTCT

National PMTCT programme option	Pregnant and breastfeeding women with HIV		HIV-exposed infant	
Use lifelong ART for all pregnant and breastfeeding women ("Option B+")	Regardless of WHO clinical stage or CD4 cell count		Breastfeeding	Replacement feeding
	Initiate ART and maintain after delivery and cessation of breastfeeding		6 weeks of infant prophylaxis with once-daily NVP	4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)
Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")	Eligible for treatment ^a	Not eligible for treatment ^a		
	Initiate ART and maintain after delivery and cessation of breastfeeding ^b	Initiate ART and stop after delivery and cessation of breastfeeding ^{b,c}		

^a CD4 count ≤ 500 cells/mm³ or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

^b Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

^c In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery.

Background

ARV drugs are used for pregnant and breastfeeding women with HIV primarily for the mother's health and to prevent the exposed child from becoming infected. It may also offer benefits for preventing the sexual transmission of HIV. The 2010 WHO PMTCT guidelines (82) recommended lifelong ART for women eligible for treatment (based on the 2010 eligibility criteria of CD4 counts ≤ 350 cells/mm³ or presence of WHO clinical stage 3 or 4 disease) and ARV prophylaxis for PMTCT for women with HIV not eligible for treatment. For those not eligible for treatment, two prophylaxis regimens were recommended: "Option A", AZT for the mother during pregnancy, single-dose NVP (sd-NVP) plus AZT and 3TC for the mother at delivery and continued for a week postpartum; and "Option B", triple ARV drugs for the mother during pregnancy and throughout breastfeeding. Prophylaxis was recommended to start as early as 14 weeks of gestation, and both prophylaxis options included four to six weeks of peripartum NVP or AZT for the infant, regardless of whether the mother was breastfeeding. Countries were advised to choose a national approach for their ARV option for PMTCT based on operational considerations.

To accelerate the rapid global scaling up of ART and PMTCT in resource-limited settings, ensure equitable access to ART for pregnant women and achieve the global goal of eliminating new paediatric infections and keeping mothers alive (83), recommendations need to be further simplified, standardized and harmonized. In 2011, Malawi implemented a new approach of lifelong ART for all pregnant and breastfeeding women with HIV regardless of CD4 count or clinical status, commonly referred to as "Option B+" (84–86). WHO issued a programmatic update in April 2012 (87) outlining some of the operational advantages of Option B and the emerging strategy of Option B+.



These 2013 guidelines recommend ART (one simplified triple regimen) for all pregnant and breastfeeding women with HIV during the period of risk of mother-to-child HIV transmission and continuing lifelong ART either for all women or for the women meeting eligibility criteria for their own health. Option A is no longer recommended.

Rationale and supporting evidence

Advantages of a standardized ART regimen for all pregnant and breastfeeding women with HIV

Although available data continue to show that the Option A and B prophylaxis regimens have similar efficacy in clinical trial settings (88–92), the complexities of Option A have been an impediment to scaling up PMTCT in many countries. These complexities include different treatment and prophylaxis regimens; the requirement for CD4 measurement to determine treatment eligibility and type of regimen; changing antepartum-intrapartum-postpartum regimens; the need for an additional postpartum ARV “tail” in mothers; and extended NVP prophylaxis in infants.

By contrast, providing an optimized, fixed-dose combination first-line ART regimen of TDF + 3TC (or FTC) + EFV (see section 7.2.2) to all pregnant and breastfeeding women with HIV provides important programmatic and clinical benefits, including the following.

- **Ease of implementation.** The same simplified ART regimen is administered to all pregnant women (regardless of “eligibility” for treatment) and continued during pregnancy and labour and postpartum.
- **Harmonized regimens.** The optimized first-line fixed-dose combination regimen can be harmonized with guidelines for ART in non-pregnant adults.
- **Increased coverage of ART.** This ensures that immunocompromised women who do not have access to CD4 testing receive appropriate ART without delay.
 - **Vertical transmission benefit.** Provides coverage with ART to maximize the prevention of infant infections.
 - **Maternal health benefit.** Will delay disease progression over the course of treatment (93).
- **Acceptability.** Reviews conducted for these guidelines generally indicated strong community preference and acceptability for this approach.
- **Sexual prevention benefit.** ART will reduce sexual transmission of HIV to sexual partners (18).

The Guidelines Development Group also considered the overall evidence from the systematic review of 21 observational studies (19–39) and three randomized controlled trials (3,18,40) used in the evaluation of when to start ART in adults (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes; see section 7.1.1). The recommendation to increase the use of ART in pregnant and breastfeeding women is made with the understanding that there are limited ARV drug options in resource-limited countries. It also recognizes the need to balance the benefits of starting ART in pregnant and breastfeeding women with the possible risks of ARV drug toxicity to the mother and fetus and infant during pregnancy and breastfeeding. Other issues the Guidelines Development Group considered included costs; cost–effectiveness and health system burden (94,95); issues related to adherence and retention (96), HIV drug resistance, ART failure and the availability of future treatment options; and ensuring treatment access for all people who meet current guidelines on eligibility for treatment.

Lifelong ART versus stopping ART after the risk of mother-to-child HIV transmission ends

The recommendation to provide lifelong ART to all pregnant and breastfeeding women with HIV or to continue ART only for those meeting treatment eligibility criteria for the woman's health is conditional, based on the epidemic setting and country programme, and because of the lack of conclusive evidence on the impact and efficacy of fully implementing lifelong ART.

In generalized epidemic settings and in settings with limited access to CD4 testing, limited partner testing, long duration of breastfeeding or high rates of fertility, the benefits of lifelong ART for all pregnant and breastfeeding women with HIV are clear. It will assure maximum coverage for those needing treatment for their own health, avoid stopping and starting drugs with repeat pregnancies, provide early protection against mother-to-child transmission in future pregnancies, reduce the risk of HIV transmission to HIV-serodiscordant partners and improve maternal health. With the new treatment eligibility threshold of CD4 ≤ 500 cells/mm³, approximately 60% of HIV-infected pregnant women will meet treatment eligibility criteria for their own health (97). Although not well quantified, it is likely that at least an additional 10–20% of women would become eligible for treatment over the subsequent two years after birth.

In countries with concentrated epidemics that have high access to CD4 testing, adequate capacity to provide ART to the pregnant and breastfeeding women eligible for treatment, low fertility rates and/or where breastfeeding for mothers with HIV is not recommended, consideration can be given to stopping the ARV drugs in women not eligible for ART after the period of mother-to-child transmission risk has ended. Regardless of the approach, special effort and supportive initiatives are needed to optimize adherence, especially during breastfeeding, where many programmes currently have poor follow-up, and to assure effective linkages to long-term treatment. Chapter 10 provides additional guidance for national programmes on making the decision between lifelong ART and stopping ART (Box 10.4).

Enhanced ARV toxicity surveillance for exposure throughout pregnancy and the breastfeeding period is critical to evaluate the safety of this approach for women, the fetus and the child. This is especially true as an increasing number of women already receiving ART become pregnant, resulting in much higher levels of ARV drug exposure during early gestation (see Sections 7.2.2 on “What ART regimen to start with” and 7.4 on “Monitoring and substitutions for ARV drug toxicities”). In addition, implementation research is important to ensure that the many gaps in knowledge associated with lifelong ART are addressed.

Transition from the 2010 guidelines to the 2013 guidelines

The new 2013 guidelines recommend that countries currently implementing Option A based on the 2010 guidelines (82) should transition, with appropriate planning, to initiating ART for all pregnant and breastfeeding women with HIV; the 2013 guidelines no longer recommend Option A. Countries moving towards Option B and those currently implementing Option B should consider the advantages and disadvantages of implementing lifelong ART for all pregnant and breastfeeding women in their setting.

Clinical considerations

Section 10.6 (Implementation considerations for key recommendations, Box 10.4) discusses clinical and implementation considerations relevant to programme managers for moving towards lifelong ART for all pregnant and breastfeeding women. A toolkit for managing the transition to lifelong ART for pregnant and breastfeeding women has been developed (98), including a readiness assessment checklist (Annex 6).

Key research gaps

The Guidelines Development Group emphasized the need for more research to support the new recommendations, to inform programmatic decisions and to promote optimal implementation. Key research gaps include the following.

ARV toxicity surveillance. Additional research is needed on the safety and acceptability of lifelong ART for pregnant and breastfeeding women, and their infants, especially in low-resource settings, where malnutrition and comorbidities are more common than in resource-rich countries and monitoring capacity is limited. Better data are needed on mothers' health outcomes, pregnancy outcomes (such as stillbirth, low birth weight and prematurity) birth defects and health outcomes for infants and young children (see Box 7.2).

Maternal and child health outcomes. Research is needed to better define the long-term outcomes in terms of both mother-to-child transmission at the end of breastfeeding and maternal health. In addition to short-term outcomes (such as impact on early mother-to-child transmission rates, which are now commonly measured at six weeks), assessments of long-term outcomes with maternal ART are critical to measure final transmission rates at the end of breastfeeding and HIV-free survival; the health of the mother and children infected or uninfected with HIV; retention in care (for those with both low and high CD4 counts); the long-term success of first-line ART; and HIV drug resistance.

Adherence and retention. Research is needed to determine how to optimize acceptability, adherence and retention on ART in pregnant and breastfeeding women, including among the women initiating lifelong ART who do not meet current eligibility criteria for their own health. Research is also needed on health systems and community interventions to optimize lifelong ART for pregnant and breastfeeding women with HIV, and the potential impact of different ART initiation strategies in different populations.

7.1.3 ARV drugs and duration of breastfeeding

Recommendations

The key principles and recommendations established in 2010 remain, including:

National or subnational health authorities should decide whether health services will mainly counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context.

In settings where national authorities have decided that maternal and child health services will mainly promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival.

- Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided (*strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months*).

Background

The primary aim of WHO recommendations regarding HIV and infant feeding is to improve the HIV-free survival of HIV-exposed infants. This includes reducing the risk of HIV transmission through breast-milk, primarily by providing ARV drugs, while avoiding malnutrition and the increased risk of serious infections in infants and children through unsafe feeding practices.

In 2010, WHO recommended that ARV drugs be provided either to the mother or the infant throughout breastfeeding to reduce the risk of postnatal HIV transmission (82, 99). In countries that recommended breastfeeding with ARV drugs, it was recommended that women with HIV should “continue breastfeeding for the first 12 months of life” and “only stop once a nutritionally adequate and safe diet without breast-milk can be provided” (99). This recommendation was based on evidence that the maximum benefit of breastfeeding in preventing mortality from diarrhoea, pneumonia and malnutrition is in the first 12 months of life and that the risk of transmitting HIV to infants through breastfeeding is low in the presence of ARV drugs (100,101). At that time, there was uncertainty about the mothers’ adherence to ARV drugs as prophylaxis and their ability to give ARV drugs to their breastfeeding infants over longer periods of time up to 18 or 24 months of age. Consequently, there was uncertainty about the level of protection against HIV transmission for children breastfeeding beyond 12 months. Finally, there were limited data on potential adverse events among infants exposed to prolonged – though low-dose – ARV drugs through breast-milk (102–104).

Since 2010, country-level recommendations on the appropriate duration of breastfeeding for women with HIV and their infants (where breastfeeding is recommended) have varied from 12 to 24 months; in some cases, the duration is not specified. Data on ARV drug coverage and adherence during breastfeeding and effective postpartum follow-up of mother–infant pairs remain limited. With increasing antenatal coverage of ARV drugs in PMTCT programmes, the relative proportion of infants infected during breastfeeding may be increasing because of inadequate ARV drug coverage during breastfeeding, emphasizing the importance of an effective postpartum prevention strategy.

The option of providing lifelong ART to all pregnant women with HIV, regardless of CD4 count or clinical stage (section 7.1.2), raises the question of whether these mothers need to limit the duration of breastfeeding.

The Guidelines Development Group therefore considered whether, in the context of pregnant women with HIV receiving lifelong ART regardless of CD4 count or clinical stage, to maintain the recommendation on the duration of breastfeeding as continued breastfeeding for the first 12 months of life or whether to recommend unrestricted duration of breastfeeding. The Guidelines Development Group considered a revision because of the potential operational advantages of extending the breastfeeding period, including:

- harmonizing and simplifying recommendations for mothers with HIV and their infants with those for mothers without HIV would likely simplify public health messaging and improve infant-feeding practices in the entire community; and
- decreasing stigma and possibly increasing acceptability by mothers and communities.

Ultimately, the Guidelines Development Group decided not to change the 2010 recommendations on HIV and infant feeding.



Rationale for not changing the 2010 WHO recommendations on HIV and infant feeding

Overall, there is no new evidence to support changing the 2010 recommendation.

The main concern about promoting unrestricted breastfeeding among mothers with HIV is that mothers may not adhere to ART throughout breastfeeding, placing their infants at risk of HIV transmission. Although this is important at any time when the infant is breastfeeding, it is of particular concern after the infant reaches 12 months of age. Before 12 months of age, breastfeeding provides major protection to the infant against death from diarrhoea, pneumonia and malnutrition. Although breastfeeding continues to provide a range of benefits to the child after 12 months of age, reductions in mortality from these conditions become less significant.

WHO recommendations acknowledge that some mothers may not be able to provide a safe and adequate diet to children beyond 12 months of age without breastfeeding and, in these situations, suggest that breastfeeding should continue. However, evidence to support this as a general approach, including the additional risk of HIV transmission and ARV toxicity surveillance data to exclude possible ARV-related adverse health outcomes for the infant, is not currently available.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for using ARV drugs during breastfeeding include:

- postnatal prophylaxis for infants remains critical: infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP (section 7.2.2);
- specific interventions (such as integrated follow-up with immunization and other well-child services) should be considered to improve postpartum follow-up of mother–infant pairs, which is often weak in most programmes; and
- communicating clearly and effectively with the community and users the value of breastfeeding with ARV drugs and local considerations regarding the duration of breastfeeding.

In addition, the Guidelines Development Group emphasized the need to support enhanced monitoring for potential toxicities from prolonged exposure to ARV drugs (such as sentinel site monitoring of infant cohorts during the first two years of life), for the next three to five years, and to continue monitoring as new drugs are introduced, to assess the effects of ARVs especially on neurodevelopmental outcomes and renal and bone health.

Key research gaps

- the risk of postpartum transmission in the context of ART, with variable duration of breastfeeding and different programme settings;
- short- and long-term infant health outcomes related to prolonged, low-dose exposure to ARV drugs (especially EFV and TDF) through breast-milk, including neurodevelopmental outcomes, nutritional status (including micronutrients), bone metabolism and growth; and
- interventions to improve adherence to postnatal ARV drugs and breastfeeding and whether initiating lifelong ART in all pregnant and postpartum women enhances adherence to ARV drugs during breastfeeding, which would enable women with HIV to breastfeed without any time restriction.

Box 7.1. Special considerations for the care and management of pregnant women

(See also Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes)

Sources of guidance:

- *Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice*. Geneva, World Health Organization, 2006 (www.who.int/reproductivehealth/publications/maternal_perinatal_health/924159084X/en/index.html).
- *Guidance on global scale-up of the prevention of mother-to-child transmission of HIV*. Geneva, World Health Organization, 2007 (www.who.int/hiv/pub/mtct/pmtct_scaleup2007/en/index.html).
- *IMAI/IMPAC clinical training for integrated PMTCT services*. Geneva, World Health Organization, 2013 (www.who.int/hiv/topics/mtct/training/en).

General guidance

- Pregnant women with HIV should receive at least the minimum package of recommended antenatal visits and pregnancy care, and additional interventions such as screening for sexually transmitted infections, nutritional support and infant feeding and family planning counselling should be considered.
- There is a high risk of HIV transmission during labour and delivery. This risk can be minimized by following several key principles and practices, including reinforcing recommended antenatal clinic visits, especially high-risk management in the late third trimester; promoting facility-based delivery by trained skilled birth attendants; avoiding unnecessary instrumentation and premature rupture of membranes by using a partograph to monitor stages of labour; and non-invasive suction of nasogastric secretions and washing away blood in the newborn.

Additional measures to reduce HIV transmission include the following:

- The early identification of mothers with HIV and providing ARV drugs to both the mother and the newborn baby are essential.
- For mothers presenting at labour with unknown HIV status, rapid HIV testing should be done during labour or immediately postpartum.
- For women testing positive, ARV drugs should be provided to both the mother and child in accordance with current treatment recommendations and with consideration of extended prophylaxis to the infant (see section 7.2.2).
- Health care workers should follow universal precautions for all deliveries, including those involving mothers with HIV.
- Special efforts should be made to ensure that delivery care is provided in a non-stigmatizing and supportive manner.
- Although Caesarean section has been shown to protect against HIV transmission, especially in the absence of ARV drugs or in the case of high viral load, WHO does not recommend it in resource-limited settings specifically for HIV infection; rather it is recommended for obstetric and other medical indications.

Box 7.1 (continued)

Women with HIV and women of unknown HIV status who deliver outside health facilities should be encouraged to be medically assessed at a maternal and child health facility as soon as possible after delivery and to begin or continue appropriate HIV interventions.

Providing follow-up, linkages to care and treatment and postpartum care are especially important for women with HIV and their HIV-exposed infants. Initial care of the child is usually scheduled at the first immunization visit at four to six weeks, including reinforcement of safe feeding practices, review of ARV coverage and early infant diagnosis testing. Follow-up care for the mother should ideally be scheduled at the same time and should include a postpartum check, family planning counselling, review of ARV regimen and adherence support.

7.1.4 When to start ART in children

New recommendations

NEW

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count
 - Infants diagnosed in the first year of life (*strong recommendation, moderate-quality evidence*)
 - Children infected with HIV one year to less than five years of age (*conditional recommendation^a, very low-quality evidence*).
- ART should be initiated in all HIV-infected children five years of age and older with CD4 cell count ≤ 500 cells/mm³, regardless of WHO clinical stage
 - CD4 count ≤ 350 cells/mm³ (*strong recommendation, moderate-quality evidence*)
 - CD4 count between 350 and 500 cells/mm³ (*conditional recommendation^b, very-low-quality evidence*).
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (*strong recommendation, moderate-quality evidence*).
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection (*strong recommendation, low-quality evidence*).

^a This recommendation is conditional because of the lack of evidence supporting earlier initiation in this age group, but this approach is expected to provide significant programmatic advantages in settings with limited access to immunological testing, high burden of paediatric HIV disease and low ART coverage among children, since simplifying eligibility criteria for initiating ART is likely to increase ART coverage in children infected with HIV and improve their health outcomes. Priority for ART initiation should be given to children younger than two years of age, because of higher mortality risk, and to children between two and five years of age with advanced disease (WHO HIV clinical stages 3 and 4 or with CD4 count ≤ 750 cells/mm³ or $<25\%$, whichever is lower), regardless of WHO clinical stage (*strong recommendation, very-low-quality evidence*) (105).

^b This recommendation is conditional because of the lack of evidence in this population for individual benefit as a result of initiating ART earlier; however, this approach is expected to provide significant programmatic advantages in settings with high coverage of paediatric ART and a programmatic need to align with ARV drug recommendations for adults. If this recommendation is not adopted, ART should be initiated at WHO HIV clinical stages 3 and 4 or with CD4 count ≤ 350 cells/mm³ regardless of WHO clinical stage (*strong recommendation, very-low-quality evidence*) (105).

Table 7.4. Summary of recommendations on when to start ART in children

Age	When you start
Infants (<1 year)	Treat all individuals
1 year to less than 5 years	Treat all individuals (children ≤ 2 years or with WHO stage 3 or 4 or CD4 count ≤ 750 cells/mm ³ or $<25\%$ as a priority)
5 years and above	WHO stage 3 or 4 Or CD4 ≤ 500 cells/mm ³ (CD4 ≤ 350 cells/mm ³ as a priority)

Background

Infants and young children have an exceptionally high risk of poor outcomes from HIV infection. Up to 52% of children die before the age of two years in the absence of any intervention (106). By five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults (107,108).

The scaling up of early infant diagnosis programmes has increased the identification of infants infected with HIV, but initiating ART early for those who have been found to be infected remains poor. Most HIV-infected children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults (28% versus 57% globally in 2011) (11).

Diagnosing and retaining children exposed to HIV and children infected with HIV in care also presents unique challenges because of their dependence on a caregiver. Loss to follow-up has been particularly high along the continuum of care (109), with retention especially challenging for children who are in HIV care but not yet eligible for ART.

Some countries are already introducing immediate ART for children younger than five years based on operational and programmatic grounds (110,111).

The 2010 WHO guidelines aligned clinical and immunological criteria for ART eligibility for children older than five years with those for adults (that is, treat for WHO clinical stage 3 or 4 disease or CD4 ≤ 350 cells/mm³) (105). They also recommended treating all children infected with HIV younger than two years of age regardless of clinical or immunological status. For children between two and five years of age, it was recommended that those with WHO stage 3 or 4, clinical disease or CD4 $<25\%$ or ≤ 750 cells/mm³ be treated (105).

The review of evidence in 2013, together with operational considerations and values and preferences expressed by care providers, has led to revised recommendations to simplify and expand treatment in children, including initiating ART in all children up to five years and to increase the CD4 count threshold for ART initiation to ≤ 500 cells/mm³ in children 5 years and older, aligning with the new threshold in adults.



Rationale and supporting evidence

These recommendations are based on strong operational and programmatic advantages resulting from simplification of criteria for initiating ART, despite the lack of clinical benefits to support treatment regardless of CD4 or clinical stage beyond infancy. Similarly, for programmatic purposes and given that disease progression in children five years and older is comparable to that of young adults, alignment with ART initiation criteria for adults was considered of high value.

Evidence for increasing the age threshold for early ART to five years

CD4 count and WHO clinical stage can identify children at increased risk of disease progression and death. Previous recommendations were based on observational studies demonstrating that untreated children in the second year of life continue to experience high rates of death and illness compared with children without HIV (106). Child-survival curves suggest that the mortality for children older than two years of age and with CD4 exceeding 25% is about 1–2% per year (107,108).

A systematic review identified only one randomized clinical trial, PREDICT (112), informing this issue (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The trial enrolled 300 children (1–12 years old, median age 6.4 years) with CD4 counts above 15% and without CDC clinical stage C disease, randomizing them to either immediate treatment or deferred treatment until the CD4 count fell below 15%. AIDS-free survival, neurodevelopmental outcomes and growth parameters did not differ between groups (113).

A causal modelling study was also undertaken using prospective data collected by the leDEA-Southern Africa network on 5732 ART-naïve children 24–59 months old (median age 3.3 years) who had CD4 counts above the existing eligibility thresholds of 25% or 750 cells/mm³ (114) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The study did not show any survival benefit from early treatment in this population, but a large proportion of children in this age range would rapidly become eligible under the existing criteria, since most children with CD4 count of 750 cells/mm³ or higher at enrolment into care reached the CD4 treatment threshold within three years. More specifically, 32% of this subset of the cohort fell below the thresholds for eligibility after one year and 60% after two years.

Operational and programmatic advantages

Despite the lower risk of progression in children 2–5 years old compared with children younger than two years and the low quality of evidence, the Guidelines Development Group emphasized the operational and programmatic advantages of removing the CD4 barrier to treatment for children under 5 years of age. Treating all children younger than five years of age is expected to simplify paediatric treatment and facilitate a significant expansion of ART coverage for young children. Although this has not been assessed as an outcome, programmatic data suggest that retention is better among children on ART than among those in care but not started on ART (109). Increasing ART coverage and targeting these children for HIV care may also facilitate the treatment of other preventable causes of under-five mortality. This approach will likely represent a small increased burden on current systems (115). Note that late diagnosis is still occurring, and a large proportion of the children identified as infected with HIV would already be eligible for ART based on the 2010 recommendations.

Community values and preferences

Expanding ART to every child younger than five years of age is expected to be well accepted. Assessment of the values and preferences of people living with HIV, caregivers and health care providers of children with HIV showed that earlier initiation is preferable because it is believed to facilitate family-based care, prevent loss to follow-up and improve adherence (116). Nevertheless, there is a risk of resistance if treatment is initiated early in young children and

adherence is poor or drug supplies are suboptimal; this is particularly the case for the youngest children, among whom harmonizing the formulations for children and adults is most difficult. However, the benefits of treatment are likely to outweigh these risks.

Where access to immunological testing is limited, the burden of paediatric HIV disease is high and paediatric ART coverage is low, simplifying the eligibility criteria for initiating ART may significantly improve the overall health outcomes for children with HIV (117). National programmes need to determine how best to implement this recommendation and whether to recommend universal treatment for all children younger than five years or to focus on universal treatment for infants younger than one year and apply clinical and immunological criteria for children one to five years old. When ART initiation is expanded regardless of clinical and immunological status beyond infancy to all children younger than five years, treatment of children younger than two years should be given priority because of their higher risk of death and rapid disease progression. In addition, expanding ART services will require ensuring retention in care and should be matched with concomitant expansion of interventions to support adherence.

Evidence for increasing the CD4 threshold to 500 cells/mm³

The criteria for initiating ART in children five years of age and older are the same as for adults. Although there are limited data to assess the clinical impact of treating children with a CD4 count between 350 and 500 cells/mm³ and the benefits of ARV drugs in preventing sexual transmission are not a factor for this population, this approach has programmatic advantages resulting from harmonizing the criteria with those for adults. It may be most feasible in settings with high ART coverage. As in the case of adults, treating children with CD4 counts ≤ 350 cells/mm³ should be a high priority since they have the highest risk of disease progression.

Coinfection with HIV and HBV

Small cohort studies in which both HIV and HBV are endemic report rates of chronic HBV among children with HIV between 1% and 49% (118). HBV is often acquired in infancy or early childhood and, unlike among adults, may have an immunotolerant phase that lasts throughout childhood and adolescence. Unfortunately, the natural history of the disease among children with HIV is still poorly known, and the benefits from initiating ART earlier in these children remain to be assessed.

Clinical considerations for scaling up ART among children

Section 10.6 discusses implementation considerations relevant to programme managers (see Box 10.6). An additional important implementation consideration for clinicians and other health care providers is that expanding the initiation of ART regardless of clinical and immunological status to children younger than five years eliminates the need for determining the CD4 count to initiate treatment in this age group and avoids delaying ART in settings without access to CD4 testing. However, the availability of CD4 testing, including determining the baseline CD4 count and percentage, remains important to ensure appropriate treatment monitoring in the absence of viral load monitoring.

Key research gaps

More data are needed to define potential clinical benefits and the impact of initiating ART early on morbidity for children younger than five years as well as immunological response and virological response over time. The impact of initiating ART earlier on retention, adherence and potential HIV drug resistance among children with less advanced disease needs to be investigated further. Data are also needed to inform the optimal approach to initiating ART in children coinfecting with HBV.

7.2 What ART regimen to start with (first-line ART)

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising a non-thymidine NRTI backbone (TDF + FTC or TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than three years. For children younger than three years, a PI-based regimen is the preferred approach (Table 7.5).

Table 7.5 Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens ^{a b}
Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)
Children 3 years to less than 10 years and adolescents <35 kg	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC or AZT + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

^a For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

^b ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

7.2.1 First-line ART for adults



New recommendations

NEW

- First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI)
 - TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (*strong recommendation, moderate-quality evidence*).
 - If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended:
 - AZT + 3TC + EFV
 - AZT + 3TC + NVP
 - TDF + 3TC (or FTC) + NVP (*strong recommendation, moderate-quality evidence*).
- Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (*strong recommendation, moderate-quality evidence*).

Table 7.6 Summary of first-line ART regimens for adults^a

First-line ART for adults (including pregnant and breastfeeding women and people with TB and HBV coinfection)	
Preferred regimens	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Special circumstances ^c	Regimens containing ABC, d4T ^b and boosted PIs

^a For adolescents, see section 7.2.4 on first-line ART for children three years and older which includes adolescents infected with HIV (10 years and older).

^b Using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used. The duration of therapy with this drug should be limited to the shortest time possible and include close monitoring.

^c Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

Background

The 2010 WHO ART guidelines (2) recommended that ART in treatment-naïve adults should initially consist of an NNRTI (either NVP or EFV) plus two NRTIs, one of which should be 3TC (or FTC) and the other AZT or TDF. The guidelines emphasized the importance of avoiding d4T as a preferred option in first-line regimens because of its well-known mitochondrial toxicity, using regimens that are potentially less toxic and more suitable for most people, preferably as fixed-dose combinations given the clinical, operational and programmatic benefits. The recommended regimens had better toxicity profiles than d4T but were considered comparable in terms of efficacy, since there was no evidence that AZT is virologically superior to d4T, AZT superior to TDF, TDF superior to d4T or ABC, or EFV superior to NVP.

NEW


The phasing out of d4T as a preferred option in first-line ART has been variable. Some countries have made rapid and substantial progress, whereas others have taken a gradual approach, such as avoiding d4T only for people starting ART or not using d4T in pregnant women (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

WHO (119,120) promotes a more affordable and efficient approach to treatment, including simpler, single-pill, once-daily ART regimens. The 2013 guidelines promote further simplification of ART delivery by reducing the number of preferred first-line regimens and focusing on regimens that may be used across a range of populations.

Rationale and supporting evidence

The move to TDF + 3TC (or FTC) + EFV as the preferred first-line option

A systematic review comparing six regimens showed moderate-quality evidence indicating that a once-daily combination of TDF + 3TC (or FTC) + EFV is less frequently associated with severe adverse events and has a better virological and treatment response compared with other once- or twice-daily regimens (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). An additional systematic review showed people receiving NVP are twice as likely as those receiving EFV to discontinue treatment because of adverse events (121).

The Guideline Development Group also reviewed a published meta-analysis and a further updated analysis (122, 123) that showed no increased risk of birth defects with EFV compared with other ARV drugs used during the first trimester of pregnancy (122). 3TC and FTC are pharmacologically comparable (123). TDF + 3TC (or FTC) + EFV offers good potential for harmonizing treatment across different populations: TDF/FTC or TDF/3TC are the preferred NRTI backbone for people coinfecting with HIV and HBV and can be used among people coinfecting with TB and among pregnant women. EFV is the preferred NNRTI for people with HIV and TB (pharmacological compatibility with TB drugs) and HIV and HBV coinfection (less risk of hepatic toxicity) and can be used among pregnant women, including those in the first trimester.

If TDF + 3TC (FTC) + EFV cannot be used, other once- or twice-daily NNRTI-containing regimens (AZT + 3TC + EFV, AZT + 3TC + NVP, and TDF + 3TC (or FTC) + NVP) can be used as alternative first-line regimens in ART-naïve people. Despite being considered equivalent options, they have potential disadvantages compared with preferred regimens. Use of other drugs such as ABC and boosted PIs are acceptable as potential backup options in special situations but are not recommended as preferred alternatives, considering the principles of optimizing ARV drugs.

NVP in pregnant women

There are continued concerns about the higher risk of adverse events with NVP compared with EFV, and about the use of NVP in women with HIV with CD4 cell counts above 250 cells/mm³, with some studies showing an increased relative risk for severe hepatic and skin reactions in pregnant women using NVP at higher CD4 cell counts (124–126). A systematic review (127), updated in 2013 (134) of the risk of NVP-associated toxicity in pregnant women suggests that the frequency of adverse events is elevated but no higher than that observed in the general adult population. The evidence supporting the theory that pregnant women with HIV who have high CD4 counts are at increased risk of adverse events compared with the general population with HIV is weak. The need for lead-in dosing for initial use of NVP and the fact that it is not available as a fixed-dose combination with TDF + 3TC (or FTC) are important considerations. NVP should therefore be used with caution in pregnant women and women who might be pregnant and only after considering the risk and benefits and available alternatives (see section 7.3.2).

Alternatives to NVP, such as ABC and boosted PIs, are acceptable but should only be used when NVP is not available.

Using alternative regimens and phasing out d4T

The currently recommended alternative regimens (such as AZT instead of TDF or NVP instead of EFV (Table 7.7) are comparable in therapeutic efficacy but have potential clinical and programmatic disadvantages compared with the preferred options. Individuals who are already clinically stable on an alternative regimen with no contraindications can consider continuing that regimen based on national guidance or switch to the preferred options to simplify treatment management, reduce cost, improve tolerability, enhance adherence and promote better regimen sequencing. In special circumstances, ABC and boosted PIs are acceptable but should only be used when other options are not available.

Use of d4T-containing regimens should be discontinued and restricted to cases in which other ARV drugs cannot be used, and the duration of therapy with this drug should be limited to the shortest time possible and include close monitoring. In settings in which d4T regimens are still used as a preferred option for initiating ART, a plan for phasing out d4T should be implemented, preferably towards using TDF-based first-line regimens (2,128,129). Section 10.6 (Box 10.7) further discusses the issue of phasing out d4T.

TDF toxicity

A systematic review on TDF toxicity (Web Annex www.who.int/hiv/pub/guidelines/arv2013annexes) indicates that TDF has a low rate of renal toxicity in the short to medium term, especially among people with pre-existing, or risk factors for, renal disease. Prospective cohort data show that TDF is associated with modest reduction in renal function (measured by the decrease in the estimated glomerular filtration rate) (130,131) and reduction in bone mineral density, but the clinical significance and magnitude of these side effects, especially with prolonged therapy, need to be investigated further. Further research is also needed to determine whether laboratory screening and monitoring of TDF toxicity should be routine or undertaken only in high-risk populations, such as people with hypertension or diabetes or those using boosted PIs. Since TDF renal toxicity is usually tubular, glomerular function tests do not provide a direct measure, and no other simple test can detect renal tubular toxicity. Section 7.4 discusses this issue further.

Evidence suggests that the overall improvement in renal function resulting from ART can offset the risk of TDF toxicity among people with HIV who do not have secondary renal disease.

HIV-2 infection

A systematic review of treatment options for individuals with HIV-2 (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) rated the evidence in all observational studies as being of very low quality, with serious risk of bias, inconsistency and imprecision. Since HIV-2 is naturally resistant to NNRTIs, treatment-naïve people coinfecting with HIV-1 and HIV-2 should be treated with a regimen containing three NRTIs (TDF + 3TC (or FTC) + AZT or AZT + 3TC + ABC or a ritonavir-boosted PI plus two NRTIs. If a PI-based regimen is used, the preferred option for first-line therapy should be LPV/r, since this will be procured in low-income settings for both second-line treatment for adults and for first-line treatment for children. SQV/r and DRV/r are alternative boosted-PI options, but they are not available as heat-stable fixed-dose combinations.

7.2.2 First-line ART for pregnant and breastfeeding women and ARV drugs for their infants



New recommendations

NEW

- A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped (*strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants*).
- Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (*strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding*).

Note: For the recommendations on infant prophylaxis, the GRADE ratings and recommendations shown are from the 2010 guidelines and were not reviewed by the Guidelines Development Group for the current guidelines.

Background

The 2010 WHO guidelines on PMTCT (82) recommended a choice of four different regimens for pregnant and breastfeeding women with HIV who required ART for their own health: AZT + 3TC or TDF + 3TC (or FTC) plus either NVP or EFV. Because of concerns about the increased risk of toxicity of NVP among pregnant women with higher CD4 counts (132–134), the recommended regimens for pregnant women who did not require treatment for their own health and who were receiving triple ARV regimens for PMTCT were AZT + 3TC or TDF + 3TC (or FTC) + EFV as the preferred NNRTI regimens. Alternative regimens were AZT + 3TC plus either LPV/r or ABC, rather than NVP. Although TDF and EFV were recommended, there were limited safety data on their use during pregnancy and breastfeeding.

The 2010 WHO guidelines (82) also recommended four to six weeks of infant NVP (or AZT) as post-exposure prophylaxis for all infants born to mothers who were receiving triple ARV regimens for treatment or prevention. Daily NVP infant prophylaxis throughout breastfeeding was recommended if the mother was not receiving a triple ARV regimen.

In clinical trials, infant prophylaxis has been shown to be especially important for PMTCT when the mother has received limited or no antepartum ARV drugs and when viral suppression has not yet been achieved (135–137). This continues to be a recommended component of PMTCT regimens in resource-rich countries as added protection against exposure to HIV during labour, even when mothers receive ART during pregnancy and when the mother is not breastfeeding (138). The data informing this recommendation have not changed since 2010.

Rationale and supporting evidence

The 2013 guidelines emphasize simplifying and harmonizing first-line therapy. A once-daily fixed-dose combination regimen is recommended, with TDF as the preferred NRTI and EFV as the preferred NNRTI, in combination with 3TC or FTC for all adults – including pregnant and breastfeeding women – as the preferred regimen to improve health outcomes and facilitate adherence and drug procurement (see section 7.2.1 and Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

The ideal first-line regimen for pregnant and breastfeeding women with HIV has low cost; is available as a fixed-dose combination; is safe for both pregnant and breastfeeding women and their infants; is well tolerated; has low monitoring requirements and a low drug-resistance profile; is compatible with other drugs used in clinical care; and is harmonized with the recommendations for non-pregnant adults. The regimen of TDF + 3TC (or FTC) + EFV is available as a once-daily fixed-dose combination and is the recommended first-line regimen for adults because of simplicity, affordability (the cost has declined significantly since 2010) and efficacy against HBV.

Safety is a critical issue for pregnant and breastfeeding women and their infants as well as women who might become pregnant. Although data on EFV and TDF use in pregnant women remain limited, more data have become available since 2010 and provide increased reassurance for recommending TDF + 3TC (or FTC) + EFV as the first-line ARV regimen for pregnant and breastfeeding women (122,139,140). Sections 7.3.1 and 7.5.2 provide more detail on the overall rationale for the recommended first-line regimen, including toxicity and monitoring issues.

Safety of EFV in pregnancy

Early data suggesting birth defects, including anencephaly, microphthalmia and cleft palate among primates with EFV exposure *in utero* (141) and some isolated case reports and retrospective clinical data on neural tube defects among humans (142) have led to concern about using EFV in the first trimester of pregnancy or in non-pregnant women with childbearing potential. The United States Food and Drug Administration and European Medicines Agency advise against using EFV in the first trimester and in women of childbearing potential unless the potential benefits outweigh the potential risks; however, the British HIV Association recently changed its recommendation to allow EFV to be used in the first trimester (143).

Because the risk of neural tube defects is limited to the first five to six weeks of pregnancy and because pregnancy is rarely recognized this early, especially in resource-limited settings, any potential risk of neural tube defects with the use of EFV would be primarily in women who become pregnant while already receiving EFV. Evaluation of prospectively collected data in humans is reassuring; an updated systematic review and meta-analysis, including the Antiretroviral Pregnancy Registry (47,134), reported outcomes for 1502 live births to women receiving EFV in the first trimester and found no increase in overall birth defects and no elevated signal for EFV compared with other ARV exposure in pregnancy (140). With one identified neural tube defect, the estimated prevalence from the systematic review continues to be about 7 per 10 000 population (0.07%), which is comparable to the estimates of 0.02–0.2% in the general population in the USA (138). Because neural tube defects are relatively rare events and there are limited exposures in the Antiretroviral Pregnancy Registry and in the meta-analyses, current available data are sufficient to rule out a potential increased risk greater than three-fold or up to 0.21% (the more limited data available for the 2010 guidelines were sufficient to rule out a 10-fold increased risk). Although the Guidelines Development Group emphasized that better data on birth defects are needed, it felt confident that this potential low risk should be balanced against the programmatic advantages and the clinical benefit of EFV in preventing HIV infection in infants and for the mother's health.



Safety of NVP in pregnancy: (see section 7.2.1)

Safety of TDF in pregnancy and during breastfeeding

Potential concerns about the safety of TDF include renal toxicity (see section 7.4.3), adverse birth outcomes and effects on bone density. A systematic review assessed the toxicity of fetal exposure to TDF in pregnancy (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In the Antiretroviral Pregnancy Registry, the prevalence of overall birth defects with exposure to TDF in the first trimester was 2.4% of 1612 live births and did not differ from the background rate in the USA. A limited number of studies showed no difference in fetal growth between infants exposed or not exposed to TDF (144,145). TDF has limited penetration into breast-milk, which would limit potential toxicity for the breastfeeding infant. However, there have been no studies of TDF among lactating women, who normally have bone loss during breastfeeding that stabilizes after lactation. More extensive studies are ongoing of TDF bone and renal safety in pregnancy and breastfeeding for both the mother and child.

The once-daily TDF + 3TC (or FTC) + EFV fixed-dose regimen is simple and convenient, and harmonizing the recommendations for pregnant and non-pregnant women simplifies supply chain management. Based on available data and experience, the Guidelines Development Group felt that the clear benefits of this regimen for pregnant and breastfeeding women (and women of childbearing potential) outweigh the potential risks (see section 7.5.2).

Infant prophylaxis

Table 7.8 Simplified infant prophylaxis dosing recommendations (adapted from (82))

Simplified infant prophylaxis dosing recommendations: NVP

Infant age	Daily dosing
Birth ^a to 6 weeks ^b	
• Birthweight 2000–2499 g	10 mg once daily
• Birthweight ≥2500 g	15 mg once daily
> 6 weeks to 6 months ^c	20 mg once daily
> 6 months to 9 months	30 mg once daily
> 9 months until breastfeeding ends	40 mg once daily

^a Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

^b Recommended for 6 weeks, but 4 weeks may be considered in settings with replacement feeding.

^c Dosing beyond 6 weeks of age in special situations in which prolonged dosing of up to 12 weeks should be considered (such as the mother having had limited ART and not being likely to be virally suppressed; the infant is identified as HIV exposed after birth and is breastfeeding (Table 7.9). This is based on the dosing required to sustain exposure among infants of >100 ng/ml with the least dose changes.

Simplified infant prophylaxis dosing recommendations: AZT (only recommended in settings with replacement feeding)

Infant age	Daily dosing
Birth ^a to 6 weeks	
• Birthweight 2000–2499 g ^a	10 mg twice daily
• Birthweight ≥2500 g	15 mg twice daily

^a Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

No new data inform any change in the recommendations on infant prophylaxis. For breastfeeding infants, six weeks of infant NVP is recommended; for infants receiving replacement feeding, four to six weeks of infant NVP or AZT continues to be recommended. If toxicity from infant NVP requires discontinuing the drug or if infant NVP is not available, infant 3TC can be substituted. Several studies (146,147) have safely used infant prophylaxis during breastfeeding with 3TC.

Although the Guidelines Development Group did not formally review this, it considered several scenarios in which longer infant prophylaxis might be appropriate. Because several weeks or months are required for maternal ART to achieve viral suppression and a breastfeeding infant may not be protected against postnatal transmission during that period, or when a breastfeeding mother initiates ART very late in pregnancy (such as less than four weeks prior to delivery) during labour or postpartum, increasing the duration of infant NVP prophylaxis to 12 weeks can be considered.

Infant prophylaxis is also important when a breastfeeding mother interrupts ART during breastfeeding, as this places her infant at increased risk of postnatal transmission. In such situations, providing daily infant NVP during the period of maternal ART interruption should be considered, and this could be stopped six weeks after maternal ART is restarted (or one week after breastfeeding ends, whichever comes first). Table 7.9 summarizes the range of scenarios for maternal and infant prophylaxis.

Table 7.9 Summary of maternal and infant ARV prophylaxis for different clinical scenarios

Scenario	Maternal ARV prophylaxis ^a	Infant ARV prophylaxis ^b	Duration of infant ARV prophylaxis
Mother diagnosed with HIV during pregnancy ^{c,d}	Initiate maternal ART	NVP ^c	6 weeks ^c
Mother diagnosed with HIV during labour or immediately postpartum and plans to breastfeed	Initiate maternal ART	NVP	6 weeks; consider extending this to 12 weeks
Mother diagnosed with HIV during labour or immediately postpartum and plans replacement feeding	Refer mother for HIV care and evaluation for treatment	NVP ^c	6 weeks ^c
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is not breastfeeding	Refer mother for HIV care and evaluation for treatment	No drug	Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Determine an alternative ART regimen or solution; counsel regarding continuing ART without interruption	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended

^aIdeally, obtain the mother's CD4 cell count at the time of initiating or soon after initiating ART; country guidelines should be used to determine whether ART is lifelong or is stopped after the risk for transmission has ended.

^bIf infant NVP causes toxicity or NVP is not available, 3TC can be substituted.

^cIf the mother is using replacement feeding, infant AZT can be substituted for infant NVP; if there is documented maternal viral suppression near delivery for a mother receiving ART and using replacement feeding, four weeks of infant ARV prophylaxis may be considered.

^dIf it is known that the mother has initiated ART less than 4 weeks before delivery, consider extending infant NVP for infants who are breastfeeding to 12 weeks.

Alternative regimens: for toxicity, intolerance or lack of availability of recommended regimens

AZT is recommended as the alternative NRTI for non-pregnant women who cannot tolerate or receive TDF. Given the extensive safety and efficacy data on AZT in pregnant and breastfeeding women, AZT is also the recommended alternative NRTI for pregnant and breastfeeding women.

For non-pregnant women who cannot tolerate or receive EFV, the recommended alternative NNRTI is NVP. However, because ART (triple ARV drugs) is now recommended for pregnant and breastfeeding women regardless of CD4 cell count, concerns remain regarding the use of NVP in women with higher CD4 counts. Although the 2010 guidelines (2,82) stated that the benefit of NVP outweighed the risk for women with CD4 counts of 250 to 350 cells/mm³, data on safety in women with CD4 counts ≥ 350 cells/mm³ are limited, and the finding of life-threatening hepatic toxicity when NVP was used for occupational post-exposure prophylaxis in individuals without HIV infection raises concerns regarding its use for individuals with higher CD4 count. However, a recent systematic review of the risk of NVP-associated toxicity in pregnant women (134) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) suggests that the frequency of adverse events is no higher than that in the general adult population. Further, data on the association between NVP toxicity and elevated CD4 cell counts are conflicting, and the risk of significant hepatic toxicity in most studies is about 3% (121). Data suggest that switching to NVP for individuals who have been treated and had viral suppression is not associated with elevated toxicity even where the immune system has reconstituted. Finally, the alternative to substituting NVP for EFV toxicity would be a PI, which is the recommended second-line therapy and is more expensive than NNRTI drugs. On balance, the Guidelines Development Group held that the overall benefit of substituting NVP for pregnant or breastfeeding women in the rare circumstances that EFV is not tolerated outweighs the potential risks.

Clinical considerations

Maintaining the drug supply chain and ensuring uninterrupted delivery of maternal ART and infant ARV drugs during pregnancy and breastfeeding are critical for PMTCT. All antenatal care and maternal and child health sites providing PMTCT services should have the capacity to initiate, support and monitor ongoing maternal ART and infant ARV drugs.

Key research gaps

Surveillance of ARV drug toxicity. Research is needed to continue to evaluate both the short- and long-term effects of EFV, TDF and other ARV drugs on pregnant and breastfeeding women, fetuses and children, including monitoring for birth defects and other adverse pregnancy outcomes and evaluating the renal and bone effects of TDF on both the woman and HIV-exposed infant.

Acceptability of EFV as first-line ART. The level of intolerance to EFV and whether switching to an alternative first-line regimen is necessary needs to be studied further, as do ways to support alternative first-line regimens in programme settings for pregnant and breastfeeding women.

Infant prophylaxis. Better data are needed on the optimal duration of infant prophylaxis when mothers receive ART, especially if the mother starts ART late in pregnancy or during the postpartum period and hence is not virally suppressed at the time of delivery or when breastfeeding begins. NVP formulations that are improved and easier to administer are needed to facilitate drug administration to neonates and infants.

Optimal management of infants identified as HIV exposed during breastfeeding.

It is important to determine the extent to which perinatal HIV exposure is missed antenatally

and the extent of maternal seroconversion, appropriate strategies for postpartum screening of infants for HIV exposure and optimal testing and prophylaxis strategies.

Stopping NNRTI-based ART (use of a “tail”). Because of the prolonged half-life of EFV (and NVP), suddenly stopping an NNRTI-based regimen risks developing NNRTI resistance. For women who choose to or must stop EFV-based ART because of toxicity or other conditions, more data are needed to determine whether an NRTI “tail” coverage is needed to reduce this risk. Pharmacokinetic modelling reviewed for the guidelines suggests that, if the NRTI backbone included TDF, such a tail may not be needed, but if the NRTI backbone included AZT, a two-week tail is advisable (EFV has a longer half-life than NVP).

7.2.3 First-line ART for children younger than three years of age

New recommendations

NEW

- A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with a NVP-based regimen (*strong recommendation, moderate-quality evidence*).
- Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained (*conditional recommendation, low-quality evidence*).

Special note: The randomized control trial supporting the use of this approach (148,161) defined virological suppression as a viral load ≤ 400 copies/mm³, with the goal of identifying the children who are more likely to be able to safely substitute LPV/r with NVP. The use of a higher viral load cut-off for determining virological suppression has not been studied in the context of this strategy.

- For infants and children infected with HIV younger than three 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 (*strong recommendation, moderate-quality evidence*).
- For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC (*strong recommendation, low-quality evidence*).

Table 7.10 Summary of first-line ART regimens for children younger than three years

Preferred regimens	ABC ^a or AZT + 3TC + LPV/r ^b
Alternative regimens	ABC ^a or AZT + 3TC + NVP ^c
Special circumstances ^e	d4T ^d + 3TC + LPV/r d4T ^d + 3TC + NVP

^a Based on the general principle of using non-thymidine analogues in first-line regimens and thymidine analogues in second-line regimens, ABC should be considered as the preferred NRTI whenever possible. The CHAIN working group developed this recommendation. Availability and cost should be carefully considered.

^b As recommended by the United States Food and Drug Administration, using LPV/r oral liquid should be avoided in premature babies (born one month or more before the expected date of delivery) until 14 days after their due date or in full-term babies younger than

14 days of age. Dosing for children younger than 6 weeks should be calculated based on body surface area (Annex 3).

^c During the finalization of these guidelines, the United States Food and Drug Administration approved the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg. Due to the limited data to inform the best use of this drug in the use of this drug in this age group, the Guidelines Development Group agreed to maintain NVP as the recommended NNRTI for children under 3 years. WHO will provide further guidance as soon as the additional data become available.

^d Because of the limited options available for children younger than three years, d4T is still included among the recommended NRTIs, but its use should be restricted to the situations in which toxicity to AZT is suspected or confirmed and ABC cannot be used. The duration of therapy with this drug should be limited to the shortest time possible. Box 10.7 provides guidance on phasing out d4T.

^e Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

Background

Optimizing first-line ART in children younger than three years is critical to achieving effective and rapid control of viral replication in the context of high viral load and rapid infant growth. Considerations that may require alternative therapeutic approaches include the limited availability of drugs in appropriate formulations, the long-term toxicities of ARV drugs, difficulty with adherence and the possibility of pre-existing viral resistance because of ARV drug exposure for PMTCT.

Young children with HIV who are exposed to NNRTIs used for PMTCT have demonstrable viral resistance (150), which compromises the response to NVP-containing first-line ART (151,152). For this reason, the 2010 WHO guidelines (105) recommended the use of LPV/r-based treatment in children younger than 24 months of age previously exposed to NNRTIs. For young children not exposed to NNRTIs or whose status was unknown, an NVP-based regimen was recommended (105).

New evidence has become available for this age group suggesting the superiority of a LPV/r-based regimen regardless of PMTCT exposure (153,154). Several strategies have also been tested to overcome the challenges of using LPV/r-based regimens or to provide potent alternatives in settings in which using LPV/r is not feasible or is problematic because of the high prevalence of TB. (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

Rationale and supporting evidence

This recommendation is based on evidence of the superiority of a LPV/r-based regimen for young children balanced against feasibility considerations.

Efficacy of a LPV/r-based regimen for infants and young children

A systematic review of two randomized trials (153,154) shows that children younger than 36 months have a reduced risk of discontinuing treatment and virological failure or death if they are started on a LPV/r-based regimen instead of a NVP-based regimen. At 24 weeks, LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In addition, surveillance of drug resistance among children younger than 18 months (149,155) provides further evidence of detectable NNRTI resistance even among children without any history of exposure to ARV drugs for PMTCT or whose exposure status is unknown, suggesting that a history of exposure for PMTCT may not be an accurate marker for identifying children at higher risk of HIV resistance to NNRTI.

LPV/r is known to have a better resistance profile that protects against the selection of NRTI resistance without compromising the use of other PIs in second-line regimens (156,157–159). In addition, a potential advantage is offered by the considerable reduction in the incidence of malaria among children receiving LPV/r-based, as recently demonstrated in a randomized trial comparing the use of LPV/r versus NVP or EFV among children in Uganda receiving an artemether + lumefantrine combination for treating malaria episodes (160).



Feasibility of LPV/r in resource-limited settings

Providing an LPV/r-based regimen to infants and children younger than three years in some resource-limited settings may be challenging. The current LPV/r syrup formulation has cold-chain requirements until the point of dispensing. The syrup is unpalatable, with the potential for suboptimal adherence, as highlighted in the values and preferences survey among health workers, and the risk of metabolic complications among children who initiate LPV/r early in life is unknown. Further, LPV/r is costly and administering this with TB treatment is complex. Alternative approaches are proposed to overcome these challenges.

A recent randomized clinical trial (148,161) and an ongoing randomized clinical trial (162) have evaluated a strategy in which LPV/r is started and later substituted with an NNRTI (NVP or EFV). Such PI-sparing strategies aim to reduce exposure to LPV/r, offer an easier approach to maintaining treatment and preserve PI-based therapy for second-line ART. This approach has been shown to be safe and effective in the trial setting for children with sustained virological suppression achieved after receiving LPV/r-based first-line therapy, especially in the absence of HIV resistance to NNRTI before initiating ART (148,161). However, this approach may also add complexity to treatment programmes and may require access to virological monitoring. This strategy may therefore only be viable in settings in which viral load and/or genotype testing are available.

In settings in which none of these approaches is feasible or affordable, an NVP-based regimen provides an effective alternative, especially given the availability of two- and three-drug fixed-dose combinations. As observed in a recent randomized controlled trial, good virological outcomes (83% had a viral load less than 400 copies per ml for 3.7 years irrespective of age) can be achieved by starting children on ABC, 3TC and an NNRTI (163). EFV has not been used in this age group, however during the finalization of these guidelines the United States Food and Drug Administration approved this drug for children 3 months to 3 years old weighing more than 3.5 kg. Dosing for this population is provided in Annex 7 and further guidance on how best to use this drug as an alternative to LPV/r or NVP will be provided when additional data are available.

Choice of NRTIs

The choice of NRTIs should aim to construct a robust and durable backbone that balances minimizing toxicity, minimizing cost and maximizing feasibility. Only limited evidence (164) from head-to-head comparisons informs the selection of NRTIs (AZT or ABC) combined with 3TC in a triple ART regimen. However, the choice of first-line NRTIs affects second-line ART, and failure of AZT is known to result in the accumulation of thymidine analogue mutations, reducing susceptibility to ABC or TDF in a subsequent regimen (if two or more thymidine analogue mutations are present). The risk of this occurring is greater with an NNRTI-based regimen; using it in the context of an LPV/r-based regimen may therefore not be as critical. By contrast, HIV resistance to ABC does not lead to resistance to thymidine analogues and preserves or even increases the susceptibility of HIV to AZT and d4T for second-line use (159).

Although ABC may be preferable in the interest of ART sequencing (159,165) and harmonizing with the regimens for older children, availability is limited in resource-limited settings. In addition, the cost of ABC may be a significant barrier to adopting it in many countries, especially when combined with LPV/r. Definitive data on the comparative efficacy of ABC and AZT are expected from ongoing studies (166).

Since 2010, WHO has recommended that d4T be phased out because of its known long-term toxicity. However, in settings in which using AZT may not be advisable because of the high risk of anaemia (such as malaria-endemic settings) and in which ABC is not available, d4T remains an option within the limited treatment options for this specific age group. d4T also remains important in the situation in which toxicity to AZT is suspected or confirmed and ABC cannot

be used. However, the duration of therapy with this drug should be limited to the shortest time possible. Box 10.7 provides guidance on phasing out d4T.

In developing these recommendations, the Guidelines Development Group emphasized:

- the importance of potent, first-line regimens for which there is evidence of better virological response as indicated by randomized controlled trials in this age group;
- the need to address the increasing evidence of HIV resistance to NNRTI among children younger than 18 months, especially in the context of the recommendation to treat pregnant women with EFV-based regimens for PMTCT;
- the desirability of having one preferred regimen for children younger than three years while providing alternative strategies that remain less costly, preserve second-line options and address feasibility concerns;
- anticipating the availability of new formulations during the next few years (sprinkles or sachets containing LPV/r);
- using non-thymidine analogues in first-line regimens to preserve the response to AZT in second-line regimens and to harmonize the regimens for older children and adults, while also recognizing the additional expense;
- identifying a subset of children who can benefit from alternative strategies to preserve PIs for use in second-line ART as indicated by a randomized trial; and
- identifying a manageable regimen, such as ABC + 3TC + AZT, for use in the context of TB co-treatment that can maintain good clinical and immunological response after virological suppression on standard ART.

Clinical considerations

Section 10.6 (Implementations considerations for key recommendations, Box 10.6) discusses implementation considerations relevant to programme managers. An important consideration for clinicians and other health care providers relates to the challenges of providing LPV/r for young children. When clinicians anticipate significant difficulties in dealing with storing or administering LPV/r, using NVP (especially an NVP-based fixed-dose combination) can be considered. In addition, using LPV/r oral liquid should be avoided in premature babies or in full-term babies younger than 14 days (167). Dosing for children younger than six weeks should be calculated based on body surface area (Annex 3).

Key research gaps

The extent to which new approaches to PMTCT influence the resistance pattern of children becoming infected with HIV despite exposure to ARV drugs for PMTCT still needs to be fully explored outside trial settings. In addition, more evidence is needed to inform the optimal choice of NRTIs and to confirm the safety of EFV-containing regimens, as a first-line option or within PI-sparing strategies in the absence of viral load or genotyping. Studies to fully address the long-term metabolic implications of using LPV/r-based regimens for infants and young children are also needed.

7.2.4 First-line ART for children three years and older (including adolescents)



New recommendations

NEW

- For children infected with HIV three years and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (*strong recommendation, low-quality evidence*).

Special note: In determining the choice of NNRTI for first-line therapy, national programmes should consider the dosing characteristics of EFV (once-daily) and NVP (twice-daily) and how this aligns with the NRTI backbone. For example, NVP may be a better choice if the recommended regimen is a twice-daily option using a fixed-dose combination.

- For children infected with HIV three years to less than 10 years old (or adolescents less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order:
 - ABC + 3TC
 - AZT or TDF + 3TC (or FTC)

(*Conditional recommendation, low-quality evidence*).

Special note: Consideration should be given to the relative merits of ABC versus TDF versus AZT for this population. There is no definitive evidence to make a preferred recommendation, and each option has its respective risks and benefits. ABC can be used once daily, is available across age groups as a fixed-dose combination with 3TC and harmonizes with TDF from a resistance perspective (168). AZT has been widely used and is available as dual and triple fixed-dose combinations with NVP but is dosed twice daily and can cause severe anaemia. TDF has recently been approved for use in children (169), and the advantages include once-daily dosing. However, paediatric TDF formulations are not widely available, experience with TDF in children is limited and there are concerns about the long-term effects of bone toxicity (170,171). Considerations that support the adoption of TDF as the national recommendation include: the national programme uses TDF for adults and pregnant women and a suitable TDF fixed-dose combination formulation for children is available.

- For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:
 - TDF + 3TC (or FTC)
 - AZT + 3TC
 - ABC + 3TC

(*Strong recommendation, low-quality evidence*).

Special note: TDF-containing fixed-dose combinations are currently only available in adult, unscored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents.

ABC or boosted PIs can be used in special circumstances.

Table 7.11 Summary of recommended first-line ART regimens for children and adolescents

	Children 3 years to less than 10 years and adolescents <35 kg	Adolescents (10 to 19 years) ≥35 kg
Preferred	ABC ^a + 3TC + EFV	TDF + 3TC (or FTC) + EFV ^a
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Special circumstances^c	d4T ^b + 3TC + EFV d4T ^b + 3TC + NVP	ABC + 3TC + EFV ABC + 3TC + NVP

^a These recommendations apply to children and adolescents who are initiating first-line ART. Children and adolescents who are already taking ABC-containing regimens can safely substitute TDF for ABC, if this is needed for programmatic reasons. Children and adolescents who are on d4T-containing regimens without evidence of treatment failure can safely substitute ABC or TDF for d4T. Despite a lack of direct evidence, consideration can also be given to substituting ABC or TDF for AZT with the goal of simplifying and harmonizing treatment regimens across age groups. Including TDF in initial ART regimens for children with HBV coinfection offers the potential advantage of reducing the selection of HIV resistance to 3TC that may compromise future options for HBV treatment.

^b d4T use should be restricted to situations in which toxicity to AZT is suspected or confirmed and access to ABC or TDF is lacking. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

^c Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

Background

Despite increased access to early infant diagnosis and the widespread availability of several child-friendly fixed-dose combinations, ART coverage among children lags significantly behind that of adults. Treatment recommendations for children should be easy to implement at all levels of the health system, including the primary care level, and by all ART service providers, rather than paediatric specialists alone.

The 2010 WHO ART guidelines for children three years and older (105) recommended starting with an NVP- or EFV-containing regimen combined with an NRTI backbone. The recommended NRTI backbones, in preferential order, were 3TC + AZT or 3TC + ABC or 3TC + d4T. For adolescents with HBV, the preferred backbone was TDF + FTC or 3TC. The new recommendations in the 2013 guidelines are based on new evidence on the preferred NRTIs and NNRTIs to use in this group of children.

Rationale and supporting evidence

The United States Food and Drug Administration (172) and European Medicines Agency (173) approved using TDF for children older than two years of age, providing an opportunity to offer the same regimen to both adults and children. Harmonizing treatment recommendations with adult regimens could improve children's access to ART. Other benefits of TDF include the ability to combine it with 3TC and EFV to create a potent once-daily regimen for children (169). In addition, the fact that HIV resistance to TDF – specifically K65R – can enhance the antiviral effect of AZT may make TDF a good choice for first-line therapy in terms of sequencing NRTIs from first- to second-line regimens (165,174–176). However, experience with TDF in young children is limited, and although TDF is known to reduce bone mineral density, it is not clear whether this is permanent



and how it might affect future patterns of growth and fracture risk, as highlighted in the values and preferences survey among health workers. In addition, TDF formulations for younger children are not widely available and to date there are no TDF-containing paediatric fixed-dose combinations. ABC shares many of the benefits of TDF (once-daily dosage and a favourable resistance profile) but, in contrast to TDF, ABC has been more thoroughly studied in children and is generally well tolerated. ABC is also available in paediatric fixed-dose combination formulations but is significantly more costly. Further, among people with HLA-B*5701, it can cause potentially fatal hypersensitivity; although this is very rare among African children, it can affect up to 3–4% of Caucasian and Asian children (177).

A systematic review based on observational data indicates that EFV has a better short-term toxicity profile and is associated with better virological response than NVP (121,178). Most children currently receiving ART are treated with regimens that contain NVP, whereas in adults, EFV is increasingly being selected as the preferred NNRTI. The primary reason for this discrepancy relates to the relative availability of NVP or EFV in fixed-dose combinations for children or adults. Children who are well controlled and stable on NVP-containing regimens do not need to substitute EFV for NVP, but EFV would be a better choice for those initiating ART with other once-daily drugs.

In developing these recommendations, the Guidelines Development Group emphasized:

- using potent first-line regimens;
- the convenience of once-daily dosing and the use of fixed-dose combinations whenever possible;
- using non-thymidine analogues – either ABC or TDF – in first-line regimens to maximize the response to AZT in second-line ART; and
- providing treatment recommendations for older children and adolescents that are aligned with those for adults.

Clinical considerations for scaling up ART for children

Section 10.6 (Implementations considerations for key recommendations, Box 10.6) discusses implementation considerations relevant to programme managers. An important consideration for clinicians and other health care providers relates to whether and how regimen changes can be introduced among children who are clinically stable. As children get older, new fixed-dose combinations become available and programmes transition into different first-line regimens. Modifying the ART regimens of clinically stable people can be considered to simplify treatment management and harmonize the ART regimens in use. Table 7.12 summarizes considerations for simplifying and harmonizing ART for children with no history of treatment failure.

Table 7.12 Considerations for simplifying and harmonizing ART for children with no history of treatment failure^a on any regimen

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	<ul style="list-style-type: none"> • Reduced risk of d4T-related toxicity • May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen) 	<ul style="list-style-type: none"> • Aligned with adult regimens
LPV/r	No need to change, but consider substituting NVP or EFV for LPV/r if there is sustained virological response on LPV/r	<ul style="list-style-type: none"> • May improve adherence as a result of better palatability and use of fixed-dose combinations in more manageable formulations (once-daily scored tablets) • Reduced risk of metabolic alterations 	<ul style="list-style-type: none"> • Aligned with adult regimens • Preserve PI for second-line ART • No cold-chain requirement • Reduced drug cost
AZT	No need to change but may consider changing to ABC or TDF	<ul style="list-style-type: none"> • May improve adherence as a result of once-daily dosing (if on EFV) • May reduce the risk of exacerbating anaemia 	<ul style="list-style-type: none"> • Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	<ul style="list-style-type: none"> • Fixed-dose combinations can be used (if also on EFV) 	<ul style="list-style-type: none"> • Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV particularly from age 3 years	<ul style="list-style-type: none"> • May improve adherence as a result of once-daily dosing (if combined with ABC or TDF) 	<ul style="list-style-type: none"> • Aligned with adult regimens

^aDefined based on the criteria for treatment failure adopted nationally.

Key research gaps

The long-term efficacy and safety of TDF, ABC and EFV and the recommended combination need further investigation. More data are needed on the bone, growth and renal toxicity profiles of TDF in children and adolescents, especially in the context of malnutrition and stunting. Similarly, adverse events associated with EFV during adolescence, such as central nervous system effects, require investigation to ensure safe harmonization with adult treatment regimens. Toxicity surveillance systems implemented alongside ART at sentinel sites can provide data to better understand the frequency and clinical relevance of these toxicities.

7.2.5 TB co-treatment in children with HIV



TB is one of the most common opportunistic infections affecting children with HIV. Selecting regimens that are compatible with TB therapy is therefore essential. Interactions between rifampicin and LPV/r or NVP mean that co-treatment in children under three years is challenging, but a recent large randomized controlled trial (163) of ART in children has generated preliminary evidence on the efficacy of triple nucleoside therapy which, despite limited data in the context of TB co-treatment, offers a suitable option for children who require TB treatment while already receiving ART (Table 7.13).

The recommended regimens for children diagnosed with TB and starting ART are consistent with the 2010 recommendations and are summarized in Table 7.13, together with broader guidance on choosing regimens for co-treatment of HIV and TB.

Table 7.13 Summary of recommended ART regimens for children who need TB treatment

Recommended regimens for children and adolescents initiating ART while on TB treatment ^{a b}		
Younger than 3 years		Two NRTIs + NVP, ensuring that dose is 200 mg/m ² or Triple NRTI (AZT + 3TC + ABC) ^c
3 years and older		Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC) ^c
Recommended regimen for children and infants initiating TB treatment while receiving ART ^a		
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP, ensuring that dose is 200 mg/m ² or Triple NRTI (AZT + 3TC + ABC) ^c
	3 years and older	If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC) ^c

Table 7.13 (continued)

Recommended regimen for children and infants initiating TB treatment while receiving ART ^a		
Child on standard PI-based regimen (two NRTIs + LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC) ^c or Substitute NVP for LPV/r, ensuring that dose is 200 mg/m ² or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose ^d
	3 years and older	<p>If the child has no history of failure of an NNRTI-based regimen: Substitute with EFV^e or Triple NRTI (AZT + 3TC + ABC)^c or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose^d</p> <p>If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC)^c or Continue LPV/r consider adding RTV to achieve the full therapeutic dose^d</p> <p>Consider consultation with experts for constructing a second-line regimen</p>

^a Ensure optimal dosing of rifampicin based on new dosing guidelines (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

^b Substitute ARV drugs based on an age-appropriate ART regimen in line with nationally recommended first-line ART.

^c 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 therapy ends. Based on the findings from the ARROW trial (163), this regimen should be considered as the preferred option for children younger than three years who are receiving a LPV/r-based regimen when starting TB treatment. The United States Food and Drug Administration approval for the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg offers a potential alternative to the triple NRTI approach. An EFV-based regimen in children under 3 years is still not recommended as pharmacokinetics data are needed to ensure that the co-administration of rifampicin does not decrease drug levels below the therapeutic level. Triple NRTI should also be considered as the preferred regimen for children older than 3 years with a history of failure on a NNRTI-based regimen.

^d Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.

^e Substitution with EFV should be considered as the preferred option (179), and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.



7.3 Monitoring response to ART and the diagnosis of treatment failure



7.3.1 Laboratory monitoring before and after initiating ART

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARV drugs. Table 7.14 summarizes recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for coinfections and noncommunicable diseases.

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 cell count TB screening	HBV (HBsAg) serology ^a HCV serology <i>Cryptococcus</i> antigen if CD4 count ≤ 100 cells/mm ³ ^b Screening for sexually transmitted infections Assessment for major noncommunicable chronic diseases and comorbidities ^c
Follow-up before ART	CD4 cell count (every 6–12 months)	
ART initiation	CD4 cell count	Haemoglobin test for AZT ^d Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF ^e Alanine aminotransferase for NVP ^f
Receiving ART	CD4 cell count (every 6 months) HIV viral load (at 6 months after initiating ART and every 12 months thereafter)	Urine dipstick for glycosuria and serum creatinine for TDF ^e
Treatment failure	CD4 cell count HIV viral load	HBV (HBsAg) serology ^a (before switching ART regimen if this testing was not done or if the result was negative at baseline)

^a If feasible, HBsAg testing should be performed to identify people with HIV and HBV coinfection and who therefore should initiate TDF-containing ART.

^b Can be considered only in settings with a high prevalence of cryptococcal antigenaemia ($>3\%$) (180).

^c Consider assessing the presence of chronic conditions that can influence ART management such as hypertension and other cardiovascular diseases, diabetes and TB.

^d Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

^e Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low BMI, diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

^f 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 cells/mm³ and HCV coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

7.3.2 Monitoring the response to ART and the diagnosis of treatment failure

New recommendations

NEW

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (*strong recommendation, low-quality evidence*).
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (*strong recommendation, moderate-quality evidence*).

Special notes: Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a three-month interval, with adherence support between measurements) after at least six months of using ARV drugs. Viral load testing is usually performed in plasma; however, certain technologies that use whole blood as a sample type, such as laboratory-based tests using dried blood spots and point-of-care tests, are unreliable at this lower threshold, and where these are used a higher threshold should be adopted.

Viral load should be tested early after initiating ART (at 6 months) and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm virological failure where possible.

Background

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine whether and which ART regimens should be switched in case of treatment failure. Before 2010, WHO guidelines on ART recommended using clinical outcomes and CD4 count for routinely monitoring the response to ARV drugs. However, the value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings.

The 2010 WHO guidelines recommended that countries consider phasing in viral load testing to monitor the response to ART and use a viral load threshold above 5000 copies/ml in an adherent person with no other reasons for an elevated viral load (such as drug interactions, poor absorption and intercurrent illness). However, most ART programmes in resource-limited settings still do not have access to viral load testing and continue to rely on clinical and immunological monitoring. This limited use of viral load monitoring has been identified as a key reason for the lower than expected rates for switching ART regimens in resource-limited settings.

Rationale and supporting evidence

Although evidence from clinical trials for a survival benefit of viral load testing is limited, it can provide an early indication of treatment failure, and the 2013 guidelines strongly recommend using it for detecting virological failure and/or confirming treatment failure among people with evidence of clinical and/or immunological failure (Table 7.15). Since several clinical and epidemiological studies show that the risk of HIV transmission is very low when the viral load is lower than 1000 copies/ml (181), the Guidelines Development Group also recommended reducing the viral load threshold for treatment failure from 5000 copies/ml to 1000 copies/ml.

NEW



Table 7.15 WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) ^a after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome ^b occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure ^a
	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	
Immunological failure	Adults and adolescents CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm ³	Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (182). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
	Children Younger than 5 years Persistent CD4 levels below 200 cells/mm ³ or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm ³	
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support	The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

^a See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 1.

^b Section 6.1 discusses immune reconstitution inflammatory syndrome.

Virological monitoring (viral load) versus immunological (CD4) and clinical monitoring (WHO clinical staging)

The main rationale for recommending viral load monitoring as the preferred approach compared with immunological and clinical monitoring is to provide an early and more accurate indication of treatment failure and the need to switch to second-line drugs, reducing the accumulation of drug-resistance mutations and improving clinical outcomes. Measuring viral load can also help to discriminate between treatment failure and non-adherence (183) and can serve as a proxy for the risk of transmission at the population level (76).

There is still limited evidence to support any additional survival benefit of viral load monitoring over CD4 and/or clinical monitoring among individuals with HIV receiving ART. A systematic review identified three randomized clinical trials on virological versus immunological and clinical monitoring (184–186) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Compared with immunological and/or clinical monitoring, adding viral load monitoring has not been associated with reduced mortality. In one of these trials (185), no significant difference in the incidence of clinical failure, switching to second-line regimens and resistance mutations was found. One cohort modelling study among adults also found that adding virological monitoring to clinical and/or immunological criteria made no difference in mortality or new AIDS-defining illnesses (187). Although randomized controlled trials have not yet shown that viral load monitoring translates into survival gains, follow-up has been limited (less than five years) and longer follow-up is required to examine the longer-term impact on survival, resistance profile and HIV transmission.

A systematic review provided moderate-quality evidence that current WHO guidelines on immunological and clinical monitoring for treatment failure have poor sensitivity and lower positive predictive value for identifying virological failure in adults (187–200) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). This means that many of the people who are identified with immunological failure in fact have adequate virological suppression and risk being misclassified as having treatment failure and switched unnecessarily to second-line therapy. A further systematic review using data in children also provided moderate-quality evidence that immunological criteria (201–204) have low sensitivity and positive predictive value for identifying children with virological failure.

Immunological monitoring versus clinical monitoring

Where viral load monitoring is unavailable, clinical monitoring and CD4 monitoring are recommended (205). Although a systematic review of two randomized controlled trials (184,206) provide moderate-quality evidence of mortality and morbidity benefits with CD4 and clinical monitoring compared with routine clinical monitoring in adults receiving ART, these trials largely focused on CD4 and clinical monitoring in people who initiated ART at CD4 counts below 200 cells/mm³ (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Existing immunological and clinical criteria may have decreased sensitivity and specificity to detect treatment failure in people who initiate ART at higher CD4 counts, and more accurate immunological criteria for these people remain to be identified.

Routine versus targeted viral load monitoring to detect treatment failure

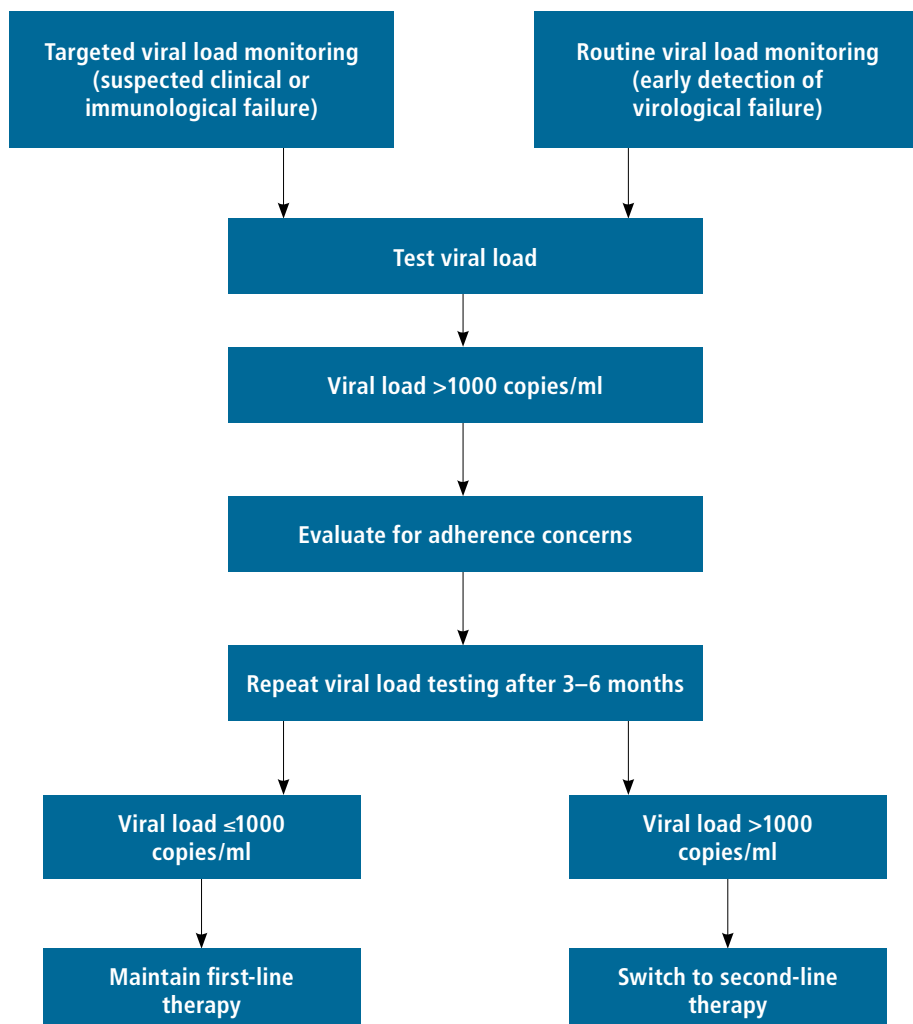
Viral load should be monitored routinely (every 6–12 months) to enable treatment failure to be detected earlier and more accurately. In settings with limited access to viral load testing, a targeted viral load strategy to confirm failure suspected based on immunological or clinical criteria (Table 7.15) should be used to avoid unnecessary switching to second-line ART. Targeted viral load monitoring is less costly than routine viral load testing, but as with clinical and immunological monitoring, has the potential to delay switching to second-line ART and may subsequently increase the risk of disease progression, selection of ARV drug resistance and HIV transmission.

Threshold for defining virological failure

The optimal threshold for defining virological failure and for switching ART regimens has not been established. The rationale for the threshold of 1000 copies/ml was based on two main sources of evidence. First, viral blips or intermittent low-level viraemia (50–1000 copies/ml) can occur during effective treatment but have not been associated with an increased risk of treatment failure unless low-level viraemia is sustained (207). 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 (181,208,209).

Most standard blood and plasma viral load platforms available and being developed have good diagnostic accuracy at this lower threshold. However, the sensitivity of dried blood spots for viral load determination at this threshold may be reduced (210,211). Programmes relying on dried blood spot technology for viral load assessment may therefore consider retaining the higher threshold (3000–5000 copies/ml) until sensitivity at lower thresholds is established (212–214).

Fig. 7.1 Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children



Special considerations for children

These guidelines aim to harmonize monitoring approaches for children with those recommended for adults. As more children start ART earlier and at higher CD4 counts, viral load monitoring to detect treatment failure and lack of adherence will be increasingly beneficial. In addition, viral load may be instrumental for implementing treatment strategies to preserve second-line options as children age (such as switching from LPV/r to an NNRTI once virological suppression is sustained) (see section 7.3.3).

Evidence from one randomized controlled trial conducted in several countries (including the United States of America, European countries, Brazil and Thailand, PENPACT1 (158), suggests that switching treatment at lower viral load thresholds does not lead to better clinical and virological outcomes but does minimize the development of HIV drug resistance, especially for NRTIs when an NNRTI-based regimen is used. In this context, alignment with the viral load thresholds recommended for adults is advisable. However, viral load results in the first six months after initiating ART should be interpreted carefully, as infants and young children may require longer to achieve virological suppression because of high baseline viral load.

The recommendation to initiate ART for all children younger than five years of age regardless of clinical and immunological criteria means that CD4 cell count testing at baseline is not required for initiating ART. However, where viral load monitoring capacity is limited or unavailable, CD4 monitoring – including baseline measurement and CD4 percentage for children younger than five years of age – will still be important for monitoring treatment response.

As in the case of adults, lack of viral load or CD4 capacity should not prevent children from starting ART. The results from a recently completed trial show that mortality and disease progression are comparable between clinical monitoring and laboratory monitoring, especially in the first year of treatment (163).

Clinical considerations for scaling up viral load testing

Section 10.6 (see section on implementation considerations for key recommendations, Box 10.3) discusses clinical and implementation considerations relevant to programme managers. Additional implementation considerations for clinicians and health workers include the following.

- **Access to ART should be the first priority.** Lack of laboratory tests for monitoring treatment response should not be a barrier to initiating ART.
- **Setting priorities.** If viral load testing is limited, it should be phased in using a targeted approach to confirm treatment failure. This may be especially relevant in populations receiving ARVs to reduce HIV transmission, such as pregnant and breastfeeding women and among serodiscordant couples, for whom sustained viral load suppression is critical to the efficacy of the strategy.

7.4 Monitoring and substitutions for ARV drug toxicities



7.4.1 Guiding principles

- The availability of laboratory monitoring is not required for initiating ART.
- Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

7.4.2 Major types of ARV toxicities

The 2010 WHO ART guidelines recommended 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 were advised (but not required) for specific high-risk people using certain drugs. Table 7.16 lists key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment. More data are needed on whether routine or periodic laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all individuals or only people at higher risk.

Table 7.16 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 gene	If ABC is being used in first-line ART, substitute with TDF or AZT or d4T If ABC is being used in second-line ART, substitute with TDF
	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval	LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors
ATV/r	Indirect hyperbilirubinaemia (clinical jaundice)	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Nephrolithiasis and risk of prematurity	Risk factors unknown	
AZT	Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropaenia CD4 count ≤ 200 cells/mm ³	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with d4T
	Lactic acidosis or severe hepatomegaly with steatosis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	

Table 7.16 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
d4T	Peripheral neuropathy, lipodatrophy or lipodystrophy	Older age CD4 count ≤ 200 cells/mm ³ Concomitant use of isoniazid or ddl	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If DRV/r is being used in second-line ART, substituting with ATV/r or LPV/r can be considered. When it is used in third-line ART, limited options are available
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	NVP. If the person cannot tolerate either NNRTI, use boosted PIs
	Hepatotoxicity	Underlying hepatic disease – HBV and HCV coinfection Concomitant use of hepatotoxic drug	
	Convulsions	History of seizure	
	Hypersensitivity reaction, Stevens-Johnson syndrome	Risk factors unknown	
	Potential risk of neural tube birth defects (very low risk in humans) (122,140)		
	Male gynaecomastia		
ETV	Severe skin and hypersensitivity reactions	Unknown	Limited options are available



Table 7.16 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea	Risk factors unknown	
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs CD4 >250 cells/mm ³ in women CD4 >400 cells/mm ³ for men First month of therapy (if lead-in dose is not used)	EFV. If the person cannot tolerate either NNRTI, use boosted PIs
	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome)	Risk factors unknown	
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Limited options are available

Table 7.16 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF (169)	Tubular renal dysfunction, Fanconi syndrome	Underlying renal disease Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC If TDF is being used in second-line ART (after d4T + AZT use in first-line ART), substitute with ABC or ddl
	Decreases in bone mineral density	History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir)

7.4.3 Monitoring TDF toxicity

TDF nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease (130).

According to a systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes), no studies have properly compared monitoring strategies for people receiving TDF, such as routine toxicity monitoring versus care with no monitoring or incidental monitoring in case of perceived clinical need. One clinical trial (the DART trial) comparing laboratory with clinical monitoring showed that individuals receiving TDF have an increased risk of reduced estimated glomerular filtration rate but no increased risk of renal failure over a median five years of follow-up (low-quality evidence). A few observational cohort studies reported that using TDF was associated with an increased risk of chronic kidney disease. However, the exposure time to TDF in all these studies was considered too short to indicate a long-term increased risk for renal failure, the occurrence of bone fractures or changes in fat distribution.

The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory to initiate treatment with TDF. However, it is advisable for high-risk people (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. High frequency of glycosuria has also been found in people without diabetes biopsied for TDF nephrotoxicity with increased serum creatinine compared with TDF-treated people with a normal glomerular filtration rate, suggesting that dipstick glycosuria may be a cost-effective screening test for serious TDF-induced kidney injury (215).

TDF-related decreases in bone mineral density have been observed in children, although it is unclear how reducing bone mineral density might impact future growth patterns or the risk of bone fracture. In addition, an accurate and feasible method to measure bone mineral density still needs to be identified, and significant uncertainty remains around how best to monitor TDF-related bone toxicity among children. Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while children are receiving treatment with TDF (169).

Clinical considerations

- Laboratory monitoring is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring may be used to assess for hypertension.
- Urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without diabetes using TDF-containing regimens.
- If the creatinine test is routinely available, use the estimated glomerular filtration rate^a at baseline before initiating TDF regimens.
- Do not initiate TDF when the estimated glomerular filtration rate is <50 ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure.
- Monitor growth in children using TDF.

^a Using the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) formulas for estimation. An online calculator is available at <http://nephron.com/cgi-bin/CGSI.cgi>.

CG formula: $eGFR = (140 - \text{age}) \times (\text{Wt in kg}) \times 0.85 \text{ (if female)} / (72 \times \text{Cr in mg\%})$.

MDRD formula: $eGFR = 175 \times \text{SerumCr} - 1.154 \times \text{age} - 0.203 \times 1.212 \text{ (if patient is black)} \times 0.742 \text{ (if female)}$.

Key research gaps

More data are needed on how to best monitor renal function in people using TDF-containing regimens (whether toxicity monitoring should be routine or targeted in high-risk groups, with alternative drugs for high-risk people). In addition, more data are needed to understand the frequency and clinical relevance of reduced bone mineral density in children. More accurate and affordable methods to monitor bone toxicity should be identified for this specific population.

7.4.4 Toxicity monitoring for other ARV drugs

AZT

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin is recommended before initiating ART, mainly among adults and children with low body weight, low CD4 counts and advanced HIV disease. People with HIV with severe anaemia at baseline (haemoglobin <7.0 g/dl) should avoid AZT as first-line therapy.

NVP

The laboratory measurement of liver enzymes has very low predictive value for NVP-containing regimens. However, monitoring hepatic enzymes is recommended if feasible, especially for women with HIV who have CD4 cell counts >250 cells/mm³ and individuals with HIV who are coinfecting with HBV or HCV. Section 7.2.1 provides more information on the safety of NVP among individuals with high CD4 cell counts.

EFV

The main type of toxicity of EFV is central nervous system side effects, which typically resolve after a few weeks. However, in some cases, they can persist for months or not resolve at all. Despite concerns about the potential risk of teratogenicity associated with using EFV during pregnancy, a recent meta-analysis found no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARV drugs (122). Section 7.3.2 provides more information on the safety of EFV among pregnant women.

7.4.5 Drug substitutions for ARV drug toxicity

Drug regimen or single agent substitutions may be required for drug toxicity and to avoid drug interactions. Section 7.4.3 provides guidance on managing specific types of ARV drug toxicity.

Clinical considerations

- Delaying substitutions or switches when there are severe adverse drug effects may cause harm and may affect adherence, leading to drug resistance and treatment failure.
- When drug interruptions are required, such as for severe and life-threatening adverse events related to toxicity, it is important to consider the various half-lives of ARV drugs. For example, when a NNRTI needs to be discontinued, a staggered approach should be used by prolonging the use of the NRTI backbone for two to three weeks. Alternatively, the NNRTI could be temporarily substituted with a boosted PI.

7.4.6 Drug substitutions for ARV drug toxicity

Providers should be aware of all drugs that people with HIV are taking when ART is initiated and new drugs that are added during treatment maintenance. There are several key drug interactions (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

WHO TB treatment guidelines review key considerations for managing coinfection with TB and HIV (216). A key contraindicated drug combination includes rifampicin and PIs. When people coinfect with TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r and SQV/r can be used for the duration of TB treatment, if the boosting dose of RTV is increased or double the standard dose of LPV/r is used (see section 7.6.1). For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered.

Ribavirin and peginterferon alpha-2a are often used for treating HCV. Administration of these agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfect with HCV and HIV and receiving AZT may need to be switched to TDF.

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 fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV.

WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria (217). One recommended artemisinin-based combination therapy is artesunate and amodiaquine. EFV increases the concentrations of amodiaquine and has been associated with significant elevations of liver transaminases. Alternative artemisinin-based combination therapies (such as artemether plus lumefantrine, artestunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine) could be used to prevent severe toxicity in people with HIV.

WHO recommends methadone and buprenorphine for treating opioid dependence (218). Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People receiving methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives (219). Limited data suggest potential drug interactions between many ARV drugs (especially some NNRTIs and RTV-boosted PIs) and estrogen-based hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the ARV drug. 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 to compensate for any possible reduction in the effectiveness of the hormonal contraception.

Concomitant use of boosted PIs and NNRTI 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.

WHO recommends using statins for people with a 10-year cardiovascular risk exceeding 30% (220). Boosted PIs may lead to increased concentrations of lovastatin and simvastatin. Increased concentrations may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidaemia agents should be used to prevent severe toxicity among people with HIV.

Table 7.14 Key ARV drug interactions and suggested management^a

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and peg-interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with d4T
Boosted PI (ATV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose or substitute with three NRTIs (for children)
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent (for example pravastatin)
	Estrogen-based hormonal contraception	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
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
NVP	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole)

^a This table was developed using the University of Liverpool’s drug interaction charts, a resource which can be found online at www.hiv-druginteractions.org. A more comprehensive table of ARV drug interactions is available on the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes).

Box 7.2 Surveillance of ARV drug toxicity

WHO commissioned systematic reviews on specific types of toxicities associated with key ARV drugs and laboratory monitoring strategies to consolidate and update technical guidance (140,169). The reviews highlighted remaining evidence gaps in the potential increased risk of toxicity associated with the long-term use of ARV drugs, the use of ARV drugs during pregnancy and in breastfeeding mothers, children and adolescents and populations with associated risk factors and in laboratory monitoring for toxicity.

The available evidence is limited to studies with limited sample size or short duration. It is essential to monitor the use of ARV drugs in resource-limited countries where toxicities may present a different pattern in association with environmental or behavioural factors, the prevalence of other conditions and where ARV drugs are used in association with other medicines. Implementing toxicity surveillance will provide the opportunity to produce evidence on specific types of toxicity, increase confidence in the use of the drugs, identify populations with risk factors and plan preventive strategies.

The Guidelines Development Group encouraged WHO to strengthen toxicity surveillance activities to increase evidence on toxicity in key areas. These areas cover a potential increased risk of toxicity associated with the long-term use of ARV drugs, renal and bone toxicity associated with using TDF among adults and children, the safety of using EFV- and TDF-containing regimens during pregnancy and in breastfeeding mothers and using TDF among children, adolescents and populations with associated risk factors. Developing laboratory markers to monitor renal function among people using TDF is another important area for research.

Several toxicity surveillance activities have already started with WHO support, using standardized approaches at sentinel sites in resource-limited settings. Targeted and systematic surveillance is being conducted in Côte d'Ivoire to monitor renal toxicity associated with TDF in first- and second-line regimens, with an assessment of laboratory monitoring needs in three sentinel sites. A similar approach is being implemented in Viet Nam to assess renal toxicity associated with TDF and central nervous system toxicity associated with EFV in people who use ARV drugs to prevent HIV infection, such as in serodiscordant couples. In the Lao People's Democratic Republic, anaemia associated with AZT and hypersensitivity associated with NVP are monitored using a targeted and systematic surveillance approach. In Malawi, a surveillance programme will monitor infant growth, following mothers who are breastfeeding and receiving TDF.

The implementation of a pregnancy registry, including a surveillance programme for birth defects, is recommended where feasible to assess the safety of ARV drugs and any other medicines during pregnancy and risk factors for adverse pregnancy outcomes, including maternal health outcomes, premature births, stillbirths, low birth weight and congenital abnormalities. WHO, the United States President's Emergency Plan for AIDS Relief, the United States Centers for Disease Control and Prevention and the United States National Institutes of Health support the establishment of ARV pregnancy registries and birth defect surveillance in sentinel sites in Malawi, South Africa and Uganda to assess the use of EFV-containing regimens at large scale among pregnant women.

Surveillance of ARV drug toxicity will help to better understand the long-term risk of ART toxicity and optimize the management of ARV drugs for HIV treatment and prevention in all populations.

7.5 What ART regimen to switch to (second-line ART)

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age (Table 7.18).

Table 7.18 Summary of preferred second-line ART regimens for adults, adolescents, pregnant women and children

Second-line ART			Preferred regimens	Alternative regimens
Adults and adolescents (≥10 years), including pregnant and breastfeeding women			AZT + 3TC + LPV/r ^a AZT + 3TC + ATV/r ^a	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r
Children	If a NNRTI-based first-line regimen was used		ABC + 3TC + LPV/r ^b	ABC + 3TC + LPV/r ^b TDF + 3TC (or FTC) + LPV/r ^b
	If a PI-based first-line regimen was used	<3 years	No change from first-line regimen in use ^c	AZT (or ABC) + 3TC + NVP
		3 years to less than 10 years	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP

^a DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.

^b ATV/r can be used as an alternative to LPV/r for children older than six years.

^c Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

7.5.1 Second-line ART for adults and adolescents



New recommendations

NEW

- Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).
 - The following sequence of second-line NRTI options is recommended:
 - After failure on a TDF + 3TC (or FTC)–based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.
 - After failure on an AZT or d4T + 3TC–based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
 - Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (*strong recommendation, moderate-quality evidence*).
- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (*strong recommendation, moderate-quality evidence*).

Table 7.19 Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen ^a	
Adults and adolescents (≥10 years)	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r
Pregnant women	Same regimens recommended for adults and adolescents	
HIV and TB coinfection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily)
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)	

^a ABC and ddI can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

Background

The 2010 WHO ART guidelines recommended that second-line adult regimens include a boosted-PI plus two NRTIs (determined by the drug used in first-line therapy). Those guidelines placed a high value on using simpler second-line regimens, ideally heat-stable formulations and fixed-dose combinations (once-daily formulations when possible).

Except for the recommendation for people with HIV and TB, the recommendations in 2013 remain unchanged from the 2010 recommendations.

Rationale and supporting evidence

Protease Inhibitor (PI) options for second-line ART

Since first-line ART should preferably be based on an NNRTI, PI-based regimens are recommended for second-line therapy. Of the PI options, ATV/r and LPV/r are preferred. DRV/r is an alternative but is currently not available as a fixed-dose combination, although one is in development. The other PIs (FPV/r, IDV/r and SQV/r) are not available as heat-stable fixed-dose combinations and/or are associated with high pill burden and higher frequency of side effects.

The Guidelines Development Group emphasized the importance of simplifying second-line ART by reducing the pill burden and limiting the number of preferred second-line regimens that could be used across populations (adults, adolescents, children, pregnant women and people coinfecting with TB, HBV and HCV). The use of less toxic, more convenient and more efficacious heat-stable fixed-dose combinations was also considered critical.

A systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) of data from six clinical trials comparing drugs used for second-line ART (ATV/r, LPV/r and DRV/r) concluded that there was no evidence to support changing the recommendation in the 2010



guidelines (221–226). These studies showed low- to very-low-quality evidence (downgraded in the GRADE evaluation primarily for indirectness and imprecision) for using ATV/r or DRV/r (once-daily) over LPV/r (twice-daily) or vice versa as preferred boosted PI options. ATV/r was considered to be comparable to LPV/r in one trial among ART-experienced individuals (221). In a trial among ART-naïve individuals, ATV/r showed a better virological response and better retention in care when compared with LPV/r (224). In two studies, people receiving DRV/r-containing regimens also showed better virological response and retention in care than people receiving LPV/r, both in treatment-naïve and experienced people (222,226). This evidence was downgraded to low or very low quality, primarily for indirectness and imprecision. DRV/r has been used for second-line therapy in high-income settings. However, two key factors currently preclude DRV/r as a preferred option in these guidelines. These include the high cost and it not being available as a heat-stable fixed-dose combination. Additional research is required to better understand sequencing strategies for PIs in second- and third-line therapy. The different drug toxicity profiles of ATV/r and LPV/r, the contraindication of ATV/r and rifampicin and the lack of WHO approval for its use in children younger than six years provide additional grounds for maintaining both PIs as equal options (Table 7.20). The Guidelines Development Group recommended that DRV/r should be maintained as a preferred third-line drug. However, using it as an alternative option to LPV/r or ATV/r for second-line therapy can be considered, especially when competitively priced fixed-dose combinations are available.

NRTI backbone

The Guidelines Development Group maintained the rationale adopted in 2010, recommending drug sequencing consistent with ART-optimizing principles (in particular, availability as fixed-dose combinations and tolerability) and resistance mutation risk, based on the NRTIs used in the first-line regimen. If a thymidine analogue NRTI (AZT or d4T) was used in the failing first-line regimen, TDF should be used in the second-line regimen. If a non-thymidine analogue NRTI was used in first-line ART (that is, TDF), AZT should be used in second-line ART. Other NRTI drugs such as ABC and ddI are acceptable as potential back-up options in special situations but are not recommended as preferred alternatives, since they have no specific advantage and add complexity and cost.

For individuals coinfecting with HIV and HBV whose first-line regimen contained TDF + 3TC (or FTC), these NRTIs should be continued in the second-line regimen for the anti-HBV activity and to reduce the risk of hepatic flares, regardless of the selected second-line regimen, which should be AZT + TDF + 3TC (or FTC) + a boosted PI.

For people with active TB disease receiving rifampicin, all boosted PIs in standard doses are contraindicated because of drug interactions and significant reductions in PI plasma concentrations (227–230). In this situation, LPV/r and SQV/r may be used with an adjusted, super-boosted dose of RTV (LPV/r 400 mg/400 mg twice daily or SQV/r 400 mg/400 mg twice daily) or doubling the LPV/r daily dose (LPV/r 800 mg/200 mg twice daily), but this is associated with high levels of toxicity and requires close clinical and laboratory monitoring. The recommendation to use LPV/r 800 mg/200 mg twice daily is based on evidence graded as low-quality, and it is associated with a similar level of toxicity as LPV/r 400 mg/400 mg twice daily (230,231). However, this option may be less complex and more feasible, since LPV/r is widely available as a single formulation, whereas RTV is not. However, when rifabutin is used in place of rifampicin, all boosted PIs can be concomitantly administered in their standard doses (Table 7.20).

Clinical considerations

Clinical and programmatic simplification can be promoted in the sequencing from first- to second-line ART. If AZT- or d4T-based regimens are failing, a second-line regimen with once-daily dosing for boosted PI and NRTI components (such as TDF + 3TC (or FTC) + ATV/r) should

be adopted. If a TDF-based regimen is failing, twice-daily dosing for boosted PI and NRTI components (such as AZT + 3TC + LPV/r) should be adopted.

Key research gaps

Several ongoing studies comparing various drugs and ARV classes (232–236) will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches (the results are expected after 2014). Further investigation is needed of the role of DRV in second- and third-line regimens (optimal dosing in adults and children, once versus twice daily, fixed-dose combinations with other boosting agents and integrase inhibitors and sequencing strategies). Several trials are underway that are examining induction and maintenance using PI/r monotherapy in maintenance. The potential of including rifabutin as part of fixed-dose combinations for TB treatment also needs to be explored.

Table 7.20 Comparative analysis: ATV/r versus LPV/r versus DRV/r

Major parameters	ATV/r	LPV/r	DRV/r
Consistency with paediatric regimens	No ^a	Yes	No ^b
Number of pills per day (standard dose as a fixed-dose combination)	1	4	2 to 4
Convenience (once- versus twice-daily regimen)	Once daily	Twice daily	Once or twice daily
Safety in pregnancy	Yes	Yes	Yes
Gastrointestinal intolerance (diarrhoea)	Not frequent	Common	Not frequent
Availability of co-formulations (as heat-stable fixed-dose combinations)	Yes	Yes	No ^d
Use with a TB treatment regimen that contains rifampicin	No	Yes ^c	No
Hyperbilirubinaemia	+	–	–
Dyslipidaemia	±	+	±
Potential for future reduction in cost	Low	Low	High
Accessibility in countries (registration status)	Low	High	Low
Availability of generic formulations	Yes	Yes	No

^a Approved only for children >6 years old.

^b Approved only for children >3 years old.

^c Only if used in higher doses.

^d A heat stable FDC is currently under development.

7.5.2 Second-line ART for children (including adolescents)



New recommendations

NEW

- After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI. *(Strong recommendation, moderate-quality evidence)*
- After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken. *(Conditional recommendation, very-low-quality evidence)*
- After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI. *(Conditional recommendation, low-quality evidence)*
- After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC. *(Strong recommendation, low-quality evidence)*
- After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC). *(Strong recommendation, low-quality evidence)*

Table 7.21 Summary of recommended first- and second-line ART regimens for children (including adolescents)

	Children	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	No change ^a
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV
		AZT + 3TC + LPV/r	ABC or TDF ^b + 3TC + EFV
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r ^c
		TDF ^b + 3TC (or FTC) + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC ^c (or FTC) + LPV/r ^c

^a No change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on the recent approval of the use of EFV in children less than 3 years, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

^b TDF may only be given to children >2 years.

^c ATV/r can be used as an alternative to LPV/r in children older than 6 years.

Background

Recommending potent and effective second-line regimens for infants and children is especially difficult because of the current lack of experience in resource-limited settings and the limited formulations available. This highlights the importance of choosing potent and effective first-line regimens and ensuring their durability and effectiveness by optimizing adherence.

The 2010 WHO guidelines recommended a regimen based on a PI boosted with RTV and combined with two NRTIs as the second-line treatment for children who fail a regimen of two NRTIs plus an NNRTI (105). For infants and young children exposed to an NNRTI as part of PMTCT interventions and starting a PI-based regimen in first-line ART, the recommendation for second-line was to use two new NRTIs and an NNRTI, as this was the only new drug class available.

The recommendations are now better informed by paediatric clinical trial data (156,158,237) and observational data (157). The Guidelines Development Group also considered operational and programmatic issues including the availability of heat-stable formulations and fixed-dose combinations for children.

Rationale and supporting evidence

After reviewing data for adults and children and considering factors such as the availability of a heat-stable fixed-dose combination, optimal daily dose, regimen harmonization with adults, high cost and availability of alternatives, the main recommendations established in the 2010 guidelines were maintained.

For children for whom a LPV/r-based first-line regimen has failed, NNRTIs remain the only new drug class that can be introduced. Randomized data among older children (158) provide indirect evidence supporting the safe use of an NNRTI-based second-line regimen, but concerns remain about this approach for infants and young children. Based on the suboptimal performance of NVP-based regimens (and the limited data available to inform the use of EFV) in children younger than three years (153,154) and the potential rapid re-emergence of archived NNRTI-resistant HIV, second-line NNRTI-based regimens are expected to have limited durability in this age group (238).

Increasing evidence suggests that, in young children for whom LPV/r-based regimens have failed, selection of major PI mutations is rare and accumulation of thymidine analogue mutations is very limited (156,237,239,240). In this context and in the absence of robust second-line alternatives such as DRV/r-containing regimens, the Guidelines Development Group recommended that children younger than three years of age should be maintained on LPV/r until the age of three years, despite treatment failure. However, a more rapid switch should be considered in situations in which failure results from poor adherence because of the poor palatability of LPV/r or in cases of advanced HIV disease. In such cases, children younger than three years should be switched to a NVP-based regimen, and close monitoring should be provided to ensure adequate adherence.

For children starting first-line ART with an NNRTI-based regimen, PI-based regimens remain the recommended choice for second-line therapy. LPV/r is the preferred option, but ATV/r and DRV/r may be considered if more appropriate formulations become available.

Despite its toxicity profile and limited role in TB and HIV coinfection, ATV/r is a promising alternative to LPV/r for children older than six years of age. ATV/r has some advantages over LPV/r, including lower cost and the potential for once-daily dosing. DRV/r is the PI of choice following LPV/r or ATV/r treatment failure and would be valuable as a third-line drug or as second-line therapy in young children for whom first-line ART with LPV/r has

NEW



failed. However, ATV/r is currently only licensed for use among children older than six years and DRV/r in children older than three years. Neither ATV/r nor DRV/r is currently available as a co-formulated fixed-dose combination for children. The Paediatric ARVs Working Group identified appropriate doses of both drugs using current WHO weight bands and simply scaling down from the current adult fixed-dose combination tablets. Validation studies are urgently needed to develop adequate paediatric formulations.

Unboosted PIs (such as fosamprenavir (FPV), DRV and ATV) and other PIs (such as IDV/r, SQV/r, FPV/r and TPV/r) are associated with reduced virological suppression, high pill burden and/or a higher frequency of side effects and are therefore discouraged (241).

Notably, liquid RTV requires cold storage, is unpalatable, has significant gastrointestinal intolerance and is poorly tolerated by infants and children. The heat-stable 100-mg fixed-dose combination tablet formulation of LPV/r for children is better tolerated but cannot be cut or crushed; many children have difficulty in swallowing this tablet whole. Data on whether LPV/r can be given once daily are expected soon from an ongoing randomized trial (242). New heat-stable paediatric sprinkle formulations appear to be a suitable alternative and will be available in the near future (243).

The sequencing of NRTI was determined based on optimizing principles for ARV drugs and the need to maximize antiviral activity despite the selection of resistance mutations. If a thymidine analogue NRTI drug (AZT or d4T) was used in the failing first-line regimen, ABC or TDF should be used in the second-line regimen. If a non-thymidine analogue drug (ABC or TDF) was used in the first-line regimen, AZT should be used in the second-line regimen. The added value of ddI in second-line regimens is unclear; continuing 3TC despite the likely presence of 3TC resistance is the preferred option. HIV harbouring 3TC resistance with the M184V mutation may have reduced viral replication and may also induce some degree of resensitization to AZT or TDF, although this is based on in vitro data (165,244).

Key research gaps

More evidence is needed to inform the choice of second-line regimens for young children for whom an LPV/r-based first-line regimen has failed. Validation studies to assess simplified dosing for ATV/r and DRV/r fixed-dose combinations are critical to ensure future effective alternatives. Innovative second-line strategies such as PI + integrase inhibitors or induction and maintenance using PI/r monotherapy among children should also be investigated.

7.6 Third-line ART



New recommendations

NEW

- National programmes should develop policies for third-line ART (*conditional recommendation, low-quality evidence*).
- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs (*conditional recommendation, low-quality evidence*).
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (*conditional recommendation, very low-quality evidence*).

Background

In 2010, WHO made recommendations on third-line ART in the context of limited evidence to guide third-line strategies. Although there were few studies of newer agents, cohort data showed high mortality among people for whom second-line ART had failed (245).

Rationale and supporting evidence

The Guidelines Development Group maintained the recommendations established in the 2010 WHO guidelines. In so doing, the Guidelines Development Group emphasized balancing the need to develop policies for third-line ART with the need to expand access to first-line and second-line ART. It also recognized that many countries have financial constraints that limit the adoption of third-line regimens.

Data from randomized controlled trials are available for DRV/r, etravirine (ETV) and raltegravir (RAL), but most studies have been conducted in well-resourced or middle- to high-income countries. Taken together, these data support the efficacy of these agents in highly ART-experienced patients. In a published pooled subgroup analysis, DRV/r plus an optimized background regimen (OBR) chosen by genotyping and phenotyping was shown to be superior to the control group (boosted PI + OBR plus the optimized background regimen, where the investigator selected the boosted PI) among highly treatment-experienced individuals (222). DRV/r was also shown to be non-inferior to LPV/r among treatment-experienced people after 96 weeks (223). Among individuals with limited treatment options, RAL + OBR provided better viral suppression than the OBR alone for at least 96 weeks (246,247). Similarly, ETV + OBR provided better viral suppression and improved immunological response than the optimized background regimen alone after 96 weeks (248). In people with multidrug-resistant HIV who have few remaining treatment options, the combination of RAL, ETV and DRV/r was well tolerated and was associated with a rate of virological suppression similar to that expected among treatment-naïve people (249,250).

Evidence from post-marketing reports indicates higher rates of hypersensitivity to ETV than previously reported (251). ETV + RAL is not approved for use in individuals younger than 16 years of age. There are limited data on the use of these newer drugs in infants, children and pregnancy, including very limited pharmacokinetic and safety data.

NEW


Special considerations for children

Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used in treating adults such as ETV, DRV and RAL may be possible (for details on using these drugs in children, see Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

Clinical considerations

The criteria for diagnosing the failure of second-line ART are the same as those used for diagnosing the failure of first-line ART. The demand for second- and third-line regimens will increase as access to viral load monitoring improves and first-line ART continues to be scaled up. Although developing a policy on access to third-line ART is desirable, it should not compromise access to initiation of first-line ART. The costs of potential third-line drugs, such as DRV, ETV and RAL, are not well established in resource-limited settings but are expected to be higher than those of first- and second-line regimens.

Key research gaps

Many areas require more information to guide second- and third-line ART for resource-limited settings, including monitoring critical outcomes for people receiving second-line ART, studying once-daily dosing for DRV/r and RAL as an alternative to NRTI-based regimens in second-line ART, and developing heat-stable formulations of DRV/r. Pharmacovigilance research is needed, including studies on the long-term safety and potential drug–drug interactions with TB, malaria, hepatitis and opioid substitution therapy drugs. As the epidemic matures in low- and middle-income countries, pilot studies are urgently needed on implementing third-line ART in settings with limited capacity and resources in the health system.