

CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY

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4 CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY

4.1 Preparing people living with HIV for ART

Before people start antiretroviral therapy (ART), health-care providers should initiate a detailed discussion about the willingness and readiness of patients to initiate ART, the antiretroviral (ARV) drug regimen, dosage, scheduling, likely benefits, possible adverse effects and the required follow-up and monitoring visits. In the case of children with HIV, this conversation should directly involve the caregiver and include discussion about disclosing their HIV status. Retesting all people living with HIV before initiating ART is recommended to ensure a correct diagnosis of HIV infection. Initiation of ART should always consider nutritional status, any comorbidities and other medications being taken to assess for possible interactions, contraindications and dose adjustment.

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

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

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

4.1.1 Accelerated ART initiation

NEW

Good practice statement

Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness.

ART initiation is often seen as a non-emergency intervention, and various approaches are used to help prepare people to begin treatment. However, there is increasing recognition of the benefits of accelerated ART initiation, for example, in pregnant women, in order to avoid unacceptably high rates of loss to follow-up after HIV diagnosis. However, concerns remain that accelerated initiation of ART may lead people to start before they are ready, with adverse consequences for adherence and treatment outcomes.

Current implementation experience of rapid ART initiation is largely derived from experience with option B+ (lifelong ART for all pregnant and breastfeeding women). Although ART initiation in these programmes is not necessarily on the same day as testing, the majority of women initiate treatment within a short space of time. Of nearly 22 000 women who started ART under option B+ in Malawi, 17% were lost to follow-up six months after ART initiation. Loss to follow-up was highest among women who began ART at large clinics on the day they were diagnosed with HIV (1).

A systematic review (2) identified two ongoing studies that evaluated accelerated ART initiation, including treatment initiation on the same day as HIV diagnosis to reduce loss to follow up. The Rapid Initiation of Antiretroviral Therapy to Promote Early HIV/AIDS Treatment in South Africa (RapIT) study randomized individuals to rapid initiation versus standard care (3). Preliminary data showed a relative risk of 1.33 of initiation of ART in 90 days, with a risk difference of 24% (73% in the standard-of-care arm compared to 97% in the rapid initiation arm). The START-Streamlined Initiation trial is examining accelerated ART initiation in Uganda (4). START components include (i) real-time point-of-care CD4 testing, (ii) targeted knowledge transfer to health-care workers and (iii) feedback and reporting to the clinic and providers.

Findings from community consultations show that early ART initiation is acceptable, but universal same-day ART initiation following HIV diagnosis is considered to be challenging because of the wide variation in individuals' understanding of the implications of test results and preparedness to commence lifelong treatment (5). There is a perceived difference in motivation to start ART when sick compared to when healthy.

While these guidelines recommend initiation of ART in all people with HIV regardless of CD4 cell count or disease stage, and preliminary data suggest that accelerated ART initiation is possible, the available data are currently inadequate to support a recommendation in these guidelines in favour of same-day or otherwise accelerated ART initiation.

The following principles may inform future guidance.

- Treatment should be started based on a person's informed decision to initiate ART.
- Interventions to remove barriers to ART initiation once an individual is diagnosed HIV positive should be implemented.
- HIV programmes should promote treatment literacy among all people with HIV, including information on the benefits of early treatment, the lifelong commitment required, the risks of delaying treatment and available adherence support.
- Care providers should be trained to support shared decision-making.
- Although ART initiation is rarely urgent, it may need to be expedited in certain circumstances, such as serious ill health and for pregnant women in labour whose HIV test result is positive.


4.2 What to expect in the first months of ART

Although ART is a lifelong commitment, the first months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but opportunistic infections (OIs) and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of treatment. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are most common when the people starting ART already have advanced HIV disease with severe immunodeficiency and existing coinfections and/or comorbidities, severely low haemoglobin, low body mass index and very low CD4 cell counts or are severely malnourished (6,7). Poor adherence in this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

4.3 When to start ART

4.3.1 When to start ART in adults (>19 years old)

Recommendation

- **ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence).** 
- As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤ 350 cells/mm³ (strong recommendation, moderate-quality evidence).

Sources:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization 2015 (<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en>).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Since they were first published in 2002, WHO guidelines on ART have evolved as the body of evidence to support earlier initiation of ART has grown (8). The 2013 WHO ARV guidelines recommended initiating ART for all adults with HIV and a CD4 count at or below 500 cells/mm³, regardless of WHO clinical stage, giving priority to those with severe or advanced HIV disease (WHO clinical stage 3 or 4) or a CD4 cell count at or below 350 cells/mm³ (9). This strong recommendation was based on moderate-quality evidence from three randomized controlled trials (10–12) and 21 observational studies (13–34), showing that initiating ART at or below a CD4 threshold of 500 cells/mm³ compared with later initiation reduced the risk of progression to AIDS and/or death, TB and a non-AIDS-defining illness and increased the likelihood of immune recovery. In addition, high-quality evidence from one randomized controlled trial indicated that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners in heterosexual couples (11).

Mathematical models and ecological studies also suggested that initiating ART earlier could affect HIV incidence at the population level if there is high uptake and sustained HIV testing, ART coverage and retention (35–39). For people with certain clinical conditions – TB, hepatitis B virus (HBV) coinfection requiring HBV treatment and during pregnancy and breastfeeding – and for HIV-serodiscordant couples, the 2013 guidelines recommended initiating ART regardless of WHO clinical stage or at any CD4 cell count.

Global ART coverage for all people living with HIV had reached approximately 41% – or 15 million people – by March 2015 (40). According to the WHO Country Intelligence Database, by June 2014, 60% of the 58 WHO HIV focus countries had adopted the CD4 threshold of 500 cells/mm³ or less for initiating ART and 7% had already moved the CD4 threshold to above 500 cells/mm³ (41). Although the median CD4 count at the time of ART initiation is increasing, it remains significantly lower than 350 cells/mm³ in almost all settings, including high-income countries (42,43). Late presentation for treatment is associated with high early mortality rates, higher direct health-care costs and poor retention in care (44–46). Increasing knowledge of HIV status, strengthening links between testing and care, modifying health systems to manage patient volumes and ensuring optimal long-term retention and adherence remain significant challenges in many settings (47).

Rationale and supporting evidence

Initiating ART among all adults living with HIV regardless of WHO clinical stage or at any CD4 cell count

Since 2013, evidence and programmatic experience have continued to favour earlier initiation of ART because it results in reduced mortality, morbidity and HIV transmission outcomes. Increasing evidence from systematic reviews and cohort analyses also indicates that untreated HIV infection may be associated with the development of several non-AIDS-defining conditions, including cardiovascular, kidney and liver disease, several types of cancer and neurocognitive disorders (48–51), and that initiating ART earlier reduces such events and improves survival. Recent evidence from a large randomized controlled trial also shows that, as demonstrated for heterosexual serodiscordant couples, ART substantially reduces sexual transmission to HIV-negative sexual partners among homosexual couples (52).

The recommendation to initiate ART at any CD4 cell count was based on a systematic review with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) evidence profiles that assessed the quality and strength of the evidence from one randomized controlled trial (53) and 17 observational studies (18,19,22–26,28,30,34,37,54–59) reporting clinical, immunological) reporting clinical, immunological and virological outcomes and HIV transmission.

In the analysis of data from the single randomized controlled trial (TEMPRANO), moderate-quality evidence (downgraded from high quality because of imprecision) showed that initiating ART at a CD4 cell count above 500 cells/mm³, in the absence of other treatment indications, leads to less severe HIV morbidity (combined outcome of death, AIDS and severe non-AIDS diseases such as malignancies and bacterial diseases) compared with treatment initiation at a CD4 cell count at or below 500 cells/mm³ (53).

Data from another randomized controlled trial (START study), although supportive of the new recommendations, were unpublished at the time of the Clinical Guideline Development Group meeting for these guidelines (60). The START study was planned for completion in 2018, but after an interim analysis in mid-2015, the trials Data Safety Monitoring Board advised immediate dissemination of the findings because of predefined stopping rules. Data from this study could not be incorporated into the systematic review or GRADE table because the comparison groups did not match the review population, intervention, comparator and outcome question (PICO) and therefore could not be considered in relation to the quality of the evidence. Box 4.1 summarizes the study's key findings.

Box 4.1. Strategic Timing of Antiretroviral Treatment (START) study

The study enrolled 4685 people with CD4 counts higher than 500 cells/mm³ at 215 sites in 35 countries. Twenty-seven per cent of the participants were women and approximately half were men who have sex with men. The study examined the rates of serious AIDS-defining illness or death among people who were randomized to receive immediate ART versus deferred ART (until their CD4 count dropped below 350 cells/mm³). The median baseline CD4 count was 651 cells/mm³ in the intervention group that initiated ART at enrolment. In the deferred group, the median CD4 count at ART initiation was 408 cells/mm³. Follow-up lasted for a mean of 3 years. A total of 86 events (death, serious AIDS events and serious non-AIDS events) occurred among those with later treatment initiation, whereas 41 events occurred among those who started ART immediately, representing a 57% reduction in negative outcomes among those treated early. In both groups, most events occurred when CD4 counts were higher than 500 cells/mm³. The study also showed that immediate ART reduced both serious AIDS-related and serious non-AIDS-related events, but the benefit was greater for AIDS events. TB, Kaposi sarcoma and lymphoma – the most common AIDS-related events – all occurred less frequently in the immediate ART group. Cancer rates (combined AIDS and non-AIDS malignancies) were lower in the immediate ART group, but cardiovascular disease rates were similar between the groups. The occurrence of drug-related adverse events was not significantly different between the two groups. These effects were consistent in countries at different income levels and across geographical regions.

Analysis of the observational studies found a significantly lower risk of HIV disease progression (57), and modelling from the TEMPRANO randomized controlled trial data demonstrated the potential lower rates of HIV transmission to uninfected partners (53), but the evidence was rated as very low quality in both cases. However, interim data from the HPTN 052 clinical trial indicated that early ART is highly effective in preventing the sexual transmission of HIV (61). Similar to the START trial, relevant data from the HPTN 052 were unpublished at the time of the guidelines review meeting and were not incorporated into the systematic review due to a different comparator from that of the review. Box 4.2 summarizes these data.

Box 4.2. The HIV Prevention Trials Network (HPTN) 052 study

HPTN enrolled 1763 HIV serodiscordant couples from 13 sites in nine countries and followed them for approximately four years. Ninety-seven per cent of the couples were heterosexual. The HIV-positive partners in the participating couples were randomly assigned to immediate ART initiation or ART initiation was delayed until their CD4 counts fell below 250 cells/mm³ or they were diagnosed with an AIDS-related illness. All participants in both groups received counselling on safe sex practices, free condoms, treatment for sexually transmitted infections (STIs), frequent HIV testing and evaluation and treatment for any complications related to HIV. The median CD4 count at study entry was 436 cells/mm³. Seventy-eight initially HIV-negative partners became infected with HIV and 46 of 70 (66%) had their linkage status confirmed, i.e. their HIV infection could be linked to the HIV-positive partner using phylogenetic analysis.

Three of the 46 linked infections occurred in the early ART arm and 43 in the delayed ART arm, leading to a 93% risk reduction for linked transmissions. In the final analysis, all linked partner infections that were diagnosed after ART initiation occurred when the virus was not suppressed by the treatment regimen (four from a total of eight cases). There were no linked partner infections when the HIV-positive partner's virus was stably suppressed by ART. The results show that ART is highly effective at preventing the heterosexual transmission of HIV if viral suppression is achieved and maintained.

Moderate-quality evidence from the TEMPRANO trial showed that initiating ART at a CD4 count above 500 cells/mm³ was not associated with an increased risk of grade 3 or 4 adverse events (53). Low-quality evidence from observational data showed an increased risk of any severe laboratory adverse event and hepatic adverse events in individuals initiating ART at a CD4 count above 500 cells/mm³, although this was not associated with treatment discontinuation (55).

Programmatic data from several countries that are offering earlier ART either to all people living with HIV or to specific populations have shown significant increases in ART uptake and linkage to care, reduction in the time between HIV diagnosis and ART initiation regardless of baseline CD4 cell count and an increase in the median CD4 value at ART initiation. Retention in care has not differed between individuals who start at CD4 counts above 500 cells/mm³ compared with those whose initiation to ART was based on the standard of care (62–64).

Initiating ART among adults with severe or advanced HIV disease or with a CD4 count at or below 350 cells/mm³ as a priority

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 cell counts. The strength and quality of evidence for this recommendation established in the 2010 WHO guidelines on *Antiretroviral therapy for HIV infection in adults and adolescents* (65) remains unchanged. Moderate-quality evidence from two randomized controlled trials and several observational studies shows that initiating ART at CD4 counts at or below 350 cells/mm³ significantly reduces mortality, disease progression and the incidence of OIs, especially TB and non-AIDS-defining conditions (66). Furthermore, several studies and programmatic data suggest that late diagnosis (often defined as a CD4 count at or below 350 cells/mm³) and late treatment initiation are very common, even in high-income settings (67,68).

Comparing benefits and harm

The benefits of earlier ART initiation include fewer events caused by severe HIV morbidity and disease progression, improved uptake and initial linkage to care, better immune recovery and decreased HIV transmission. Despite being statistically significant, the comparative outcome differences among study arms with higher baseline CD4 cell counts (e.g. CD4 counts between 350 and 500 cells/mm³, compared to those with CD4 counts over 500 cells/mm³) were modest. Furthermore, not all observational studies have consistently demonstrated the beneficial effect of initiating ART at a CD4 cell count at or above 500 cells/mm³ on mortality, the incidence of inflammation-related non-AIDS events and ongoing viral replication, compared with initiation at CD4 count at or below 500 cells/mm³. Concerns have also been expressed that, given limited resources, very early treatment could result in some people who urgently need treatment being displaced by those for whom treatment would be beneficial but is less urgently needed. The long-term safety profile of ART and the implications of earlier treatment initiation on drug resistance, toxicity, adherence and retention need to be closely monitored. Follow-up will be needed to evaluate the potential harm and benefits of ART over a lifetime.

It is increasingly recognized that, in settings with a high burden of HIV and TB infections, increasing ART coverage is associated with decreasing TB case notifications, and this is likely to improve when ART is started earlier.

A modelling study based on national cohort data from four countries in sub-Saharan Africa concluded that programmatic gains and mortality reduction were accrued by eliminating the pre-ART period, suggesting that making treatment available to everyone will strengthen the continuum of care (69).

Cost and cost-effectiveness

The same modelling study indicates that expanding the ART eligibility criterion to above 500 cells/mm³ or regardless of CD4 cell count and linking to HIV care could result in 6–14% fewer people dying from HIV-related causes during the next decade (69). In this study, the majority of the impact is caused by programmatic simplification, leading to more people initiating ART in a timely manner and therefore avoiding adverse outcomes during the pre-ART period rather than direct therapeutic benefits. The increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing people from acquiring HIV

infection. The modelling suggests that such a change is likely to be cost-effective in many settings if individuals initiating ART are adherent to treatment and retained in care. Costs will increase significantly but will be far less than if the additional outreach interventions required for maintaining people in pre-ART care are also included.

According to estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS), expanding ART to all people living with HIV is projected to avert 21 million AIDS-related deaths and 28 million new infections by 2030 (70). However, these benefits require high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The cost implications at the regional and country levels can also vary and should be further explored, as countries have different levels of current treatment coverage and local cost considerations, depending on their context and resources.

Equity and acceptability

Disclosure of HIV status is essential for accessing adherence support and may be particularly difficult for people who have never been ill. For this reason, initiating ART among adults with severe or advanced HIV disease or with a CD4 count at or below 350 cells/mm³ is recommended as a priority in these guidelines. Additional concerns that mandatory or coercive approaches will be used among at-risk marginalized populations highlight the importance of adequate patient information, informed consent, appropriate health worker training and rights-based legal frameworks to facilitate access.

A community-led global consultation examined the acceptability of earlier initiation of ART at a higher CD4 count for people living with HIV, caregivers and service providers and found that earlier initiation was considered acceptable (5). Participants in the consultation emphasized the need for collaborative decision-making with service providers to ensure that the ultimate decision to initiate ART rests with the person living with HIV. Motivation to start and adhere to treatment may be more difficult for people who feel well and have higher CD4 counts than for people who are or have been ill. Stigma and discrimination continue to act as barriers to treatment access and adherence. Critical factors in promoting ongoing engagement in care and adherence include ensuring a stable supply of free or affordable ARV drugs, facilities that are easily accessible and that ensure confidentiality, sympathetic providers and appropriate adherence support.

A qualitative literature review showed that acceptability of earlier treatment is greater when people know that treatment reduces mortality risk. Service providers recognize the clinical and preventive benefits of earlier ART and the need for earlier ART initiation for asymptomatic people. Among people living with HIV, acceptance increases when they also have comorbidities or conditions associated with a higher risk of HIV transmission. Issues cited in the literature supported those identified in community consultations (71).

Feasibility

According to cohort and national programme data, the number of people needing treatment could increase by up to 35% if ART is initiated at any CD4 count rather than at or below 500 cells/mm³ (70). Modelling estimates predict that this increase would be lower, in the range of 7–21% over five years, because not all people living with HIV are diagnosed and therefore, unlikely to initiate care and treatment immediately. 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 number of people who

actually access treatment unless there is also increased uptake of HIV testing, stronger linkage to care, adequate treatment monitoring and sustained adherence support. Late presentation for treatment is still common, with the median CD4 count at ART initiation being below 350 cells/mm³ in the majority of settings, including in high-income countries (66,67).

Implementation considerations

Regardless of the epidemic profile and disease burden, priority should be given to people with symptomatic HIV disease or with a CD4 count at or below 350 cells/mm³ who are at high risk of mortality and most likely to benefit from ART in the short term.

Initiating ART at CD4 counts above 500 cells/mm³ may involve the need for additional human, infrastructure and financial resources. Countries have different health system capacity and are at different levels of ART coverage and programme quality. A phased approach to implementation may be needed, especially in settings with a high burden of HIV, low ART coverage, low rates of testing, modest pre-ART care, scarce human resources, limited laboratory capacity, budget constraints and/or competing health priorities. In such settings, equity considerations and giving priority to those who most need treatment should guide implementation (see section 8.2 “Dissemination and implementation”).

The increased need for ART associated with early initiation may place demands on the health system in some settings, which could increase the risk of drug resistance, such as drug stock-outs, insufficient patient preparation and suboptimal adherence. To maximize the long-term effectiveness of first-line ART regimens and ensure that people are taking the most effective regimen, the scaling up of ART should be accompanied by measures to monitor and improve service quality at the site and programme levels (see sections 6.12 “Improving the quality of HIV care services” and 6.13 “Procurement and supply chain management”).

In all settings, continued monitoring will be needed of the long-term safety profile of ARV drugs, and the implications of earlier initiation for drug resistance, toxicity and adherence. It also remains essential to address the structural and social barriers to accessing treatment faced by key populations, such as criminalization, stigma and discrimination (72–74).

Research gaps

Several ongoing implementation trials are evaluating the feasibility, acceptability, cost-effectiveness and impact of immediate treatment for all people living with HIV regardless of CD4 cell count at the population level (SEARCH and MaxART studies) (75,76). Primary outcome results are not expected before 2017 or 2018. Three large randomized trials are examining the population effect of early ART initiation on HIV incidence and mortality (Botswana Combination Prevention Trial, HPTN-071 [PopART] study and 12249 ANRS TasP trial), with results expected after 2016 (77–79).

Other research priorities include assessing the incidence of short- and long-term severe adverse events as a result of increased exposure to ART, barriers to and enablers of adherence and long-term retention in care, the impact of early initiation of ART on the cascade of care and the magnitude of the prevention benefit, especially among key populations and adolescents.

4.3.2 When to start ART in pregnant and breastfeeding women

NEW

Recommendation

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).

Source: HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/adolescents/en>).

Background

Programmes for the prevention of mother-to-child transmission (PMTCT) were some of the earliest public health interventions that used ARV drugs to reduce the risk of acquisition of HIV. Initially, the regimens recommended by WHO were short courses or single doses of ARV drugs given to the mother and to the infant in the first few days of life. With the scaling up of national HIV programmes from 2003, WHO guidelines made an important shift, recommending that pregnant women living with HIV should be assessed for treatment eligibility and those considered eligible for treatment should be offered lifelong combination ART for their own health, while those who were not eligible should receive short courses of ARV prophylaxis for PMTCT. Although eligibility criteria have changed and the preferred regimens for ART and for PMTCT prophylaxis have evolved, this distinction between treatment and prophylaxis became a fixture of PMTCT programmes.

In 2013, the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9) recommended that all pregnant and breastfeeding women should be initiated on ART regardless of clinical eligibility. This recommendation was supported by programmatic experience (including from Malawi, which has pioneered universal ART access for all pregnant women), demonstrating that prophylaxis for PMTCT (using different drugs at different times in the course of pregnancy, labour and delivery, as well as long duration of infant prophylaxis while breastfeeding) was more challenging to implement in the field than giving ART to all pregnant women (especially if the ART regimen was a once-daily fixed-dose combination tablet). However, the 2013 WHO guidelines (9) still offered programmes the option to either continue ART lifelong in all women (option B+) or to stop ART after the period of mother-to-child transmission risk in women who did not otherwise meet eligibility criteria (option B). Option B+ was considered to be of the greatest benefit in settings with a high HIV prevalence, high fertility and long duration of breastfeeding, in which initiating ART in all pregnant and breastfeeding women would reduce HIV incidence and prevent HIV transmission in both current and future pregnancies.

Following the release of the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9), many countries adopted option B+ as the preferred approach for PMTCT programmes in both high- and low-prevalence settings. The 2014–2015 Global AIDS Response Progress Report showed that the majority of countries, including almost all the 22 high-priority countries included in

the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (80) are now either piloting or implementing lifelong ART for all pregnant and breastfeeding women living with HIV at a national scale. A readiness assessment checklist includes guidance for countries planning this transition (Annex 9).

Increasing evidence to support earlier ART initiation among all adults, together with widespread uptake of option B+ and emerging programme data on its success in practice, all support a revised recommendation in 2015 that moves away from “options” for PMTCT and instead advocates that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment, regardless of clinical or CD4 cell count or stage of disease.

Providing ART to all pregnant and breastfeeding women living with HIV serves three synergistic purposes: (i) improving the mother’s health; (ii) preventing mother-to-child transmission of HIV; and (iii) preventing the transmission of HIV from the mother to a sexual partner. It is important to note that these recommendations are relevant for all epidemic settings, although implementation will be context specific. Because ART has individual health benefits for all individuals living with HIV, the recommendation applies to both breastfeeding and non-breastfeeding populations.

Rationale and supporting evidence

The evidence on options B and B+ and the clinical and immunological impact of stopping ART among postpartum women was reviewed by the Clinical Guideline Development Group in the context of increasing data showing the benefit of ART at all stages of HIV disease and the recommendation to initiate ART among all adults with HIV at any CD4 cell count.

A systematic review (81) compared option B and option B+ in terms of maternal health outcomes. The review did not identify any randomized controlled trials or observational studies that directly compared the outcomes of options B and B+. However, 18 studies reported on option B outcomes – comprising four randomized controlled trials (82–85), three single-arm trials (86–88) and 11 cohort studies (89–99) – and 10 cohort studies reported on outcomes associated with option B+ (100,101–108). All the studies evaluating option B+ suggested that women experienced health benefits in terms of immunological and clinical parameters. None of the studies included in the review reported on how option B+ affected HIV transmission rates to partners, although this is an important likely benefit for women who remain on lifelong ART.

As the key difference between option B and option B+ is not when ART is started but whether it is stopped, literature on the clinical and immunological impact of stopping ART among women during the postpartum period was also evaluated in a separate review. Five cohort studies and one randomized controlled trial were identified, which examined changes in clinical and immunological parameters following discontinuation of ARV drugs. The majority of these studies used the historical threshold (2010 recommendations) for ART eligibility of CD4 count below 350 cells/mm³, and in several cases, mothers were receiving ARV prophylaxis rather than ART, but all showed a gradual decline in immune function after ARV drugs were stopped. Using the time frame of six months after discontinuation, 6–20% of women with a baseline CD4 count below 500 cells/mm³ had reached the eligibility threshold of 350 cells/mm³. A lower baseline CD4 count was also associated with a 2.5-fold higher risk of WHO stage 2 or 3 clinical events (109).

Apart from the impact on clinical and immunological outcomes, there are programmatic consequences of stopping ARV drugs among postpartum women. In one cohort study from Malawi, loss to follow-up post delivery was much higher in women with a baseline CD4 above 350 cells/mm³ (who were not eligible for treatment) than those with a CD4 below 350 cells/mm³ (who were eligible and started on ART) (110). The findings were similar in a South African cohort where the women who were considered ineligible for ART were twice as likely to be lost to follow up at six months postpartum as the women who had started treatment (111). A key challenge to implementation of option B is the difficulty of distinguishing between those who were eligible for lifelong treatment and those who were not, prior to initiation of ART.

An increasing body of evidence demonstrates the advantages of lifelong ART for pregnant and breastfeeding women and adds to the compelling data from randomized controlled trials (53,60) suggesting that all adults with HIV benefit from ART at any CD4 cell count, regardless of their clinical stage of disease.

Comparing benefits and harm

The majority of countries are moving to adopt universal ART for all pregnant and breastfeeding women. The benefits include improved health outcomes, lower rates of mother-to-child transmission and the potential for reduction of horizontal transmission of HIV. Although there is no documented evidence for this reduction in horizontal transmission, rates of partner serodiscordance are high. In one study among couples in five African countries, between 30% and 40% of women living with HIV were in serodiscordant relationships (112). In a recent demographic health survey in Kenya, rates of discordance were reported to be above 50% (113). Another important potential benefit of universal ART for pregnant and breastfeeding is that women may be less likely to drop out of care after the end of the transmission risk period and may avoid some of the clinical and operational complexities of repeated cycles of stopping and starting ART in subsequent pregnancies.

The possible harm of offering lifelong ART to all pregnant and breastfeeding women living with HIV (as opposed to only those who are “eligible”) includes the potential for cumulative drug toxicity and the possibility of poor adherence with long-term use, leading to the development of drug resistance. In general, these risks for pregnant and breastfeeding women are similar to those for non-pregnant adults. Pre-conception ART may be associated with added risks related to both the outcomes of pregnancy and newborn morbidity. To date, no evidence suggests a significantly increased risk of congenital anomalies associated with the currently recommended first-line ARV drug regimens (114). Special considerations for toxicity monitoring for pregnant and breastfeeding women are discussed in section 4.6.6 “Monitoring of and substitutions for ARV drug toxicities”.

Overall, the health benefits of universal ART for pregnant and breastfeeding women outweigh potential harm, but the decision to initiate treatment remains a personal one that must be made on the basis of informed consent.

Feasibility and resource use

As with all populations, the costs associated with implementing universal ART for pregnant and breastfeeding women will require increased resources, especially in the

short term. In a cost-modelling exercise, the total cost (including drugs, diagnostics and service delivery) of keeping a woman on option B+ was estimated at US\$ 2069 over five years (115). However, as maintaining a woman off ART also incurs costs for monitoring and follow-up, the incremental cost of moving from option B to option B+ was relatively low and varied between US\$ 92 and US\$ 605, depending on the baseline CD4 cell count and breastfeeding status. Several model-based analyses have assessed the cost-effectiveness of strategies for PMTCT of HIV, with many finding options B and B+ to be cost saving or highly cost-effective compared with option A (AZT for the mother during pregnancy, single-dose NVP plus AZT and 3TC for the mother at delivery and continued for a week postpartum and 6 weeks of infant NVP prophylaxis). When outcomes beyond the mother-to-child transmission of HIV are considered, such as maternal health, preventing the mother-to-child transmission of HIV in future pregnancies and preventing horizontal transmission, option B+ has been found to be highly cost-effective compared with option B (116,117).

Equity and acceptability

A qualitative literature review on the acceptability of option B+ indicated high acceptability of lifelong ART among pregnant and breastfeeding women as well as service providers (71). Women have raised concerns of ARV drug toxicity for themselves and their infants but generally value the health benefits and the ability to protect their children and their partners from HIV (118,119). The review also highlighted some of the challenges of lifelong treatment, including disclosure to partners and employers, stigma, lack of support, and costs and time off work associated with clinic visits and drug pickups.

Early programme experience from South Africa suggests that pregnant women find same-day initiation of ART (starting ART on the day of HIV diagnosis) acceptable, especially because in this setting, many women may already be aware of their status, have high levels of treatment literacy and can access support services (120). By contrast, same-day ART initiation in Malawi during the early years of the roll-out of option B+ was associated with a high rate of early loss to follow-up, with many women failing to return for a second visit (1). For national programmes, it is important to strike a balance between starting pregnant women without delay and ensuring that women are adequately prepared, have accepted lifelong ART and have access to support systems, including peer support, to promote treatment adherence.

Although universal ART for all people living with HIV is generally acceptable, there are legitimate concerns about access to lifelong treatment, the limited range of treatment options and the long-term sustainability of ART. As countries implement these recommendations, the right of women to informed consent for all medical services – including the initiation of ART – remains paramount. An approach to ART that is rights based and that offers women the opportunity to make an informed decision will probably result in better acceptability and improved health outcomes.

Implementation considerations

Many concerns raised about the recommendation to provide lifelong ART to all pregnant and breastfeeding women relate to implementation. Although routine testing in antenatal care settings is well established and continues to be recommended by WHO, the goal should be to test pregnant woman at the first antenatal care visit in order to maximize the benefit of early ART. When implementing this recommendation, programme managers

must ensure the quality and accuracy of HIV testing, including retesting all women who test positive prior to initiating ART. Newly diagnosed women should be counselled about the benefits of lifelong treatment as well as the importance of adherence and regular follow-up. Although ART should be initiated without delay, it is important to allow women to make an informed choice. Experience from Malawi and other national programmes that were early adopters of option B+ shows that ART services can be effectively decentralized and provided within maternal, newborn and child health clinics (see section 6.10.1 “Delivering ART in maternal and child health-care settings”).

Integration of services benefits mothers and their infants, and is feasible in settings with a high burden of HIV. However, achieving integration will depend on the context and the resources available in terms of staff time and physical space. In one retrospective cohort study from Malawi, 45% of the women interviewed reported that, although they started ART in an antenatal care clinic, they were referred to separate ART services soon after delivery (106). There is no consistent model for when to transition mothers on ART out of maternal, newborn and child health services, but a cohort study (121) from South Africa highlighted the importance of this potential additional loss point in the care cascade. In a retrospective review of women referred to ART clinics in the postpartum period, up to 25% did not remain in care five months after referral (121). Roll-out of universal ART for pregnant women should be accompanied by messaging and outreach to the community to underscore the benefits of ART even for asymptomatic people and the importance of remaining in follow-up even after the period of risk for mother-to-child transmission has passed. Such messaging should be harmonized with messages for early treatment initiation for all individuals living with HIV.

Although treatment monitoring using viral load is important for all people on ART, it may be especially valuable for pregnant and breastfeeding women for whom there is added benefit in terms of PMTCT. In these guidelines, enhanced ARV prophylaxis is recommended for HIV-exposed infants at higher risk of acquiring HIV. A maternal viral load above 1000 copies/mL during the last few weeks before delivery is a reliable determinant of increased transmission risk. Viral load testing during pregnancy would be a useful tool for clinical decision-making, and as viral load testing is introduced on a national scale, pregnant and breastfeeding women should be prioritized for access.

In addition to issues related to service delivery, key considerations for national programmes include the need for strengthened data systems to track women on ART across multiple delivery sites, better laboratory support including access to viral load testing and targeted interventions to improve adherence and retention (see sections 6.4 “Linkage from HIV testing to enrolment in care”, 6.5 “Retention in care” and 6.6 “Adherence”). Women who commence lifelong ART, especially those with young children, may face considerable challenges in seeking regular HIV care and maintaining adherence to treatment regimens. Efforts to scale up treatment require a holistic approach to women’s lives and parallel investments in community-based support to improve women’s treatment literacy, preparedness and ability to remain in follow-up and adhere to treatment.

Research gaps

Significant knowledge gaps remain about how best to implement universal ART and how to address the challenges of retention and follow-up of the mother and infant pair. The

integration of ARV drug delivery in antenatal care and maternal, neonatal and childcare services (as opposed to referral to ART clinics) requires further implementation experience and assessment. Over time, an increasing proportion of women living with HIV will already be on ART prior to conception. This provides an opportunity to understand the impact of this shift in the epidemic on rates of mother-to-child transmission as well as other pregnancy outcomes, including preterm delivery and low birth weight.

Adolescents and young women living with HIV face unique challenges in preventing the transmission of HIV to their children and attending to their own health needs, including poor access to reproductive health services, poor uptake of testing and poor retention in care (122). Implementation research is urgently needed to identify the drivers of poor outcomes among adolescents, to define how adolescent-friendly maternal and newborn health services should be provided and to develop specific strategies to improve retention in care.

Although ART during pregnancy and breastfeeding provides clear public health benefits in terms of maternal health and preventing transmission to the child, the possible effects of ART (especially preconception ART) on pregnancy outcome require future research. In addition, the potential long-term harm of fetal and infant exposure to maternal drugs is not fully understood. The risk of congenital birth defects is likely to be low for the currently recommended first-line ARV drugs, but little is known about newer drugs and the possible effects on growth, development and organ maturation resulting from exposure to ART absorbed across the placenta and through breast milk.

4.3.3 When to start ART in adolescents (10–19 years of age)

NEW

Recommendations

- ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence).
- As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤ 350 cells/mm³ (strong recommendation, moderate-quality evidence).

Source:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en>).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

An estimated 2.1 million adolescents (10–19 years old) were living with HIV globally in 2013. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second-leading cause of death among adolescents worldwide (123).

Adolescence is marked by rapid physical, neurodevelopmental, emotional and social changes (124). Although accurate global data are lacking on mortality due to HIV in this

age group, adolescents appear to be underserved by current HIV services. They have significantly worse access to and coverage of ART than adults, high risk of loss to follow-up (125–127), suboptimal adherence, and special requirements for comprehensive care, including psychosocial support, and sexual and reproductive health care (128–130). Adolescents also face significant barriers to accessing essential health and support services, especially because of policy and legal barriers related to the age of consent (131).

Perinatally infected adolescents are more likely to experience chronic diseases and neurodevelopmental growth and pubertal delays in comparison to their age-matched peers. Older adolescents who acquire HIV behaviourally do not present the same clinical features but face potentially greater challenges in dealing with stigma and lack of family and community support to access care.

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9) aligned the clinical and immunological criteria for ART eligibility among adolescents with those for adults (treatment initiation for WHO clinical stage 3 or 4 disease or at a CD4 count at or below 500 cells/mm³) with the aim of enhancing programmatic simplicity and avoiding delays in treatment initiation while assessing eligibility.

Rationale and supporting evidence

The review of evidence, programmatic data, operational considerations and values and preferences expressed by young people living with HIV led to the development of a separate recommendation for adolescents in 2015. This highlights the important considerations of initiating ART and providing treatment and care for adolescents living with HIV.

The recommendation is based on the strong operational and programmatic advantages of alignment with the criteria for initiating ART among adults and children and the clinical benefits demonstrated by evidence from adult studies (53). There are some limitations in extrapolating from the evidence for adults or children and some uncertainty around the potential benefits that immediate initiation of ART may have on adolescent health outcomes, given the unique challenges that may arise in achieving long-term adherence and retention among adolescents.

A systematic review of the evidence did not identify any studies investigating ART initiation strategies specific to adolescents. This subgroup was also not captured by adult studies that assessed the clinical outcomes of immediate versus delayed ART initiation (132,133). For this reason, the overall quality of the evidence for treating all adolescents living with HIV was rated as low, as indirect evidence from adults was used.

To assess the potential benefits of starting ART earlier, a causal modelling of data from southern and western Africa and Europe was conducted. This examined 4553 ART-naïve perinatally infected adolescents 10–15 years of age (median age 12.4 years), of whom 14% presented with CD4 counts above the existing eligibility thresholds of 500 cells/mm³. In the analysis, median follow-up time was 656 days. Mortality appeared higher when ART was started very late. However, after four years of follow-up, the difference between immediate ART versus initiating ART at or below 500 cells/mm³ was not significant. These differences were similar for the adolescents who presented with a

CD4 count above 500 cells/mm³. Overall, the study did not show any clear survival or growth benefit from early initiation of treatment in this population (134).

Indirect evidence shows that perinatally infected adolescents for whom treatment initiation is delayed to 10 years of age are unlikely to normalize CD4 cell count (135) and, after onset of chronic lung disease, do not fully recover lung functioning (136), suggesting that perinatally infected adolescents who have survived through childhood untreated may have limited gains from initiating ART earlier compared with initiating treatment in younger children.

The high risk of loss to follow-up in this age group, particularly among adolescents aged 15–19 years (137–141), is an important factor in assessing the trade-off between the risks and benefits of earlier ART initiation. Adolescents are also known to have lower rates of adherence than adults and younger children (142). Two systematic reviews on adherence and viral suppression showed varying rates for adolescents (143,144), and treatment failure was observed among 10% of 1007 perinatally infected children in a multicohort analysis, with the risk being higher with a longer time on ART and when treatment was started in adolescence (145).

While indirect evidence was extracted from paediatric cohort studies for perinatally infected adolescents, no data were found that specifically addressed the key clinical features of behaviourally infected adolescents with regard to timing of ART initiation.

Clinical evidence in support of earlier treatment initiation for both perinatally and behaviourally infected adolescents is limited. Although there is a potential for ARV drugs to have adverse effects on bones, brain and other organs still in development and concerns about the risk of drug resistance due to poor adherence, experience to date suggests that aligning with the initiation criteria for adults will contribute to simplifying programming and further expanding ART coverage (146). It would also present crucial opportunities to engage adolescents living with HIV in care.

Equity and acceptability

In community consultations, adolescents, service providers, parents and caregivers emphasized the importance of ensuring that priority be given to adolescents most in need of treatment as well as the challenge of adherence (5,147–149). The key challenges identified included forgetting to take medicines, having unstable lives that are not conducive to taking daily medication, fear of disclosure and relative lack of power in treatment decision-making. This further highlights the importance of better and more tolerable formulations to support successful treatment.

Feasibility and resource use

Earlier initiation of ART among adolescents is likely to be feasible within existing health systems. Because of late diagnosis (150), many adolescents are already likely to be eligible based on the WHO 2013 initiation criteria, and the increase in the overall number of adolescents starting treatment would therefore be relatively small (147). Increased patient enrolment would nevertheless increase demands on supply chains and provider workload. The experience of some national programmes has shown that, although all adolescents aged 10–15 years can be treated, challenges include ensuring that commodities are available, strengthening laboratory systems and conducting provider training (148).

Increased demand for commodities, human resources and infrastructure is expected to require additional funding. A costing analysis shows that ARV drugs are likely to be the most significant cost driver (151). Laboratory commodities are likely to be the second largest contributor to total cost, followed by human resources and co-trimoxazole.

Implementation considerations

Ensuring that adolescents are diagnosed and receive ART in a timely manner will require developing adolescent-friendly health services (see section 6.11 “Delivering HIV services to adolescents”), appropriate provider training and programmes that strongly emphasize support for adherence and retention in care, including through peer support. Specific challenges faced by adolescent girls, such as stigma and gender inequality, will also need to be addressed.

Research gaps

How earlier ART initiation affects retention, adherence and selection of HIV drug resistance among adolescents with less advanced disease requires further investigation. Better-quality age disaggregation of existing cohort and surveillance data is also needed to improve understanding of adolescent-specific issues and needs.

4.3.4 When to start ART in infants and children younger than 10 years of age

Recommendations

ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:

- Infants diagnosed in the first year of life (strong recommendation, moderate-quality evidence);
- **Children living with HIV 1 year old to less than 10 years old (conditional recommendation, low-quality evidence).**



As a priority, ART should be initiated in all children ≤ 2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤ 750 cells/mm³ or CD4 percentage $< 25\%$, and children 5 years of age and older with WHO HIV clinical stage 3 or 4 disease or CD4 count ≤ 350 cells/mm³ (strong recommendation, moderate-quality evidence).

Sources:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en>).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Infants and young children living with HIV have an exceptionally high risk of poor outcomes, with up to 52% of children born with HIV dying before the age of 2 years in

the absence of any intervention (152). By 5 years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults (153,154). Improved access to early infant diagnosis (EID) has increased the identification of infants living with HIV, but rates of ART initiation among infants living with HIV – all of whom should be initiated on treatment – remain suboptimal. Overall, most children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults: 32% versus 40% globally in 2014 (155).

Diagnosing and retaining children exposed to and living with HIV in care present unique challenges because of their dependence on a caregiver. Loss to follow-up has been particularly high (156), with retention especially challenging for children who are in HIV care but not receiving ART (157).

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9) aligned clinical and immunological criteria for ART eligibility for children older than 5 years with those for adults: that is, treatment was recommended for WHO clinical stage 3 or 4 disease or CD4 cell counts at or below 500 cells/mm³. ART was also recommended for all children living with HIV younger than 5 years of age, regardless of clinical or immunological status, based largely on operational advantages. For children between 1 and 5 years of age, it was recommended that those younger than 2 years of age with WHO stage 3 or 4 clinical disease or CD4 percentage below 25% or CD4 cell count below 750 cells/mm³ be given priority. For infants younger than 1 year of age, a strong recommendation to treat regardless of clinical and immunological conditions was maintained, while recognizing the challenges of treating infants in their first 2 weeks of life because of lack of treatment options for which safe and effective dosing has been established and the lack of experience globally. Treatment is further complicated by the high rates of prematurity and low birth weight in low- and middle-income countries.

Countries with a high burden of HIV among children have rapidly adopted the WHO 2013 treatment initiation criteria (155), and some countries have decided to expand ART to all children and adolescents younger than 15 years to simplify ART delivery (158).

Rationale and supporting evidence

A review of the evidence, together with programmatic data and operational considerations, has led to revised recommendations in 2015 to initiate ART in all children with HIV, aligning the recommendation for children with the recommendations for adults and adolescents.

A systematic review (132) conducted in 2013 and updated in 2015 identified only one randomized controlled trial, PREDICT, which assessed the clinical benefit of early ART initiation among children (159). The trial enrolled 300 children (1–12 years old, median age 6.4 years) with CD4 percentage above 15% and without United States Centers for Disease Control and Prevention (US CDC) stage C disease, randomizing them to either early treatment or deferred treatment until the CD4 percentage fell below 15%. There was no difference in AIDS-free survival or neurodevelopmental outcomes between the two arms, but height gain was better among those initiating ART earlier (160).

Causal modelling (161), also updated in 2015 using a broader set of prospective data, assessed outcomes for 7358 ART-naive children 5–10 years old (median age 7.2 years), of

whom 26% (1903) presented with CD4 counts exceeding the existing eligibility threshold of 500 cells/mm³. In this analysis, after five years of follow-up, early ART showed a slight but significant mortality benefit compared to waiting for the CD4 count to fall below 500 cells/mm³. The causal modelling analysis also showed significantly better growth response among those starting ART immediately (134).

Other evidence suggests that initiating ART earlier could mitigate the negative effects of HIV infection on growth and pubertal and nervous system development (135,162–167).

Earlier initiation of ART may also promote immune recovery. In a retrospective cohort study of the long-term effects of ART on CD4 cell evolution in children receiving ART based on the 2010 WHO initiation criterion, children with a greater degree of immunosuppression at baseline did not recover enough to reach normal values (CD4% >25%) even after five years of ART, whereas the CD4 percentage among children starting ART at higher CD4 levels normalized within a year of receiving ART (168). As shown by the normalization of inflammatory markers, earlier ART initiation is also likely to reduce HIV-induced chronic immune activation, thus potentially limiting the onset of chronic lung disease and increased risk of cardiovascular disease, for which clinical correlates are still missing among children (169).

The recommendation to start ART immediately is conditional for children living with HIV from 1 to less than 10 years of age because of the paucity of evidence supporting ART initiation regardless of the clinical and immunological conditions in this population (134). However, this approach is expected to provide significant programmatic advantages, especially in settings with limited access to immunological testing, a high burden of HIV disease and low ART coverage among children.

Comparing benefits and harm

In addition to clinical considerations, earlier initiation of ART is likely to expand coverage in this age group. A rapid assessment to assess the implementation of a policy to treat all children younger than 15 years in Uganda identified a 74% increase in the number of children newly initiating ART and an increase in ART coverage among children from 22% to 32% between 2013 and 2014 (146). No drop in the testing and ART coverage for infants was noticed, and the proportion of children receiving ART at lower-level health facilities increased from 29% to 35%, suggesting that simplifying the criteria for initiating treatment could also be instrumental in effectively decentralizing ART services. In addition, the time from eligibility to ART initiation significantly decreased, suggesting that simpler initiation criteria allowed more rapid treatment initiation. Programmatic experience suggests that children receiving ART have better retention than those in care but not receiving ART (146). The retention rates in Uganda appeared to be comparable among children starting ART when eligible or with CD4 counts above 500 cells/mm³, but there was a reduction in retention at six months, highlighting the need to ensure that children and caregivers receive appropriate counselling and support to stay in care (145).

The potential harm of earlier ART initiation includes short-term side-effects that may predispose children to suboptimal ART adherence and subsequently treatment failure (170,171), along with the emergence of drug resistance and the need for second- and third-line regimens, for which options suitable for children are still limited. Treatment failure was observed in 10% of cases in the multicohort analysis, with the risk being higher the longer children are on ART and the older they are when initiating ART (145).

Increasing demands on the health system, drug stock-outs and consequent treatment discontinuation may also contribute to treatment failure and HIV drug resistance. Long-term side-effects and chronic disease may result in increased morbidity and affect the quality of life in adulthood. On balance, the likely clinical and programmatic benefits of earlier ART are likely to outweigh these potential types of harm.

Equity and acceptability

Expanding ART to every child living with HIV is expected to increase equity and be well accepted. In community consultations, the acceptability of earlier treatment for children living with HIV from the perspectives of parents, caregivers and health-care providers was based on the perceived health benefits for the child. However, psychosocial support for parents and caregivers, especially for disclosure, was highlighted as critical to facilitating initiation and improving adherence (172).

Feasibility and resource use

Implementing this recommendation is likely to be feasible, as it represents a relatively small increased burden on current health systems (146). Late diagnosis is still common (150), and an estimated 80% or more of children identified as being HIV positive would already be eligible for ART based on the WHO 2013 recommendations. However, larger numbers of children receiving ART may also lead to higher demand on supply chain systems and increased provider workload. Laboratory monitoring will need to be strengthened to monitor treatment efficacy and identify treatment failure among children. The experience of some national programmes has demonstrated that treating all children with HIV is feasible but highlights the importance of secure commodity supplies, adequate health worker training and the need to ensure sustainability of resources (146).

Increased demand for HIV commodities, human resources and infrastructure may require increased funding. A costing analysis in Zambia has shown that ARV drugs are likely to be the most significant cost driver, accounting for 81% of total costs among children 0–14 years old. Laboratory commodities were the second largest contributor to total cost, followed by human resources and co-trimoxazole (151).

Implementation considerations

As ART is expanded to all children regardless of clinical and immune status, priority for treatment should be given to certain groups of children. These include children younger than 2 years or children with WHO stage 3 or 4 disease or CD4 percentage below 25% or CD4 count at or below 750 cells/mm³ (if younger than 5 years) and CD4 counts at or below 350 cells/mm³ (if older than 5 years). This is because of their higher risk of death and rapid disease progression.

Implementation approaches should include using opportunities to deliver ART for children in maternal, newborn and child health settings (173).


Expanding ART services for children will require strategies to improve retention in care and support adherence. Careful clinical monitoring remains essential to assess the risk of treatment failure, but lack of laboratory monitoring should not be a barrier to initiating ART (174).

Research gaps

How earlier ART affects retention, adherence and potential HIV drug resistance among children with less advanced disease requires further investigation. Optimal service delivery models are also needed to ensure rapid identification of and ART initiation among HIV-infected infants and children as well as strategies to provide an integrated package of care to reduce overall child mortality.

4.3.5 Timing of ART for adults and children with TB

Recommendations

- ART should be started in all TB patients living with HIV, regardless of CD4 cell count (strong recommendation, high-quality evidence).^a 
- TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high-quality evidence).^a
- HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm³) should receive ART within the first two weeks of initiating TB treatment.
- ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of antituberculosis treatment, regardless of the CD4 cell count and clinical stage (strong recommendation, low-quality evidence).

^a The quality of evidence for this recommendation was upgraded to high in 2015.

Source (children): Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Early initiation of ART for patients with HIV-associated TB is critical in reducing morbidity and mortality. Since 2010, WHO has recommended that ART be started in all TB patients living with HIV, regardless of CD4 cell count, as soon as possible within the first 8 weeks of TB treatment. Since then, several additional results from randomized controlled trials have been published. In 2015, a systematic review was conducted to reassess the optimal timing of ART initiation among people living with HIV and active TB to minimize death, AIDS-defining events, severe treatment-related adverse events and incidence of IRIS.

Rationale and supporting evidence

The review of evidence focused on the relative benefits of early ART started within 2 weeks (defined as “earlier initiation”) or 8 weeks (defined as “early initiation”) of TB treatment initiation, compared to ART initiated after 8 weeks (defined as “delayed initiation”). Early and earlier initiation was also compared to delayed ART, initiated after 8 weeks but before completion of TB treatment. Particular consideration was given to people with profound immunosuppression (CD4 cell count less than 50 cells/mm³).

High-quality evidence from eight trials (175–182) showed that, across the CD4 strata, early ART (within 8 weeks of TB treatment) is associated with a reduction in overall mortality, compared with ART initiated after 8 weeks of TB treatment or after TB treatment is completed. In a subanalysis of patients with a CD4 count of less than 50 cells/mm³, the reduction in mortality was statistically significant (175,178,183,184). High-quality evidence from four trials also demonstrated a reduction in mortality when ART was started within 2 weeks of starting TB treatment, compared with delayed initiation but during TB treatment, across all CD4 counts (175–177,181). Similarly, earlier ART for patients with a CD4 count of less than 50 cells/mm³ was associated with a reduction in mortality (175,184). Furthermore, one trial found a significant reduction in the combined outcome of AIDS-defining illness or death among this group (185).

Overall, the systematic review found similar levels of grade 3 or 4 non-IRIS adverse events among patients starting ART early or earlier with all CD4 cell counts compared to delayed ART (186). Subanalysis of patients with a CD4 cell count of less than 50 cells/mm³ showed similar findings when comparing early ART with delayed ART within 24 weeks of starting TB treatment.

The evidence showed a tendency towards reduction in AIDS-defining illnesses across all CD4 strata when early and earlier ART were compared with delayed initiation during TB treatment. Subanalysis of patients with a CD4 count of less than 50 cells/mm³ showed similar findings with early ART (175) and earlier ART compared with delayed ART within 24 weeks of starting TB treatment.

However, overall there was a statistically significant, higher incidence of IRIS in patients who initiated ART within 8 weeks when compared with delayed ART initiation across the CD4 strata and in the subanalysis of CD4 count less than 50 cells/mm³. A separate subanalysis was conducted of high-quality evidence from five randomized controlled trials to assess IRIS-related mortality. While there was a statistically significant increase in IRIS-related mortality associated with early ART, the number of deaths was small (9/335) in comparison with overall deaths (177,178,180,182,187,188).

Based on this evidence, ART should be started in all TB patients living with HIV, regardless of CD4 count because of the overall benefit of early ART. A direct comparison of the effect of starting ART within 2 weeks compared with after 2 weeks but within 8 weeks of TB treatment was not feasible. However, ART initiation within 2 weeks is important in people with CD4 cell counts less than 50 cells/mm³ because mortality in this group is particularly high. Inability to measure CD4 cell count should not be a barrier to starting ART earlier.

Data from the reviewed studies primarily included adults and adolescents and were not disaggregated according to age, so it was not possible to measure the effect of early ART among children with HIV-associated TB. However, data from one observational study in South Africa showed increased mortality and poorer virological response in children with HIV-associated TB when ART was initiated more than 8 weeks after starting TB treatment, particularly in children with severe immunosuppression (189). The existing strong recommendation developed in 2010 that was based on low-quality evidence is therefore maintained in these guidelines.

Caution is needed in people living with HIV with TB meningitis, as immediate ART is significantly associated with more severe adverse events when compared with initiation of ART 2 months after the start of TB treatment (190).

Feasibility and resource use

Among HIV-positive TB patients detected globally in 2013, 70% were given ART during TB treatment, showing the overall feasibility of the intervention (191). Routine data on the timing of ART is not reported globally. However, data are collected in special surveys in some countries. For example, survey findings undertaken in 22 randomly selected ART centres across India suggested the feasibility of early ART in TB patients, with 70% of patients receiving ART within 30 days and 88% within 2 months (Rewari, WHO India, unpublished data, June 2015). No important differences in resource use are expected when comparing early and late timing of ART among TB patients, as it is anticipated that all patients will start ART within a few months. However, the increased incidence of IRIS associated with early ART initiation may require additional resources to diagnose and manage this condition.

Implementation considerations

Patients should be closely followed up to assess the occurrence of side-effects related to co-treatment and of TB-associated IRIS, which is common in patients with TB started on ART but usually self-limited. Stakeholders and service providers should establish mechanisms to ensure that people living with HIV receive TB treatment along with ART, emphasizing integrated and patient-centred care, preferably at the same location (see section 6.10.2 “Delivering ART in TB treatment settings and TB treatment in HIV care settings”).

Research gaps

Research gaps include questions addressing the optimal timing of initiation of ART in children living with HIV being treated for TB and patients with drug-resistant TB. There is also a need for studies that compare the effect of starting ART within 2 weeks and from 2 weeks but within 8 weeks of TB treatment. More research is also needed into the optimal timing of initiation of ART in adults and children with TB meningitis.

4.3.6 Diagnosis and treatment of recent HIV infection

Recent HIV infection is defined as the period up to 6 months following HIV acquisition, during which specific anti-HIV antibodies become detectable by serological tests (seroconversion) and when the viral load steady state (set point) and viral reservoirs are usually established (192–194). During the first weeks of this phase, people recently infected with HIV can (but will not always) develop an acute clinical syndrome associated with the initial and rapid burst of viraemia characterized by the presence of some self-limited clinical signs and symptoms – such as fever, myalgia, pharyngitis and rash – that usually subside after 2–4 weeks (195). During this early stage of HIV infection, the immune system also starts to get damaged and the frequently unsuspecting infected person may be most infectious to others (196–198).

With the increasing availability of more accurate diagnostic testing, more effective drug regimens and better knowledge of the dynamics of HIV transmission and viral reservoirs, early diagnosis during recent HIV infection has been viewed as an opportunity for treatment and prevention interventions, with a potentially important public health impact (11).

Clinical studies have indicated that initiation of ART during recent HIV infection can reduce the size of the latent viral reservoir and delay viral rebound after ART discontinuation (199–203). Diagnosis and treatment of people with very early HIV infection are therefore potentially critical for research on a cure for HIV, because such people are likely have smaller reservoirs, decreased viral replication and genetic diversity, sustained T-cell and B-cell function and better immune restoration potential. In addition, they have a lack of extended inflammatory responses and comorbidities associated with chronic infections and no or limited previous exposure to ARVs (11). There are several clinical trials addressing this subject (204–208).

HIV transmission can be greatly amplified during recent infection (209,210) because the HIV founder viruses causing early infection are particularly infectious (211) and the viral loads of people with recent infection are exceptionally high (212). The diagnosis and treatment of people with recent HIV infection may therefore represent a potentially significant public health intervention. However, the proportion of transmission events attributable to recent infection is challenging to study and estimate, because of the difficulty of diagnosis. The impact of HIV transmission during the early stages of infection has been modelled in different settings and population groups, with studies showing quite divergent results, suggesting that anywhere from 2% to 89% of HIV transmission can occur during this stage of infection (209,213–222). This large variation between studies can be explained by the variability of several key factors, such as duration of infection, behaviour, use of barrier methods, clustering and epidemic phase, which influence the proportion of transmissions that can take place during early HIV infection in different settings but need to be better understood.

Identifying people with recent HIV infection is complicated by the brevity of the phase, the non-specific symptoms associated with the acute infection and the initial absence of anti-HIV antibodies. Because traditional and point-of-care HIV diagnostic tests cannot accurately detect the earliest phase of infection, the diagnosis of recent infection relies on direct detection of the virus, which is complex, costly and not widely available. Finding people with recent infection either in longitudinal cohorts of subjects at high risk for acquiring the virus or through cross-sectional screening has proven very difficult, and the opportunity for diagnosis is generally missed during this phase (223). There are also substantial financial, technical and logistical barriers involved in diagnosis, linkage and treatment (224,225).

In light of the opportunities and challenges, WHO has not yet established a diagnostic strategy or any specific recommendation to identify or treat people during this phase of infection. However, important areas of research have been identified that will help to guide surveillance, diagnosis and management of recent HIV infection, particularly in low- and middle-income countries. Further technical advances and more knowledge on the pathogenesis of the early stages of HIV infection are essential to enable more effective detection of people with recent infection in order to improve HIV treatment outcomes and prevent HIV transmission.

4.4 What to start: first-line ART

Table 4.1. First-line ART regimens for adults, pregnant or breastfeeding women, adolescents and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens ^{a,b}
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG ^c TDF + 3TC (or FTC) + EFV ₄₀₀ ^{c,e} TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG ^{c,d} TDF (or ABC) + 3TC (or FTC) + EFV ₄₀₀ ^{c,d,e} TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

^a For adults and adolescents, d4T should be discontinued as an option in first-line treatment.

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

^c Safety and efficacy data on the use of DTG and EFV₄₀₀ in pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available.


^d Conditional recommendation, moderate-quality evidence.

^e EFV at lower dose (400 mg/day).

3TC lamivudine, ABC abacavir, AZT zidovudine, DRV darunavir, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, TDF tenofovir.

4.4.1 First-line ART for adults

Recommendations

- First-line ART for adults^a should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI).
- 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 alternative options is recommended:
 - AZT + 3TC + EFV
 - AZT + 3TC + NVP
 - TDF + 3TC (or FTC) + NVP
(strong recommendation, moderate-quality evidence).
- **TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternative options to initiate ART (conditional 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).

^a Adults include pregnant and breastfeeding women, for whom additional guidance is found in Box 4.3.

3TC lamivudine, AZT zidovudine, d4T stavudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir
 Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Table 4.2. First-line ART regimens for adults (see Annex 11 for doses)

Preferred regimen	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG ^a TDF + 3TC (or FTC) + EFV ₄₀₀ ^b TDF + 3TC (or FTC) +NVP
Special circumstances^{c,d}	Regimens containing ABC and boosted PIs

^a Safety and efficacy data on DTG for pregnant and breastfeeding women and TB coinfection are still pending.

^b Efficacy data for EFV at a lower dose of 400 mg/day in the case of pregnant and breastfeeding women and TB coinfection are still pending.

^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.

^d Using stavudine (d4T) as an option in first-line treatment should be discontinued.

3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Background

WHO promotes a public health approach to ART involving less toxic, more convenient and simplified ARV regimens, with a limited number of preferred first-line options that may be used across a range of populations. Other requirements are that they should be pharmacologically compatible with recommended therapies for coinfections and comorbidities that commonly affect people living with HIV (226–232).

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9) recommend tenofovir (TDF) + lamivudine (3TC) (or emtricitabine [FTC]) + efavirenz (EFV) as the preferred first-line regimen for treatment initiation in ART-naïve adults, preferably as a fixed-dose combination (FDC). This approach has clinical, operational and programmatic benefits when compared with other NNRTI- and PI-based options (9,233). The 2013 guidelines also emphasized the importance of discontinuing the use of stavudine (d4T) in first-line regimens because of its well-known long-term mitochondrial toxicity (234–238).

Almost 70% of all people taking first-line ART were using this preferred combination at the end of 2014, but only 60% were using it as an FDC. The global phasing out of d4T as a preferred option in first-line ART has been substantial, with less than 5% of individuals living with HIV on ART using this drug (239).

A large body of clinical and programmatic evidence representing an estimated 15 million person-years of experience supports the use of EFV 600 mg in a range of settings when combined with TDF and 3TC (or FTC) (240–242). This provides a level of confidence that does not exist with the currently available alternatives, including the effectiveness of this dose in patients receiving concomitant rifampicin-based treatment for TB, and the efficacy of this regimen during pregnancy. However, observational studies suggest that up to half of people using EFV may present with central nervous system (CNS) side-effects such as dizziness, sleep disturbance, abnormal dreams and depression. These side-effects may overlap significantly with other neuropsychiatric manifestations of HIV, complicating the

establishment of the real cause and frequency of these events in patients taking EFV (243). A recent analysis of trial data found a twofold increased hazard of suicide with initial treatment using an EFV-containing regimen compared with regimens without EFV (244). However, no evident association was found in other studies (245–247).

New developments in ARV drugs and formulations include the introduction of new drug classes and dose reduction studies for some key first-line ARV drugs that show lower toxicity risk and similar or higher therapeutic efficacy when compared with current standard treatment options. This could potentially extend the benefits and durability of anti-HIV regimens (248–254).

Rationale and supporting evidence

TDF + 3TC (or FTC) + EFV as the preferred first-line ART regimen

Systematic reviews conducted to establish the preferred first-line ART regimen for the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9) found moderate-quality evidence indicating that the 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 when compared with other once- or twice-daily NNRTI- or protease inhibitor (PI)-containing regimens (255). Furthermore, TDF + 3TC (or FTC) + EFV offers the opportunity to harmonize regimens across different populations: TDF + FTC or TDF + 3TC is the preferred NRTI backbone for people coinfecting with HIV and HBV and can be used for people coinfecting with TB and pregnant women. EFV is also the preferred NNRTI for people with HIV and TB due to pharmacological compatibility with TB drugs and for people with HIV and HBV coinfection due to lower risk of hepatic toxicity. A published meta-analysis and a further updated analysis comparing the use of EFV and other ARV drugs during the first trimester of pregnancy showed no increased risk of birth defects, confirming the suitability of EFV for use in pregnant women (114,256,257).

In 2015, a systematic review was conducted of the comparative safety of EFV-containing regimens and their impact of CNS adverse events. The review showed that that 90% of patients remained on EFV-containing regimens (with a median of 78 weeks of follow-up). Although the relative risk of discontinuation due to adverse events was higher when compared with other first-line options the absolute difference was low (<5%). No difference in terms of severe adverse events was found in this comparative analysis (247).

Recent data on the safety of TDF and EFV during pregnancy are also reassuring, confirming studies reviewed for the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (257,258). There was no evidence of an increased risk of congenital anomalies with TDF or EFV compared to other ARV drugs (259,260). The risk of neural tube defect associated with EFV remains low and is comparable to the general population in the United States (259,261). (More information on TDF and EFV toxicity may be found in section 4.6 “Monitoring of and substitutions for ARV drug toxicities”.)

The availability of this regimen as a generic FDC and the significant price reductions in the past few years also support maintaining TDF + 3TC (or FTC) + EFV as the preferred option for ART initiation.

DTG and EFV 400 mg/day as new alternative options in first-line regimens

In 2015, a systematic review and network meta-analysis was conducted to assess the direct and indirect comparative evidence of the efficacy and safety of the integrase inhibitors (INSTIs) dolutegravir (DTG), raltegravir (RAL) and elvitegravir/cobicistat (EVGC/COBI) as well as EFV at the lower dose of 400 mg/day in adults with HIV (262). Seventy one trials, involving 34 032 patients randomized to 161 treatment arms were included in the review. Direct comparative evidence was obtained from seven randomized controlled trials (263–269). The analysis showed moderate-quality evidence that two NRTIs + INSTI was a generally more effective regimen (with higher viral suppression and CD4 cell recovery rates and lower risk of treatment discontinuation) than two NRTIs + EFV at the standard dose of 600 mg/day in ART-naïve adults and that DTG has a comparable effect to that of RAL but better than that of EVG + cobicistat in terms of viral suppression and treatment discontinuation. There was a non-statistically significant tendency towards increased viral suppression with DTG when compared with EFV at a lower dose of 400 mg/day.

In the same systematic review, there was moderate-quality evidence showing that EFV 400 mg/day was comparable to EFV 600 mg/day in terms of viral suppression but better in terms of CD4 cell count recovery and protective in terms of treatment discontinuation due to adverse events. Furthermore, all treatment regimens were comparable with respect to mortality or AIDS-defining illnesses (low-quality evidence) and emergent serious adverse events, with the exception of nevirapine (NVP) (moderate-quality evidence).

DTG also has other clinical and programmatic advantages when compared with EFV 600 mg, including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier when compared with EFV and other ARV drugs. Its long half-life, low cost and low dose mean that it is feasible to include this drug in a small once-daily FDC (270). DTG has documented in vitro and clinical activity against HIV-2 infection, which is naturally resistant to EFV (271,272). When compared with the standard dose of EFV, EFV 400 mg/day is also associated with lower toxicity, lower cost and smaller pill size.

The safety and efficacy of DTG and EFV 400 mg/day during pregnancy and among TB/HIV-coinfected patients using rifampicin has not been established. Pharmacokinetic studies show that rifampicin-based treatment leads to short-term reductions in drug levels of EFV at the standard dose of 600 mg/day during the first 2 weeks of treatment, but increases in EFV drug levels have been consistently observed across several pharmacokinetic studies after longer-term treatment together with rifampicin-based combinations (273). However, it is not clear whether the same consistent efficacy will be seen for the lower 400-mg dose of EFV. Similarly, rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule may be necessary, but there are very few studies and limited clinical experience with this combination, particularly in TB-coinfected patients (274).

While two recent studies suggest that pregnancy may lower EFV plasma concentrations (275,276), a recent review of six studies concluded that there was a limited effect on the pharmacokinetics of EFV at the standard 600-mg once-daily dose during the third trimester of pregnancy (277). Rates of vertical transmission of HIV in these studies were low. There are currently no published safety or efficacy data available on the outcomes of treatment with DTG during pregnancy and breastfeeding. Furthermore, calcium or iron

supplements frequently used during pregnancy could significantly reduce DTG drug levels (278). Pharmacokinetic studies of EFV 400 mg/day and DTG in pregnancy and when co-administered with TB drugs are either planned or in progress (279,280).

Single formulations and FDCs containing these two new options are expected to be available in 2017 and 2018, respectively, with forecasting projections suggesting a good potential for price reduction as a result of generic competition in the future (281,282).

The clinical and potential programmatic benefits of DTG and EFV 400 mg/day for the majority of patients warrant their inclusion as new alternative options in first-line ART. However, further research is needed to establish their suitability for use during pregnancy and concurrent rifampicin-based TB treatment.

Other alternative first-line ARV regimens

As stand-alone formulations and FDCs containing DTG and EFV 400 mg/day are not likely to be available in the next few years, the alternative regimens containing zidovudine (AZT) and NVP recommended in 2013 are maintained. If TDF + 3TC (or 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 but have potential clinical and programmatic disadvantages when compared with the preferred option and the new alternative regimens containing DTG and EFV 400 mg/day. In special circumstances, ABC and boosted PIs are acceptable as potential back-up options but are not recommended as preferred alternatives; they should be used only when other options are not available.

There are persistent concerns about the higher risk of severe adverse events with NVP compared with EFV and other ARV drugs, particularly in ART-naïve patients with high baseline CD4 cell counts (283–286). A systematic review conducted for the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* showed that people receiving NVP are twice as likely as those receiving EFV to discontinue treatment due to adverse events (256). The review of new first-line ART options conducted in 2015 confirmed this finding, with moderate-quality evidence showing that all treatment regimens investigated were comparable with respect to the occurrence of serious adverse events, with the exception of NVP (262). Some studies showed an increased risk for severe hepatic and skin reactions when using NVP, particularly among pregnant women (287–290). However, other studies, including a systematic review on the risk of NVP-associated toxicity in pregnant women, suggest that the frequency of adverse events is higher but no greater than that observed in the general adult population with HIV (291–294). The current body of evidence therefore confirms the increased risk of adverse events associated with NVP use. NVP should be used with caution as an alternative in individuals with a high baseline CD4 cell count, including pregnant women and women who might be pregnant. However, other alternative drugs with better overall toxicity profiles should be considered. More studies on this topic are still needed. (More information on NVP toxicity can be found in section 4.6.5 “Toxicity monitoring for other ARV drugs in adults, adolescents and children”.)

WHO recommends that the use of d4T-containing regimens be discontinued (295). In settings where d4T regimens are still used for initiating ART, plans for phasing out d4T should be implemented or accelerated with a view to replacing d4T with TDF-based first-line regimens (296).

Research gaps

Further research is required to determine the safety of DTG and the efficacy of EFV 400 mg/day in people with HIV/TB coinfection and in pregnant and breastfeeding women. EFV exhibits significant genetic-based interindividual pharmacokinetic variability, which can make it challenging to undertake accurate pharmacokinetic/pharmacodynamic (pK/pD) analysis. There is a need to conduct this modelling in African and non-African populations and in people without the CYP2B6 genotype.

Box 4.3. ART in pregnant and breastfeeding women and strategies for PMTCT

These guidelines provide recommendations for universal treatment at any CD4 cell count and any stage of disease, harmonized across all populations, including pregnant and breastfeeding women. The preferred first-line regimen is also harmonized for all adults and adolescents, whether pregnant or not, but there are a few key differences in terms of the alternative regimens for first-line ART. Although there are no data to suggest that any of the INSTIs including DTG have any fetal toxicity, DTG has not been sufficiently studied in pregnant women for it to be recommended as an alternative in this population, unless the perceived benefits outweigh the potential risks. In addition, the efficacy of low-dose EFV in pregnancy has not been studied. As a result, alternative first-line ART for pregnant and breastfeeding women includes only NVP in place of EFV and AZT in place of TDF. For pregnant women on second-line ART, the options are the same as for non-pregnant adults and include boosted PIs such as lopinavir/ritonavir (LPV/r) and atazanavir (ATV)/r, but it is noteworthy that a subanalysis of women given LPV/r in the PROMISE trial (297) suggests an association between the use of boosted PIs and prematurity. (See section 4.6.6 “Special considerations for toxicity monitoring during pregnancy and breastfeeding”.)

Universal ART is an important element of PMTCT, but in order to achieve elimination of new infections among children, PMTCT programmes must incorporate a spectrum of activities, including HIV prevention for HIV-negative women, access to family planning to prevent unintended pregnancy, widespread testing of pregnant women early in antenatal care and support to women living with HIV to remain adherent to ART and retained in care throughout pregnancy and breastfeeding and for life. In the case of women testing negative for HIV who live in high-burden settings, testing should be repeated later in pregnancy and during breastfeeding to identify newly acquired HIV infection.

In addition to receiving ART, pregnant women living with HIV should be offered the recommended package of pregnancy care, and additional interventions such as screening for STIs (such as hepatitis B and syphilis), nutritional support, infant feeding counselling and family planning guidance. Careful monitoring for the development of pregnancy-induced hypertension and pre-eclampsia – especially for women on ART prior to conception – is advised.

Throughout pregnancy, key principles and practices of safe motherhood should be followed, including reinforcement of recommended antenatal clinic visits and facility-based delivery by skilled birth attendants. Instrumentation should be avoided unless essential, and newborns should be washed of any blood and cared for using non-invasive techniques as much as possible. Health workers should follow universal precautions for all deliveries, including deliveries by women living with HIV. Special efforts should be made to ensure that delivery care for women living with HIV is provided in a non-stigmatizing and supportive manner.

Although elective caesarean section has been shown to protect against HIV acquisition, especially in the absence of ARV drugs or in the case of a 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.

Newborn prophylaxis remains an important aspect of PMTCT and, for mothers who start ART later in pregnancy, these guidelines propose enhanced prophylaxis recommendations that call for longer duration of prophylaxis and multiple drugs. (See section 4.4.7 “Infant prophylaxis”.)

Sources:

Packages of interventions: family planning, safe abortion, maternal, newborn, child health. Geneva: World Health Organization; 2010. (http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/fch_10_06/en).

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (<http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en>).

Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. Geneva: World Health Organization; 2010 (http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/924159084X/en).

IMAII/IMPAC clinical training for integrated PMTCT services. Geneva: World Health Organization (<http://www.who.int/hiv/topics/mtct/training/en>).

Option B/B+ toolkit, updated version May 2015. Geneva: Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children; 2015 (<http://www.emtct-iatt.org/toolkit>).

Monitoring & evaluation framework for antiretroviral treatment for pregnant and breastfeeding women living with HIV and their infants. Geneva: World Health Organization; 2015 (<http://www.who.int/hiv/mtct/iatt-me-framework/en>).

WHO recommendations on postnatal care of the mother and newborn. Geneva: World Health Organization; 2013 (http://www.who.int/maternal_child_adolescent/documents/postnatal-care-recommendations/en).

4.4.2 Fixed-dose combinations and once-daily regimens

NEW

Recommendation

Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy (strong recommendation, moderate-quality evidence).

Background

WHO has recognized the potential benefits of FDCs and once-daily regimens for ART since 2003. FDCs are recommended by WHO in other disease areas such as TB and malaria as a way to improve adherence, simplify prescribing and procurement, and reduce prescribing errors (298,299). New ARV drugs and formulations are available that support an expanded evidence base, allowing for a rigorous assessment of the clinical and programme impact of FDC once-daily regimens.

Rationale and supporting evidence

Two systematic reviews assessed the benefits of FDCs (233) and once-daily regimens (300).

The first review identified 21 studies and found that, compared to separate tablets, patients receiving FDCs tended to have higher levels of adherence, both in randomized trials and observational cohorts (233). There was also a tendency towards greater viral suppression among patients receiving FDCs in randomized trials and observational cohort studies. In all studies reporting patient preference, FDCs were preferred. The overall quality of the evidence was rated as moderate for randomized trials and low for observational studies. The second review of 19 randomized trials found that average adherence was higher for once-daily regimens than twice-daily regimens (300). The overall quality of the evidence was rated as moderate due to the risk of bias.

The Operational Guideline Development Group concluded that the recommendation favouring FDCs and once-daily regimens should be strong in view of the clear patient preference, as measured by improved quality of life (301–304), patient satisfaction (302,304–306), patient preference (302,303,307,308) and ease of regimen use (309). Programme managers and procurers have also recognized the benefits (310).


Implementation considerations

Some of the preferred regimens recommended by WHO are currently not available as FDCs, particularly for younger children, and manufacturers are encouraged to explore the potential for co-formulation. Patients may need to switch to separate tablets in case of drug substitutions due to intolerance, contraindications or development of resistance; in such cases, additional adherence counselling and monitoring may be required to manage this change. Finally, in some countries, FDC regimens are more expensive than corresponding separate-tablet regimens, and donors and procurers will need to balance cost and benefits.

4.4.3 First-line ART for adolescents

Recommendations

First-line ART for adolescents should consist of two NRTIs plus an NNRTI or an INSTI:

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, low-quality evidence).
- **TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV₄₀₀^a may be used as alternative options to initiate ART (conditional recommendation, low-quality evidence).** 

If preferred regimens are contraindicated or not available, one of the following alternative options is recommended (strong recommendation, moderate-quality evidence):

ABC + 3TC + EFV
 ABC + 3TC + NVP
 AZT + 3TC + EFV
 AZT + 3TC + NVP
 TDF + 3TC (or FTC) + NVP

^a EFV at a lower dose (400 mg/day).

Table 4.3. Summary of first-line ART regimens for adolescents

Preferred regimens^a	TDF + 3TC (or FTC) + EFV
Alternative regimens	TDF (or ABC) + 3TC (or FTC) + DTG TDF (or ABC) + 3TC (or FTC) + EFV ₄₀₀ ABC + 3TC + EFV ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Special circumstances^{b,c}	Regimens containing boosted PIs

^a To date, there is limited experience with the use of low-dose EFV and DTG in adolescents. While no age or weight restrictions apply to the use of EFV 400 mg/day, which can be used starting from a weight of 20 kg (Annex 11c), the use of DTG is approved only for adolescents who are older than 12 years and weigh more than 40 kg (311). In addition, safety and pharmacokinetic data on TB coinfection and pregnancy are still pending.

^b 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.

^c Using d4T as an option in first-line treatment should be discontinued.

3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Background

Identifying the most suitable regimen for adolescents is of critical importance in light of the documented risk of poor adherence relative to adults in some settings (143,144), which places them at high risk for treatment failure and the development of drug resistance (145).

The toxicity profile of the currently recommended first-line adult regimen – particularly the CNS effects of EFV at standard dosing – is of potential concern due to the impact that the CNS effects may have on the quality of life and level of adherence. In this context, more acceptable and forgiving regimens have been proposed for this specific age group, but introducing them while also preserving regimen harmonization remains challenging.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that adolescents be started on an EFV-containing regimen combined with TDF + FTC or 3TC to reduce pill burden and promote harmonization with adult regimens and formulations. New recommendations in 2015 are based on careful consideration of risks and benefits, the values and preferences of adolescents living with HIV and the programmatic advantage of full harmonization with first-line adult recommendations.

Rationale and supporting evidence

Two systematic reviews (312,313) were conducted to evaluate alternative first-line options for adolescents, but only one randomized controlled trial of first-line NNRTI-based versus PI-based regimens was identified. The PENPACT 1 randomized controlled trial (314) was conducted in high- and middle-income countries (Europe, USA, Brazil, Argentina, Bahamas and Puerto Rico) and included adolescents. At 4 years after ART initiation, no significant difference was detected between the two arms in terms of efficacy or toxicity, and findings did not differ based on age. However, the overall quality of the evidence is low due to the serious indirectness of the data, as adolescents were underrepresented in the trial population (the median age was 6.5 years) and many initiated regimens containing NVP or nelfinavir instead of the currently recommended first-line regimen. Overall, the potential use of PI-based regimens in first-line therapy is feasible but is likely to add complexity to treatment programmes by further diversifying the use of drugs across age groups.

In light of this and the paucity of data, it is possible to extrapolate from the evidence gathered in adults and recommend full harmonization of first-line regimens for adolescents. DTG-based and low-dose EFV-based regimens are therefore recommended as alternative preferred regimens where available and when age appropriate. These options are considered particularly suitable for adolescents in light of the potential for reduced side-effects and reduced risk of selecting drug resistance (269). DTG, which is currently licensed for adolescents 12 years of age and older and above 40 kg (315), has a very favourable genetic barrier to resistance, which would reduce the risk for selection of resistance mutations even in cases of poor adherence (316). However, due to the lack of specific comparative evidence from trials, some uncertainty remains with regard to the use of these regimens in adolescents.

Clinical considerations

In general, the choice of regimens for adolescents should be guided by:

- the need to use potent and forgiving first-line regimens that minimize toxicity;
- the convenience of once-daily dosing and the use of FDCs whenever possible;
- the use of non-thymidine analogues – either ABC or TDF – in first-line regimens to maximize the response to AZT in second-line ART; and
- the desirability of aligning recommended regimens for adolescents with those for adults.

A specific consideration for clinicians and other health-care providers relates to whether and how regimen changes can be introduced among clinically stable adolescents who started ART during childhood. As children get older, more options become available with advantages over current first-line regimens, such as FDCs, improved toxicity profile and dosing advantages. Modifying ART regimens of clinically stable adolescents may simplify treatment management and harmonize the regimens in use. The choice between a full

Table 4.4. Considerations for simplifying and harmonizing ART for adolescents with no history of treatment failure on any regimen^a

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	Reduced risk of d4T-related toxicity May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen)	Aligned with adult regimens
LPV/r	No need to change, but consider substituting LPV/r with EFV600 ^b , EFV400 ^c or DTG	May improve adherence as a result of once-daily dosing Reduced risk of metabolic alterations	Aligned with adult regimens Preserve PI for second-line ART
AZT	No need to change but may consider changing to TDF	May improve adherence as a result of once-daily dosing (if on EFV or DTG) May reduce the risk of exacerbating anaemia	Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	Fixed-dose combinations can be used (if also on EFV)	Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV600 ^b , EFV400 ^c or DTG	May improve adherence as a result of once-daily dosing (if combined TDF)	Aligned with adult regimens

^a Defined according to the criteria for treatment failure adopted nationally, preferably using viral load testing, where feasible and available.

^b EFV at standard dose (600 mg/day).

^c EFV at lower dose (400 mg/day).

ABC abacavir, AZT zidovudine, DTG daltgravir, EFV efavirenz, LPV lopinavir, NVP nevirapine, r ritonavir, PI protease inhibitor, TDF tenofovir

regimen change and single drug substitutions should be made in the context of adult regimen harmonization and the convenience of once-daily medications in the best formulations available. Table 4.4 summarizes relevant considerations for simplifying and harmonizing ART in adolescents with no history of treatment failure.

Research gaps

The long-term efficacy and safety of TDF and EFV or DTG in adolescents and the recommended regimens need further investigation. More data are needed on the bone, growth and renal toxicity profiles of TDF in adolescents, especially in the context of malnutrition and delays in growth and development (i.e. puberty). Similarly, adverse events associated with EFV during adolescence, such as CNS effects, require investigation to ensure safe harmonization with adult regimens. Toxicity surveillance systems implemented alongside ART, particularly for new approaches such as DTG or low-dose EFV, can provide data to better understand the frequency and clinical relevance of toxicities. In addition, studies to inform the development of long-acting formulations of existing and newer compounds, which would be particularly beneficial for this population, should be prioritized.

4.4.4 First-line ART for children 3–10 years of age

Recommendations

For children 3 to less than 10 years of age, the NRTI backbone should be one of the following, in preferential order (conditional recommendation, moderate-quality evidence^a):

- ABC + 3TC
- AZT or TDF + 3TC (or FTC).

For children 3 years and older, EFV is the preferred NNRTI for first-line treatment and NVP is the preferred alternative (strong recommendation, low-quality evidence).

^a Strength of evidence reviewed in 2015.

Table 4.5. Summary of recommended first-line ART regimens for children 3–10 years of age

Preferred	ABC + 3TC + EFV
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP

3TC lamivudine, ABC abacavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir

Background

Despite increased access to EID and the widespread availability of several child-friendly FDCs, ART coverage among children lags significantly behind that of adults (317). Treatment recommendations for children should be implemented at all levels of the health system, including the primary care level, and by all ART service providers, rather than paediatric specialists alone.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommended starting with an EFV-containing regimen combined with an NRTI backbone in children 3 years and older. Despite the lack of direct comparison, the recommended NRTI backbones, in preferential order, were ABC + 3TC followed by AZT or TDF + 3TC (or FTC). Although more effective and better-tolerated drugs – such as DTG – have become available for adults and adolescents since 2013, EFV remains the only widely accessible option to ensure harmonization of regimens across age groups. At the same time, new evidence has become available to inform the choice of NRTI backbone (318), leading to a revised recommendation in 2015.

Rationale and supporting evidence

A systematic review was conducted to assess the efficacy and safety of ABC-containing regimens compared to AZT and TDF-containing regimens. Only one randomized controlled trial was identified, involving the comparison of different NRTI backbones in combination with NNRTI in a large cohort of African children. This study (318) demonstrated that ABC and AZT were comparable in their clinical, immunological and virological response, as well as safety and tolerability. However, the choice of first-line NRTIs affects second-line ART, and failure of AZT results 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). For these reasons, ABC + 3TC should remain the preferred option for the first-line NRTI backbone in children in this age group.

The systematic review did not identify any study that directly compared TDF with AZT or ABC. The United States Food and Drug Administration (US FDA) and European Medicines Agency approved the use of TDF in children older than 2 years of age in 2011 (319,320), 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 (321,322). In addition, the fact that HIV resistance to TDF – specifically the K65R mutation – can enhance the antiviral effect of AZT in subsequent regimens may make TDF a good choice for first-line therapy (323–325). However, experience with TDF in young children is limited, and although TDF has been associated with reduced bone mineral density (326), the dynamics, persistence and long-term impact (future patterns of growth and fracture risk) of these changes are not well defined.

A systematic review on TDF toxicity (327) showed a decline in renal function parameters over time (creatinine clearance, hypophosphataemia, estimated glomerular filtration rate [eGFR]) and a reduction in bone mineral density at 24 weeks, suggesting that TDF toxicity among children and adolescents could be similar to that seen in adults (328,329). However, data are still lacking, and renal and bone toxicities in growing children and adolescents remain a concern. In addition, TDF formulations for younger children are not widely available and, to date, there are no TDF-containing paediatric FDCs. ABC shares many of the benefits of TDF (once-daily dosage and a favourable resistance profile) but, in contrast to TDF, ABC has been better studied in children and is generally well tolerated, without the risks of bone and renal toxicity. ABC is also available in paediatric FDC formulations but is significantly more costly than other NRTIs. Furthermore, among people with the HLA-B*5701 allele, it can cause a potentially fatal hypersensitivity. While hypersensitivity can affect 3–4% of Caucasian and Asian children, it is very rare among African children (330). A systematic review demonstrated that ABC does not lead to higher rates of toxicity or discontinuation and can be safely used for first-line or second-line ART in children and adolescents (331).

The review of evidence conducted in 2013 indicated that EFV has a better short-term toxicity profile and is associated with better virological response than NVP (332,333). Nevertheless, most children are currently treated with regimens that contain NVP due to the availability of FDCs, whereas in adults, EFV is increasingly being selected as the preferred NNRTI. 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.

Clinical considerations for scaling up ART for children

In general, the choice of regimens in this age group should be guided by:

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

An important specific 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 FDCs with advantages over current first-line regimens – such as improved toxicity profile or dosing advantages – may become available. Modifying the ART regimens in clinically stable people may be considered to

simplify treatment management and harmonize the ART regimens in use. Relevant considerations are shown in Table 4.6.

Table 4.6. Considerations for simplifying and harmonizing ART for children with no history of treatment failure on any regimen^a

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	Reduced risk of d4T-related toxicity May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen)	Aligned with adult regimens
LPV/r	No need to change, but consider substituting LPV/r with NVP or EFV if there is sustained virological response on LPV/r	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	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	May improve adherence as a result of once-daily dosing (if on EFV) May reduce the risk of exacerbating anaemia	Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	Fixed-dose combinations can be used (if also on EFV)	Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV, particularly from age 3 years onwards	May improve adherence as a result of once-daily dosing (if combined with ABC or TDF)	Aligned with adult regimens

^a Defined according to the criteria for treatment failure adopted nationally, preferably using viral load testing, where feasible and available.

ABC abacavir, AZT zidovudine, ART antiretroviral therapy, d4T stavudine, EFV efavirenz, LPV/r lopinavir/ritonavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Research gaps

The long-term efficacy and safety of TDF, ABC and EFV and the recommended combinations need further investigation. More data are needed on bone, growth and renal toxicity profiles for TDF in children, especially in the context of malnutrition and stunting. Similarly, adverse events associated with EFV particularly during adolescence, such as CNS 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. In addition, pharmacokinetic studies to inform the development of better FDCs and the introduction of newer, more potent and less toxic components, such as INSTIs and tenofovir alafenamide fumarate (TAF), remain of critical importance for this population.

4.4.5 First-line ART for children younger than 3 years of age

Recommendations

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

An LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than 3 years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen (strong recommendation, moderate-quality evidence).

Where viral load monitoring is available, consideration can be given to substituting LPV/r with EFV at 3 years of age after viral suppression is sustained (conditional recommendation, moderate-quality evidence).^a

For infants and children infected with HIV younger than 3 years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (strong recommendation, moderate-quality evidence).

^a Revised in 2015.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Optimizing first-line ART in children younger than 3 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 lead to alternative therapeutic approaches compared to those used in adults 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 exposure to ARV drugs for PMTCT (337).

Based on evidence from randomized controlled trials showing the superiority of LPV/r-based over NVP-based regimens for treating young children (338–340), the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (9) recommended the use of LPV/r-based treatment in children younger than 36 months of age where feasible, regardless of NNRTI exposure. Due to the lack of robust evidence comparing different NRTI backbones, ABC and AZT in combination with 3TC were equally recommended as the preferred NRTI backbone to be used in children younger than 3 years.

Alternative strategies were also recommended 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. These strategies included

Table 4.7. Summary of first-line ART regimens for children younger than 3 years

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

^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. Availability and cost should be carefully considered.

^b As recommended by the US FDA, using LPV/r oral liquid should be avoided in premature babies (born 1 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 (335). Dosing for children younger than 6 weeks should be calculated based on body surface area (Annex 11c). Restrictions also apply to LPV/r pellets, where administration challenges extend to infants up to 3 months of age. Additional information regarding optimal administration of this formulation will be provided as more data become available (335).

^c Challenges may arise when treatment is started in the first two weeks of life following early diagnosis at or around birth, particularly in case of prematurity or low birth weight. In these situations, an NVP-based regimen containing AZT and 3TC should be started, and NVP should be substituted with LPV/r at the earliest opportunity, preferably at two weeks when LPV/r syrup can be administered (Annex 11c). In settings where LPV/r syrup is not available and LPV/r pellets are the only formulation available, administration of NVP should continue until 3 months with close clinical monitoring for those children considered at high risk for carrying NNRTI resistance (i.e. prolonged NVP-based postnatal prophylaxis or documented NNRTI failure in the mother).

^d 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.

^e RAL is approved for use in infants and children from the age of 4 weeks, but there is very limited evidence to inform the use of raltegravir (RAL) as a first-line drug in infants and young children (336). The use of this INSTI could be considered where available in instances of poor tolerability or administration challenges with LPV/r, particularly in settings where as a result of rapid expansion of maternal treatment, infants and children are at very high risk of carrying an NNRTI resistance virus. Use of RAL should however consider the challenges of existing granule formulation, despite being suitable for use in infants 4 weeks and older, as reconstitution in water is required before administration. While dispersion of RAL chewable tablets is considered to be a potential alternative, additional information regarding the appropriateness of this approach will be provided as more data become available.

3TC lamivudine, ABC abacavir, AZT zidovudine, LPV lopinavir, r ritonavir, RAL raltegravir.

substituting LPV/r with an NNRTI (EFV if 3 years and older) once viral suppression is achieved or using a triple NRTI regimen for children who develop TB while on an ART regimen containing NVP or LPV/r.

Since 2013, new evidence has become available to inform the choice of NRTI backbone (318), and the safety and efficacy of strategies to substitute LPV/r with an NNRTI when viral suppression is achieved (341,342). This has led to revised recommendations in these guidelines.

Rationale and supporting evidence

LPV/r-based treatment as a preferred regimen for infants and young children

A systematic review of two randomized controlled trials (338–340) shows that children younger than 36 months have a reduced risk of discontinuing treatment and viral failure or death if they start an LPV/r-based regimen instead of an NVP-based regimen. At 24 weeks, LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT (338). In addition, surveillance of drug resistance among children younger than 18 months (343,344) provides further evidence of detectable NNRTI resistance even among HIV-infected infants and young children without any history of exposure to ARV drugs for

PMTCT or whose exposure status is unknown, suggesting that a history of NNRTI exposure for PMTCT may not be an accurate marker for identifying children at higher risk of HIV resistance to NNRTIs. LPV/r is known to have a better resistance profile, which protects against the selection of NRTI resistance without compromising the use of other PIs in second-line regimens (314,323,345,346). In addition, a potential advantage is offered by the considerable reduction in the incidence of malaria among children receiving LPV/r-based ART, as demonstrated in a randomized controlled trial comparing the use of LPV/r versus NVP or EFV-based ART among children in Uganda receiving an artemether + lumefantrine combination for treating malaria episodes (347).

Providing an LPV/r-based regimen to infants and children younger than 3 years in some resource-limited settings may be challenging. The current LPV/r syrup formulation requires a cold chain until the point of dispensing. The syrup is unpalatable, with the potential for suboptimal adherence, as highlighted by caregivers and health workers. In addition, the risk of metabolic complications among children who initiate LPV/r early in life is unknown. LPV/r pellets, a heat-stable formulation that recently obtained tentative US FDA approval (348,349), were shown to be more acceptable to parents and caregivers than the syrup (350) and are expected to increase the feasibility of this recommendation. However, palatability remains suboptimal, and there is still some uncertainty regarding the most appropriate way to administer this formulation to breastfed infants less than 3 months of age (335). Both formulations of LPV/r are more expensive than NVP, and administering LPV/r with TB treatment is complex because drug levels are reduced by rifampicin.

Alternative approaches are proposed to overcome these challenges. Randomized controlled trials (312) have evaluated a strategy in which LPV/r is started and later substituted with an NNRTI (NVP or EFV) after confirmed viral suppression. 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. A systematic review (341,342,351,352) has shown this approach to be safe and effective in the clinical trial setting for children with sustained viral suppression achieved after receiving LPV/r-based first-line therapy, especially in the absence of HIV resistance to NNRTI before initiating ART (352). This strategy demonstrated better outcomes when substituting LPV/r with EFV compared to NVP in children aged 3 years or older with viral suppression on LPV/r-based ART (341), leading to a revised recommendation in 2015. However, uncertainty remains with regard to the appropriateness of this strategy in children exposed to maternal ART as well as standard or enhanced postnatal prophylaxis while breastfeeding. The randomized controlled trials supporting the use of this approach defined viral suppression as a viral load of or below 400 copies/mL (342,351) or below 50 copies/mL (341), with the goal of identifying the children who are more likely to be able to safely substitute LPV/r with an NNRTI. It is important to note that the use of a higher viral load cut-off for determining viral suppression has not been studied in the context of this strategy. In addition, this approach may also add complexity to treatment programmes and, because it requires access to virological monitoring, may therefore be relevant only in settings where viral load and/or genotype testing are available.

In settings where none of these approaches is affordable or feasible, and for treating infants identified at birth or soon afterwards, an NVP-based regimen provides an effective alternative to LPV/r, especially given the availability of two- and three-drug FDCs. As

observed in a large randomized controlled trial, good virological outcomes can be achieved by starting children on ABC, 3TC and an NNRTI (174).

RAL is approved for use in infants and children (from the age of 4 weeks), and while there is very limited evidence to inform the use of RAL as a first-line drug in infants and young children (336), it could be considered where available in cases of poor tolerability to or administration challenges with LPV/r, particularly in settings where, as a result of rapid expansion of maternal treatment, infants and children are at very high risk of having NNRTI resistance. However, despite being particularly suitable for use in infants 4 weeks of age and older, the existing RAL granule formulation requires reconstitution in water and may be challenging to administer (353). Dispersed chewable tablets may be more suitable for this age group, but data on their use are not yet available.

Choice of NRTIs for infants and young children

The choice of NRTIs should aim to construct a robust and durable backbone that minimizes toxicity and cost and is most feasible. A systematic review identified one randomized trial that compared the effectiveness and safety of different NRTI backbones (312). ABC and AZT combined with 3TC were demonstrated to be comparable in terms of clinical, immunological and virological response as well as safety and tolerability profile (318). However, the choice of first-line NRTIs affects second-line ART, and failure on AZT may result in the accumulation of thymidine analogue mutations that reduce 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 be less problematic. By contrast, HIV resistance to ABC preserves or even increases the susceptibility of HIV to AZT for second-line use (354).

Although ABC may be preferable in terms of ART sequencing (354) and harmonization with regimens for older children, availability is limited in resource-limited settings. In addition, the cost of ABC may be a significant barrier to adoption in many countries, especially when combined with LPV/r. These factors, together with outcomes from a technical consultation on paediatric ARV optimization (355), led to the recommendations developed in 2013 being maintained.

Since 2010, WHO has recommended that d4T be phased out because of its known long-term toxicity. Since 2013, d4T use has reduced significantly in both adults and children. Accordingly, in settings where AZT may not be advisable because of the high risk of anaemia (such as malaria-endemic settings), access to ABC is essential.

Clinical considerations

In general, the selection of regimens for this age group should be guided by the following considerations:

- the importance of potent, first-line regimens for which there is evidence of good virological response as indicated by randomized controlled trials in this age group;
- the need to address the increasing evidence of HIV resistance to NNRTIs among children younger than 18 months, especially in the context of the recommendation to treat all pregnant and breastfeeding women with EFV-based regimens to prevent mother-to-child transmission;

- the desirability of having one preferred regimen for children younger than 3 years while providing alternative strategies that remain less costly, preserve second-line options and address feasibility concerns;
- the use of 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; and
- the identification of a subset of children who can benefit from alternative strategies to preserve PIs for use in second-line ART, as indicated by a randomized controlled trial.

An important specific consideration for health-care providers relates to the challenges of providing LPV/r to young children. When clinicians anticipate significant difficulties in storing or administering LPV/r either in liquid or pellet form, NVP (especially an NVP-based FDC) can be considered.

Dosages of LPV/r for children younger than 6 weeks should be calculated based on body surface area (Annex 11c). In addition, LPV/r oral liquid should be avoided in premature or in full-term babies younger than 14 days (335). While LPV/r pellets do not require a cold chain and overcome the procurement challenges of the syrup formulations, there is very limited experience administering these to very young infants less than 3 months of age. Additional information regarding optimal administration of this formulation will be provided as more data become available.

Challenges may also arise when treatment is started in the first 2 weeks of life following early diagnosis at or around the time of birth, particularly in case of prematurity or low birth weight. If initiating ART in an infant less than 2 weeks of age, a regimen of AZT + 3TC + NVP should be started and NVP substituted with LPV/r at the earliest opportunity, preferably at 2 weeks of age, when LPV/r syrup can be used (Annex 11c). In settings where LPV/r syrup is not available and LPV/r pellets are the only formulation available, NVP should be continued until the age of 3 months, with close clinical monitoring for children considered to be at high risk for carrying NNRTI resistance as a result of prolonged NVP-based postnatal prophylaxis or documented NNRTI failure in the mother. Where it is available, RAL could also be considered as an option in special circumstances, such as lack of LPV/r in any of the above formulations.

Table 4.8. Sequencing of ARV formulations for newborns starting treatment at around birth

	0–2 weeks	→ 2 weeks–3 months →	3–36 months
Preferred	AZT + 3TC + NVP	ABC or AZT + 3TC + LPV/r syrup	ABC or AZT + 3TC + LPV/r pellets
Alternative	AZT + 3TC + NVP		ABC or AZT + 3TC + LPV/r pellets
Special circumstances	AZT + 3TC + NVP	ABC or AZT + 3TC + RAL	

3TC lamivudine, ABC abacavir, AZT zidovudine, LPV lopinavir, NVP nevirapine, r ritonavir, RAL raltegravir.

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 needs to be explored outside trial settings. In this context, more evidence is needed to confirm the appropriate dosing and safety of EFV-containing regimens as a first-line option for children less than 3 years or as part of PI-sparing strategies in the absence of facilities for viral load measurement or genotyping. Studies are also needed to specifically address the long-term metabolic implications of using LPV/r-based regimens for infants and young children. In addition, it is of critical importance to conduct studies to explore improved and safer formulations of LPV/r for neonates and alternative options (such as INSTI) that provide highly effective and well-tolerated drugs in formulations that are palatable and suitable, particularly for administration to newborns, as well as infants and young infants.

4.4.6 TB co-treatment for children with HIV

TB is one of the most common OIs affecting children with HIV. While isoniazid preventive therapy is strongly recommended as part of the comprehensive package of HIV care for all children living with HIV, it remains poorly implemented and TB continues to be a common cause of morbidity and mortality (356). Vigilant contact tracing and routine case finding are also recommended to ensure early detection and survival. If diagnosed, ART should be started as soon as possible within 8 weeks of TB treatment initiation (see section 4.3.5 “Timing of ART for adults and children with TB”). However, selecting regimens that are compatible with TB therapy continues to be challenging, for example, due to interactions between rifampicin and LPV/r or NVP.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommended using triple-nucleoside therapy based on a randomized controlled trial in children (174). This study showed preliminary evidence on the efficacy of triple-nucleoside therapy as a suitable option for children who require TB treatment while already receiving ART, with substitution of a standard first-line regimen once TB treatment is completed (Table 4.9). Since 2010, WHO has recommended the approach of “super-boosting” LPV/r with additional ritonavir (RTV) (1:1 instead of 4:1 LPV/r ratio, i.e. equal doses of LPV and RTV) to manage rifampicin-based TB co-treatment in children on an LPV/r-based regimen. An interim analysis of an ongoing open-label non-randomized pharmacokinetic study further supports this approach (357), but a final analysis is needed to confirm these results.

Recommended regimens for children diagnosed with TB and starting ART are summarized in Table 4.9, together with broader guidance on choosing regimens for co-treatment of HIV and TB.

Table 4.9. 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		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 the 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
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 Continue LPV/r, adding RTV to achieve the full therapeutic dose ^d
	3 years and older	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, adding RTV to achieve the full therapeutic dose ^d If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC) ^c or Continue LPV/r, adding RTV to achieve the full therapeutic dose ^d Consider consultation with experts for constructing a second-line regimen

^a Ensure optimal dosing of rifampicin based on dosing guidelines (Annex 11c).

^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 (174), this regimen should be considered as the preferred option for children younger than 3 years who are receiving an LPV/r-based regimen when starting TB treatment. The US FDA 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 (358). An EFV-based regimen in children under 3 years is still not recommended because pharmacokinetic 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 an 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 (359), and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.

3TC lamivudine, ABC abacavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir.

4.4.7 Infant prophylaxis

NEW

Good practice statement

ART should be initiated urgently in all pregnant and breastfeeding women, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent mother-to-child HIV transmission is to reduce maternal viral load.^a

^a Whenever possible, all efforts should be made to identify HIV-infected pregnant women early enough to avoid the need for high-risk prophylaxis.

Recommendations

- Infants born to mothers with HIV who are at high risk of acquiring HIV^a should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed (strong recommendation, moderate-quality evidence).**
- Breastfed infants who are at high risk of acquiring HIV,^a including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone (conditional recommendation, low-quality evidence).**
- Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4–6 weeks of infant prophylaxis with daily NVP (or twice-daily AZT) (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding).

^a High-risk infants are defined as those:

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

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Although rates of mother-to-child HIV transmission have fallen in recent years, there were still an estimated 220 000 infants born with HIV in 2014. Several factors have been proposed to explain this, including women not receiving antenatal testing or treatment, women presenting late for antenatal care and women acquiring HIV during pregnancy or breastfeeding. In some countries, incident HIV infection in mothers is thought to be a significant source of new infections in children, as transmission rates are especially high in this situation (360,361). Incident HIV infection is often not diagnosed until delivery or in the postpartum period. One cohort study from Zimbabwe has reported that up to 20% of all breastfeeding-associated transmission takes place in women who acquire HIV in the postnatal period (362).

Addressing these gaps requires continued emphasis on promoting universal testing and treatment in the antenatal period, as well as retesting of HIV-negative women during pregnancy, at delivery and during breastfeeding to identify incident HIV infection, especially in high-burden settings. At the same time, it is important to revisit the approach to infant prophylaxis for the infants born to mothers who have not received early, effective ART.

WHO guidance on infant prophylaxis in the setting of maternal ART has not been modified since 2010. It is recommended that breastfeeding infants be given 6 weeks of daily NVP and that non-breastfeeding infants be given either daily AZT or twice daily NVP for 4–6 weeks.

Previous WHO guidelines have acknowledged that when maternal ART is started late in pregnancy, during labour or in the postpartum period, infants who are breastfeeding may not be adequately protected from HIV because it takes several weeks for maternal viral load to be suppressed. In such situations, programmes were advised to consider increasing the duration of infant prophylaxis to 12 weeks rather than 6 weeks of NVP. Since that time, new data have become available, showing that combination infant prophylaxis is more effective than single-drug prophylaxis for the prevention of intrapartum mother-to-child transmission in infants born to mothers who have not received antepartum ARV drugs.

The goal of the new recommendations is to optimize infant prophylaxis and further reduce rates of peripartum and breast milk transmission, especially for infants whose mothers have not benefited from optimal care.

Rationale and supporting evidence

A systematic review was undertaken to examine the evidence for increasing the number of ARV drugs provided for infant prophylaxis and/or for extending the duration of prophylaxis beyond the current recommendations for infants at high risk of HIV infection due to limited or no maternal ART and/or high maternal viral load. WHO also convened an expert consultation to review the evidence and other considerations.

The systematic review (363) focused on studies that report on outcomes following the use of combined and/or prolonged infant prophylaxis regimens compared with the current standard of care. Although some of the studies reviewed were conducted in settings where formula feeding is the norm, the findings can still be applied to breastfeeding populations, as peripartum HIV transmission is an important driver of mother-to-child HIV

transmission in both settings. Four studies met the criteria for inclusion, of which two were randomized controlled trials and two were observational studies.

HPTN 040 randomized high-risk non-breastfeeding infants whose mothers had received no ARV drugs during pregnancy to one of three infant prophylaxis regimens: single drug (6 weeks of AZT), two drugs (6 weeks of AZT plus three doses of NVP in the first week of life) or three drugs (6 weeks of AZT plus an initial 2 weeks of nelfinavir and 3TC). The intrapartum transmission rate was significantly lower with the two-drug and the three-drug regimens compared to AZT alone (364). Of the total infants, 8.4% experienced serious adverse events possibly related to study drugs and 3.4% experienced serious adverse events probably related to study drugs. Higher rates were observed in the three-drug group (12.2% and 4.9%) than in the AZT-alone group (6.9% and 3.7%) or the two-drug group (6.2% and 1.8%). Grade 2 or higher neutropaenia and anaemia accounted for the majority of serious adverse events. Only two skin-related serious adverse events were reported (one each in the two- and three-drug groups), but neither was related to the study drugs and there was no difference in mortality between study arms.

HPTN 046 was a randomized controlled trial conducted in sub-Saharan Africa. Breastfeeding HIV-exposed infants received 6 weeks of NVP and were then randomized to either receive an additional 4.5 months of NVP or placebo. In this breastfed population, infants who received 6 months of NVP experienced a 54% lower transmission rate at six months compared to those who received only 6 weeks of NVP. Most mothers in this study were not receiving ART antepartum or postpartum. However, it is important to note that, among the infants born to mothers receiving ART at the time of randomization, the postnatal transmission rate was extremely low and did not differ between those who received longer-duration NVP prophylaxis and those who received placebo. Serious adverse events in the infants did not differ between infants receiving extended NVP (16%) and those receiving placebo (15%), and the frequency of adverse events overall and mortality did not differ significantly between the treatment groups (365).

One of the observational studies identified by the review involved an analysis of 5285 "high-risk" mother–infant pairs (either no or only intrapartum maternal ARV drugs or detectable maternal viral load at delivery) from eight European cohorts. Neonatal prophylaxis was administered to 88% of infants, with 24% receiving combination neonatal prophylaxis. While infant prophylaxis significantly reduced mother-to-child transmission, there was no observed difference in transmission risk between one drug and combination infant prophylaxis: the transmission rate was 18% with no infant prophylaxis, 3.4% with a single drug and 6.3% with combination prophylaxis. However, this finding likely represented residual confounding, as combination prophylaxis was associated with known risk factors for transmission, including a fourfold increased probability that infants who were given combination prophylaxis were born to mothers with a viral load above 1000 copies/mL at delivery. The authors provided toxicity data on a subset (32%) of the cohort. Overall, there was no difference in serious adverse events between infants who received one, two or three drugs. When neutropaenia was compared between the two-drug and three-drug arms, there was a trend towards more events in the three-drug arm, but this was not significant (366).

The second observational study was a single-arm study with a historical observational control in non-breastfeeding infants in Thailand. In this study, if mothers received less

than 8 weeks of antepartum ART, the infant received AZT + 3TC + NVP for 2 weeks, followed by AZT + 3TC for an additional 2 weeks (the standard-of-care infant prophylaxis regimen is 4–6 weeks of AZT). In this study, there were no intrapartum infections in 88 mother–infant pairs compared to a predicted intrapartum transmission rate of 2.0% based on historical data when only infant AZT was received. The rate of serious adverse events in infants receiving intensified prophylaxis was 13.6%, compared to 21.7% in the historical observational cohort (367).

None of the studies reviewed addressed infants identified in the postpartum period or infants exposed to an incident HIV infection either during pregnancy or while breastfeeding. However, it is likely that the findings of the systematic review could be applicable to these settings as well.

It is important to note that the recommendations for extended prophylaxis in breastfeeding infants are predicated upon maternal ART being initiated at or before the time when infant prophylaxis is begun (whether at birth or when maternal HIV is first detected postpartum), as infant prophylaxis is intended only to provide a bridge of protection to the infant during the period in which maternal viral load is decreasing on ART.

Defining high-risk infants

Although not addressed in the systematic review, a range of factors may be considered when assessing risk.

Factors such as prolonged rupture of membranes, preterm delivery and low birth weight are no longer associated with increased risk of transmission when mothers are receiving ART. The critical determinants of transmission risk in the ART era are maternal viral load and duration of maternal ART. The following scenarios may be considered as working definitions of “high-risk”:

- incident HIV infection in a pregnant or breastfeeding woman (defined as new HIV diagnosis in a pregnant or breastfeeding woman with a prior negative HIV test during pregnancy);
- HIV exposure first identified at delivery or in the postpartum period in a breastfed infant;
- if viral load testing is available, pregnant women whose viral load exceeds 1000 copies/mL within four weeks prior to delivery; and
- if viral load testing is not available, pregnant women on ART for less than four weeks.

Modifying the testing approach

Consistent with the recommendations on EID, no specific approach to the testing of high-risk newborns is recommended. However, because infants who are first identified as HIV-exposed postpartum have a high cumulative risk of already having acquired HIV by the time prophylaxis is initiated, an HIV polymerase chain reaction (PCR) test should be performed around the time of initiating prophylaxis. This will help to minimize the risk of development of resistance due to extended prophylaxis in infected infants and help to promote linkage to timely initiation of ART.

Equity and acceptability

A qualitative literature review explored acceptability relating to the duration and number of ARV drugs used for infant prophylaxis (368). Nine published studies and one report from a global survey included the values and preferences of caregivers of HIV-exposed infants and health workers with regard to infant prophylaxis in general. Overall, the studies revealed that mothers place very high value on protecting their children from acquiring HIV and that short-term interventions in the infant to protect against transmission are generally acceptable. Some studies noted the difficulties of actually administering medication to infants, underscoring the need for better formulations and simplified dosing. Mothers expressed concern about the long-term risks of ARV drugs given to babies and noted that there was a lack of information provided on dosing and potential toxicities. In a survey of health workers, the majority noted that it would be challenging to give multiple drugs for prophylaxis and that, if a baby-friendly “infant prophylaxis tablet” were available, it would significantly increase acceptability and reduce the likelihood of prescribing errors.

Implementation considerations

The feasibility of enhanced prophylaxis is related to operational issues. These include the identification of infants at high risk and the administration of prophylaxis regimens. While maternal viral load around the time of delivery is perhaps the most reliable indicator of transmission risk, access to viral load testing and timely availability of results are limited in many settings. Point-of-care platforms may simplify virological testing at delivery, but in the absence of such advances, clinical parameters need to be simple and clear. Options for the management of incident infection and maternal refusal of ART should also be considered.

Providing multiple drugs to newborns is challenging from an operational perspective, and while AZT and NVP are proposed based on the available data, one is administered once daily and the other twice daily. Provider training will be critical to the successful uptake of these recommendations, and innovative approaches to dosing (such as using twice-daily dosing of NVP) may help to simplify administration. The availability of a dispersible FDC tablet containing doses suitable for infant prophylaxis would greatly facilitate uptake of these recommendations and should be considered a priority for drug development. When the recommended regimen is not available or feasible, use of a triple-drug FDC containing AZT, NVP and 3TC may be considered to simplify administration. It is recognized that, while there is no proven benefit to using three drugs in place of two and there is some risk of increased toxicity, in practice this toxicity is minor and short lived. As the doses contained in the commercially available triple-drug FDC are higher than the doses recommended for prophylaxis, expert consultation is advised in order to establish how the FDC tablet should be divided and administered for high-risk prophylaxis.

Research gaps

Potential areas for research include clinical and pharmacological studies to inform the development of improved ARV formulations, including FDCs in appropriate doses for newborns and infants. In addition, implementation science research to evaluate the optimal definition of high risk in the context of universal maternal ART would be valuable. Research into the use of alternative drugs for prophylaxis that are better tolerated and that may have greater efficacy for infant prophylaxis such as INSTIs could also be considered.

4.4.8 Infant feeding in the context of HIV

Recommendations

National or subnational health authorities should decide whether health services will principally counsel and support mothers known to be HIV infected to either breastfeed and receive ARV^a interventions or avoid all breastfeeding.

In settings where national authorities have decided that maternal and child health services will principally promote and support breastfeeding and antiretroviral interventions as the strategy that will most likely give infants born to mothers known to be HIV infected the greatest chance of HIV-free survival, mothers known to be infected with HIV 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.^b Breastfeeding should then stop only 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).

^a All women living with HIV are eligible for initiation of ART regardless of CD4 count.

^b Infants who are HIV infected will benefit from extended breastfeeding and should continue breastfeeding for as long as feasible and desired.

Source: Guidelines on HIV and infant feeding 2010. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241599535/en).

WHO recommendations on HIV and infant feeding highlight increasing levels of HIV-free survival of HIV-exposed infants. These guidelines have been unchanged since 2010, but updated WHO recommendations on HIV and infant feeding will be released in 2016 and will specifically address the duration and timing of breastfeeding in the context of lifelong maternal ART.

In countries where diarrhoea, pneumonia and malnutrition remain significant causes of child mortality, recommendations aim to reduce the risk of HIV transmission through breast milk. This is done primarily by providing ART to mothers living with HIV and ARV prophylaxis to their infants, while avoiding malnutrition and the increased risk of serious infections in infants and children through the promotion of breastfeeding. In other settings, avoidance of all breastfeeding is currently recommended.

WHO guidance has been 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 when the mother is receiving ART (369,370). In 2010, breastfeeding beyond 12 months was not recommended because of uncertainty about the ability of health systems to retain mothers in care and to support maternal adherence to ARV drugs over long periods of time. There were also only limited data available on potential adverse events among infants exposed to low doses of ARV drugs through breast milk (371–373).

National-level adaptation of the WHO recommendation has been very consistent, although a few countries have standardized the recommended duration of breastfeeding for mothers living with HIV at 24 months, similar to that for HIV-negative mothers. Contrary to WHO recommendations, some countries continue to recommend less than 12 months of breastfeeding.

Implementation considerations

The 2010 WHO recommendations placed major emphasis on promoting and supporting mothers living with HIV to breastfeed their infants until 12 months of age. These guidelines acknowledged that some mothers might not be able to provide a safe and adequate diet to children beyond 12 months of age without breastfeeding. In these situations, it is suggested that breastfeeding should continue while mothers are receiving ART. WHO is currently considering whether to recommend unrestricted breastfeeding among mothers living with HIV who are on ART.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for breastfeeding by mothers living with HIV while receiving ART include:

- communicating clearly and effectively to health workers, mothers and the community the effectiveness of ART to reduce the postnatal transmission risks through breastfeeding;
- highlighting the value of breastfeeding for the health, development and survival of mothers living with HIV and their children when the mother is receiving ART;
- implementing and sustaining specific interventions (such as integrated follow up with immunization and other well-child services) to improve postpartum follow up of mother–infant pairs, and supporting breastfeeding practices and ART adherence;
- emphasizing postnatal prophylaxis for infants: infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP, or if they are considered at high risk, enhanced infant prophylaxis using AZT and NVP for 6 weeks followed by either AZT and NVP or NVP alone for an additional 6 weeks (see section 4.4.7 “Infant prophylaxis”); and
- linking EID results with appropriate infant-feeding practices: infants who are HIV infected should continue breastfeeding until 24 months or longer.

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

Research gaps

Programmatic data are needed on postnatal ART adherence and patterns of retention in care, in addition to the duration of breastfeeding among women living with HIV to more accurately estimate the number of infants being infected postnatally. The incident HIV infection rate among breastfeeding mothers in areas with a high prevalence of HIV infection is also required to determine the magnitude of this population and their particular risks.

Further studies are needed of 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. The penetration of ARVs into breast milk is incompletely understood, and pharmacological studies to determine the ratio of breast milk and maternal plasma – as well as infant plasma drug levels – are needed to better understand drug levels in breast milk and the “dose delivered” to the infant for many of the ARV drugs currently in use. Such data are required for each ARV drug, as these characteristics are likely to differ between different drugs.

Greater understanding is needed regarding the relationship between viral load and postnatal transmission risk according to whether the mother is on ART or not. Research is also needed on interventions to improve retention in care and adherence to postnatal ARV drugs and breastfeeding.

4.5 Monitoring the response to ART and diagnosing treatment failure

4.5.1 Laboratory monitoring before and after initiating ART

Clinical assessment and laboratory tests play a key role in assessing individuals following a positive HIV diagnosis to assess for coinfections, noncommunicable diseases (NCDs) and other comorbidities that may have an impact on treatment response. Limited laboratory testing is also recommended for monitoring the response to treatment and possible toxicity of ARV drugs. Table 4.10 summarizes the recommended laboratory tests for HIV screening and monitoring as well as approaches to screening for coinfections and NCDs.

Table 4.10. Recommended tests for HIV screening and monitoring and approaches to screening for coinfections and noncommunicable diseases

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV testing (serology for adults and children 18 months or older; EID for children younger than 18 months) CD4 cell count TB symptom screening	HBV (HBsAg) serology ^a HCV serology Cryptococcus antigen if CD4 cell count ≤ 100 cells/mm ³ ^b Screening for STIs Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child Assessment for major noncommunicable chronic diseases and comorbidities ^c
Follow-up before ART	CD4 cell count (every 6–12 months in circumstances where ART initiation is delayed)	
ART initiation		Haemoglobin test for starting AZT ^d Pregnancy test Blood pressure measurement Serum creatinine and estimated glomerular filtration rate (eGFR) or starting TDF ^e Alanine aminotransferase for NVP ^f Baseline CD4 cell count
Receiving ART	HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter) CD4 cell count every 6 months until patients are stable on ART	Serum creatinine and eGFR for TDF ^g Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV
Suspected treatment failure	Serum creatinine and eGFR for TDF ^g Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV	HBV (HBsAg) serology ^{a,g} (before switching ART regimen if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter)

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

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

^c Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Programme (mhGAP) or national standard protocols (see section 5.3 "Prevention, screening and management of other comorbidities and chronic care for people living with HIV"). Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria. See formula for eGFR in the footnote to section 4.6.3.

^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 body mass index (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 hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

^g For HIV/HBV coinfecting individuals who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second-line regimen.

ART antiretroviral therapy, AZT zidovudine, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, EID early infant diagnosis, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, HCV hepatitis C virus, STI sexually transmitted infection, TDF tenofovir.

4.5.2 Monitoring the response to ART and diagnosis of treatment failure



Recommendations for routine monitoring

Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting^a (conditional recommendation, very low-quality evidence).

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed^b (conditional recommendation, low-quality evidence).

^a Viral load testing should be performed early after initiating ART (within 6 months), at 12 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 viral failure where possible.

^b WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL). For service delivery recommendations in these guidelines (see Chapter 6 “Service delivery”), an additional criterion is that there are no adverse drug reactions requiring regular monitoring, but this is not relevant to this recommendation.


Recommendations for diagnosis of treatment failure

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure^a (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).

Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (that is, two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.

Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV viral load. A threshold of 1000 copies/mL can be used to determine viral failure when using dried blood spot samples, as defined for testing in plasma^a (conditional recommendation, low-quality evidence).



^a Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Monitoring people on ART is important to ensure successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure. In 2013, WHO recommended viral load testing as the preferred monitoring approach to diagnose and confirm ARV treatment failure. Compared to clinical or immunological monitoring, viral load provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes (374). Measuring viral load can also help to distinguish between treatment failure and non-adherence. Studies suggest that around 70% of patients on first-line ART who have a first high viral load will resuppress following an adherence intervention (375), indicating non-adherence as the reason for the high viral load in the majority of cases. Viral load can also serve as a proxy measure for the risk of transmission and effectiveness of prevention interventions at both the individual level, especially for pregnant women (376), and at the population level (377).

Many national guidelines now recommend either targeted or routine viral load monitoring, and countries are in the process of scaling up access to these approaches. However, regular access to routine viral load testing remains limited, and this has been identified as a key reason for lower-than-expected rates of identified treatment failure in resource-limited settings (378).

Routine versus targeted viral load monitoring to detect viral failure

Viral load should be monitored routinely at 6 months, at 12 months, and then every 12 months thereafter if the patient is stable on ART to detect treatment failure earlier and more accurately. A systematic review was conducted to assess the optimal timing for initial viral load testing and thereafter (380). Despite very low-quality evidence from the review findings, the Clinical Guideline Development Group recognized the importance of clear guidance around the timing of routine viral load testing and made a conditional recommendation to synchronize routine viral load monitoring with routine monitoring systems, citing better alignment of outcomes, feasibility and acceptability (380).

In settings with limited access to viral load testing, a targeted viral load strategy to confirm suspected treatment failure based on immunological or clinical criteria should be used to avoid unnecessary switching to second-line ART regimens. Targeted viral load monitoring is less costly than routine viral load testing, but as with clinical and immunological monitoring, it 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 viral failure

The optimal threshold for defining viral failure and for switching ART regimens has not been established. WHO recommends a threshold of 1000 copies/mL based on the fact that the risk of HIV transmission and disease progression is very low when viral load is lower than 1000 copies/mL (381–383), and that below this threshold, 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 (384). Most standard viral load platforms using plasma specimens have good diagnostic accuracy at

Table 4.11. WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	<p>Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)^a after 6 months of effective treatment</p> <p>Children New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment</p>	<p>The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure^a</p>
Immunological failure	<p>Adults and adolescents CD4 count at or below 250 cells/mm³ following clinical failure^b or Persistent CD4 levels below 100 cells/mm³</p> <p>Children <i>Younger than 5 years</i> Persistent CD4 levels below 200 cells/mm³ <i>Older than 5 years</i> Persistent CD4 levels below 100 cells/mm³</p>	<p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count</p> <p>Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure</p>
Virological failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

^a See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 10.

^b Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at or below 250 cells/mm³ following clinical failure is based on an analysis of data from Uganda and Zimbabwe (379).

this lower threshold. Prior concerns regarding the sensitivity of dried blood spot specimens have been clarified through a systematic review conducted for these guidelines.

Determining treatment failure in the absence of viral load monitoring

Where viral load monitoring is not available, clinical monitoring and CD4 monitoring are recommended. However, immunological and clinical criteria have poor sensitivity and specificity to detect treatment failure, particularly at higher CD4 cell counts, and more accurate immunological criteria are yet to be identified (385). In the absence of better criteria to predict treatment failure, it is important to use CD4 cell count and clinical assessment to identify those at the highest risk of disease progression and mortality. Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. Recognizing the limitations of the current criteria, several studies have proposed alternative

approaches, including a single CD4 count at or below 250 cells/mm³ following clinical failure (379) and CD4-based risk charts with optimal cut-offs for guiding targeted viral load testing (386). Such approaches merit validation in other settings.

A cohort analysis, updated for the revision of these guidelines (387), explored the risk of mortality associated with CD4 cell counts in children and confirmed the appropriateness of existing CD4 thresholds in identifying infants and children for whom ART is failing and at the highest risk of mortality (more than 5% 1-year mortality risk). Since the publication of the 2013 guidelines, a large randomized controlled trial in children (174) has shown that CD4 monitoring provides clinical benefit over clinical monitoring after the first year on ART and that failure to thrive is a sensitive indicator of treatment failure. The association between poor weight gain and increased risk of death was described in a large observational dataset (388) emphasizing the importance of growth monitoring in the routine clinical assessment of children living with HIV (see section 4.3.4 “When to start ART in children younger than 10 years of age”) and suggesting that loss of weight or poor weight gain are potential signs of treatment failure.

Stopping CD4 count monitoring where viral load testing is available

Recent studies suggest that in situations where viral load testing is routinely available and individuals are virally suppressed, long-term CD4 cell count monitoring adds little value, and stopping the estimation of CD4 for monitoring purposes will have major cost savings. A number of countries have either reduced the frequency of or stopped routine CD4 cell count monitoring altogether in people who are stable on ART, and rely on viral load alone to monitor the response to ART and detect potential virological failure.

A systematic review identified 13 studies carried out in Asia, Africa, Europe, the United States and Australia and found that CD4 count declines among adults and children who are virally suppressed on ART are rare and mainly transient events that are mostly explained by non-HIV factors, such as concomitant immunosuppressive therapy. Overall, the evidence suggests that for individuals stable on ART who are monitored virologically, routine monitoring of CD4 could be stopped (383). This recommendation is further supported by the substantial cost savings that could be gained from stopping routine CD4 count monitoring (389–391) and modelling. The latter suggests that viral load testing is cost-effective for stable individuals if provided as part of a package of care that includes less frequent clinic visits and stopping CD4 count monitoring (see Chapter 6 “Service delivery”).

It is important to note that the evidence for children was limited to one study, in which the probability of CD4 decline was lowest (2.8%) in children older than 2 years with no or mild immunosuppression (392). CD4 count monitoring may still be warranted in children below this age.

Viral load for assessing transmission risk

In some clinical settings, viral load testing may have additional value for assessing the risk of transmission. This is especially true in the case of pregnant women where, in the absence of ART, viral load is proportionate to the risk of mother-to-child transmission (393). Although ART markedly reduces transmission risk, the same association between transmission and viral load persists. These guidelines propose enhanced infant

prophylaxis using AZT *and* NVP together, instead of AZT *or* NVP, as a means to reduce transmission in high-risk infants (394). Although risk can be defined using clinical criteria, viral load is the best determinant of risk. The opportunity to offer an intervention and potentially prevent infection in an infant is a strong rationale to prioritize rollout of viral load testing to women during pregnancy and around the time of delivery.

Dried blood spot specimens for viral load monitoring

Dried blood spot (DBS) specimens provide a way to improve the coverage and reach of viral load testing, particularly in remote and rural areas where preparation and transport of plasma specimens is limited by cold-chain requirements and lack of staff trained to perform venepuncture and plasma separation. Several countries have begun implementation of the use of DBS specimens for viral load testing using protocols recommended by manufacturers despite its off-label use, and DBS specimens have been widely used for EID with qualitative nucleic acid testing and high acceptability.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that a higher threshold for detection of treatment failure may need to be applied if DBS specimens are used due to uncertainty about the accuracy of DBS specimens for viral load testing below 1000 copies/mL.

A systematic review identified 43 studies that compared DBS specimens to plasma specimens for viral load testing. Overall, performance of DBS specimens was found to have acceptable sensitivity and specificity for identifying virological failure when compared to a reference standard of the same assay using a matched plasma specimen at 1000 copies/mL for most commonly used technologies (see Table 4.12) (395). However, it should be noted that some of the assay types were found to have low sensitivity at the time this evaluation was performed (up to June 2015) and should be avoided. While this reduced sensitivity means that plasma specimens are preferred for viral load testing, modelling suggests that if viral load testing with DBS specimens can be performed with reasonable sensitivity and specificity (>85%) then costs and outcomes are similar. Other modelling work done to support the development of these guidelines suggests that viral load testing using DBS specimens is cost-effective for determining virological failure at a threshold of 1000 copies/mL and at the level of accuracy reported by the meta-analysis

Table 4.12. Performance of assay type using DBS compared to plasma using a viral load threshold of 1000 copies/mL

Failure	Abbott RealTime	BioCentric Charge Virale	bioMerieux Nucleisens	Roche TaqMan FVE	Roche TaqMan SPEX	Siemens kPCR
Sensitivity ^a (95% confidence interval [CI])	95% (82–99%)	95% (71–99%)	84% (79–89%)	85% (77–91%)	99% (97–100%)	91% (69–98%)
Specificity ^a (95% CI)	92% (79–97%)	55% (35–74%)	95% (86–98%)	94% (85–98%)	44% (18–74%)	88% (75–94%)

^a Pooled estimates of sensitivity and specificity based on published data up to June 2015 (395).

when used to support differentiated care (i.e. less frequent clinic visits for stable individuals, as discussed in Chapter 6 “Service delivery”) (396).

An important limitation of the evidence supporting DBS specimens for viral load testing is that the majority of studies included in the review used venous whole blood specimens prepared in the laboratory using precision pipettes to dispense the blood onto the filter paper rather than based on specimens obtained in clinical settings. In addition, when plasma specimens are used for viral load monitoring, lack of integrity of the cold chain may influence accuracy. Research is needed to validate the performance of DBS specimens in routine programme settings, with an emphasis on specimen preparation done by less skilled health staff and using different types of filter paper.

Implementation considerations

Access to ART should be the first priority for all age groups, and lack of testing for monitoring treatment response should not be a barrier to initiating ART. If viral load testing capacity is limited, it should be introduced in a phased approach. Examples of phased approaches include:

- using viral load initially as a targeted test to confirm treatment failure;
- leveraging existing systems of DBS collection and transport for infant diagnosis in order to roll out viral load testing in maternal and child health settings;
- prioritizing viral load testing for pregnant and breastfeeding women, especially around the time of delivery, as sustained viral suppression is critical to prevention of transmission to the child, and documented high viral load at delivery is an indication for enhanced infant prophylaxis;
- preferentially offering viral load testing to HIV-infected infants and children for whom CD4-based criteria are particularly poor and in light of the limited drug options available for lifelong treatment; in addition, infants exposed to maternal ART and/or postnatal prophylaxis have been reported to have high risk of acquiring and selecting HIV drug resistance (343) and, as a result, are at higher risk of treatment failure early, especially if treated with NNRTI-based regimens;
- giving consideration to more frequent viral load testing in adolescents who are at the highest risk for HIV drug resistance and for whom monitoring of adherence might be particularly challenging in settings where viral load monitoring is widely available; and
- ensuring that health-care providers are adequately trained to conduct timely viral load testing and take appropriate clinical actions when the viral load is high, such as intensified adherence support and possible regimen switches.

Views expressed during a community consultation undertaken for these guidelines underscored the importance of improving literacy about viral load testing (5). It is generally understood that access to viral load testing gives clients a measure of understanding, control and motivation to adhere to and manage their HIV infection. Adherence counselling needs to address the implications of a detectable or undetectable viral load, particularly in settings where treatment success was previously described only in terms of a rising CD4 cell count.

CD4 cell count for ART monitoring should be stopped only in settings where viral load

monitoring can be assured. CD4 measurement still has an important role to play in assessing baseline risk of disease progression, particularly for individuals presenting with advanced disease, decisions regarding starting and stopping prophylaxis for OIs, and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART.

Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children are found in Annex 12.

Research gaps

While efforts continue to increase access to viral load testing, it is recognized that in some settings, viral load testing may remain difficult to access for some time. In such situations, there is a need to further validate the accuracy of alternative clinical and immunological strategies for predicting virological failure.

4.5.3 Monitoring ARV drug resistance

Current approaches to resistance testing remain too costly and complex for routine use as part of a public health approach, and WHO does not currently recommend routine resistance testing to guide ART regimen selection.

Some countries use resistance testing to inform treatment decisions. WHO recognizes the value of resistance testing for individual patients in such situations, provided that adequate treatment options are available and in-country expertise exists to properly interpret results.

To inform population-level decision-making, WHO recommends routine surveillance for HIV drug resistance (HIV-DR) in populations initiating ART and in populations on ART for 12 months and more than 48 months. The results of these surveys support the choice of recommended first- and second-line ART, and pre- and post-exposure prophylaxis (397).

Emergence of HIV-DR in treated populations is associated with factors related to patient care (and viral suppression at 12 months), patient behaviour (adherence) and clinic-level and programme management (retention on first-line ART, and procurement and supply management of ARV drugs).

Many factors are associated with the emergence of HIV-DR. Broadly, these factors may be divided into three categories: (i) viral factors (such as HIV subtype, replication capacity and pre-existing polymorphisms); (ii) drug-related factors (such as drug potency, pharmacokinetics, drug–drug interactions, tolerance and genetic barrier to resistance); and (iii) programme factors (such as adherence to prescribed ART, drug supply continuity and retention of patients on treatment). Although viral and drug-related factors are often beyond the control of public health authorities or programme managers, the monitoring of ART programme factors can alert ART clinics and national programme planners to situations that may favour population-level virological failure and/or the emergence of resistance. Once such situations have been identified, clinic- or programme-level action

may be implemented to optimize patient care, thus minimizing the emergence of preventable HIV-DR.

WHO recommends that prevention of HIV-DR be integrated into national HIV programmes, through the annual monitoring of early warning indicators (EWIs) and through the implementation of HIVDR surveillance (see section 7.6.2 “Drug resistance surveillance”).

Prescription- or pill-based methods for estimating adherence to ART are objective estimates calculated from routinely captured pharmacy data and have been demonstrated to predict virological and drug-resistance outcomes (398).

Randomized controlled trials report selection of HIV-DR in at least 70% of patients with virological failure (399), with some studies documenting no resistance at ART initiation (400). Numerous studies have documented HIV-DR in substantial proportions of patients with confirmed virological failure (401–404).

It should be possible to evaluate the recommended EWIs through routine programme data. Global targets support the indicators. Indicator analysis and action plans based on their results support optimization of HIV treatment and minimize the emergence of HIV-DR. Further information on monitoring for HIV-DR is provided in section 7.6.2 “Drug resistance surveillance”.

4.6 Monitoring of and substitutions for ARV drug toxicities

4.6.1 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.

4.6.2 Major types of ARV toxicities

As in 2013, these guidelines recommend a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. At the same time, several laboratory tests for monitoring ARV toxicity are advised (but not required) for specific high-risk people using certain drugs. Table 4.13 lists the key types of toxicity and associated risk factors for the major ARV drugs.

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

Information on systems approaches to monitoring ARV drug toxicity is provided in section

Table 4.13. Types of toxicities associated with first-, second- and third-line ARV drugs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 allele	Do not use ABC in the presence of HLA-B*5701 allele. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1A1*28 (UGT1A1*28) allele	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors.
AZT	Severe anaemia, neutropaenia	CD4 cell count of ≤ 200 cells/ mm^3	Substitute with TDF or ABC. Consider use of low-dose zidovudine (405).
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG	Hepatotoxicity Hypersensitivity reactions	Hepatitis B or C coinfection Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another therapeutic class.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline)	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms.
	Convulsions	History of seizure	For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	

Table 4.13. (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
EFV	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs).
ETV	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. ATV can be used for children older than 6 years. If LPV/r is used in second-line ART for adults, and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol misuse	
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea		Substitute with ATV/r, DRV/r or integrase inhibitors.
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm ³ in women or >400 cells/mm ³ in men)	If hepatotoxicity is mild, consider substitution with EFV, including in children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factors unknown	

Table 4.13. (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age BMI <18.5 or low body weight (<50 kg) notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC. Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

ABC abacavir, ATV atazanavir, AZT zidovudine, CNS central nervous system, DRV darunavir, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, HBV hepatitis B virus, HCV hepatitis C virus, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir, TDF tenofovir.

4.6.3 Monitoring TDF toxicity

Monitoring TDF toxicity in adults

The renal toxicity of TDF is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease, and also with bone mineral density loss (406,407). However, the incidence of clinically significant renal toxicity with TDF is very low in randomized controlled trials, with grade 3 and 4 elevations in serum creatinine reported in less than 1% of patients (408–410). In 2015, a systematic review on TDF toxicity (411) indicated that TDF was associated with fewer discontinuations overall, and fewer discontinuations due to adverse reactions compared to AZT and d4T. Nevertheless, concerns about TDF toxicity remain. The review showed that TDF is associated with modest reductions in eGFR¹ and creatinine clearance and reductions in bone mineral density in both hip and spine as well as increases in serum creatinine. The systematic review found that, compared to TDF, there was lower mortality, fewer treatment discontinuations overall, fewer discontinuations due to adverse reactions and significantly higher eGFR at 48 weeks with TAF (412).

In April 2016, the United States FDA approved TAF, an investigational pro-drug of TDF with a lower dose of active ingredient, but its availability is still very limited. The

¹ Using the Cockcroft–Gault (CG) or Modification of Diet in Renal Disease (MDRD) study formulas for estimation. CG formula: $eGFR = 140 - \text{age (years)} \times \text{body weight (kg)} \times 0.85$ (if female)/(72 \times serum Cr in mg/dL); <http://nephron.com/cgi-bin/CGSI.cgi>. MDRD formula: $eGFR = 175 \times (\text{Serum Cr})^{-1.154} \times (\text{age})^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$; http://touchcalc.com/e_gfr.

systematic review highlighted the need for further monitoring to determine whether eGFR reduction with TDF stabilizes after 48 weeks of treatment. One trial suggested that an early change in eGFR following treatment initiation was followed by stabilization (413). However, when combining the values reported in cohorts over a longer period of time, the trend suggested continued decrease in eGFR over an extended period. Further research is needed to explore whether renal impairment is reversible after stopping TDF (414–416). Overall, the incidence of chronic kidney disease remained low in patients exposed to TDF, and the incidence of acute kidney injury was very low (417–420). The 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 or risk factors.

Serum creatinine and glomerular tests may not adequately measure tubular injury. The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory for initiating treatment with TDF. However, it is advisable to detect and limit further progression of renal impairment in high-risk people. The major risks for TDF-related kidney damage are underlying kidney disease; age more than 50 years; low body weight (<50 kg), notably in females; untreated hypertension; and diabetes. Use of TDF with other nephrotoxic drugs, including those sold over the counter, nonsteroidal anti-inflammatory drugs, boosted PIs and ledipasvir, a direct-acting antiviral (DAA) drug to treat hepatitis C infection, leads to a greater initial decline in renal function. This decline may be worse when TDF is given in combination with ATV/r compared to when combined with LPV/r (420). People with impaired eGFR at baseline (<50 mL/min) should not initiate TDF.

Many countries are recommending creatinine clearance monitoring, but lack of availability should not be a barrier to TDF initiation. A systematic review (421) examined whether in settings without a standard laboratory, a urine dipstick is an effective intervention to detect loss of renal function or proximal tubular dysfunction. Evidence was also reviewed comparing urine glucose or albumin proteins on a dipstick. No evidence was found to guide practice on estimating the accuracy of urine glucose dipstick testing to detect renal toxicity in patients with HIV on TDF in the absence of laboratory capacity. In addition, indirect evidence showed poor sensitivity of urine proteinuria dipstick testing to detect renal damage in routine monitoring (422). The use of eGFR, albumin–creatinine ratio (ACR) or albumin–protein ratios or tests of low-molecular-weight proteins using urinary samples have been documented, but it is still not clear how and whether these are related to the clinically relevant target conditions for TDF toxicity (423). No recommendation could be made on a point-of-care strategy for monitoring TDF renal toxicity using urinary dipsticks (424).

Monitoring TDF toxicity in adolescents and children

The systematic review indicated that TDF toxicity among children and adolescents could be similar to that seen in adults (411). However, data are still lacking, and renal and bone toxicities in growing children and adolescents remain a concern. In the context of lack of paediatric formulations, increasing monitoring for TDF toxicity should be considered, including in young children or adolescents with low body weight who are using split adult tablets (321).

Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while adolescents and children are receiving TDF (328). When serum phosphate testing is available, by extrapolation, low serum phosphate

should give rise to concern about bone mineral density loss. Increasing dosing accuracy in children and adolescents is extremely important for reducing toxicity (329) (see Annex 11: Dosages of recommended antiretroviral drugs).

Clinical considerations

- Laboratory screening is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring should be used to assess for hypertension.
- If the creatinine test is routinely available, the eGFR at baseline should be used before initiating a TDF-containing regimen.
- TDF should not be initiated when the eGFR is <50 mL/min or in uncontrolled hypertension or diabetes and renal failure.
- Patients should be screened and treated for associated risk factors such as hypertension or diabetes and their treatment monitored.
- Growth should be carefully monitored in children using TDF.

4.6.4 Monitoring the toxicity of integrase inhibitors

New INSTIs have demonstrated a favourable safety profile and low potential for drug interaction in clinical trials (425–427). In 2015, a systematic review on the toxicity of the INSTIs RAL and DTG (411) found fewer discontinuations overall compared to EFV and NVP and a trend towards fewer discontinuations due to adverse reactions (2–3%).

DTG may cause generally mild or moderate nausea, headache and diarrhoea that do not limit treatment. Serious adverse effects include abnormal liver function, particularly in patients with HBV or HCV coinfection, and potentially serious hypersensitivity reactions (428). DTG does not need a boosting agent (such as RTV or COBI), which minimizes drug interaction potential (429). DTG is reported to affect renal function, with a 10% serum creatinine increase due to inhibition of renal transport protein and consequently an estimated reduction in creatinine clearance, but without any eGFR modification. No tubulopathy or discontinuation of DTG due to renal toxicity has been reported (429).

RAL has a favourable profile, with the most commonly reported adverse reactions – diarrhoea, nausea and headache – reported as being mild to moderate and not limiting treatment (430). Severe adverse reactions – rash, hypersensitivity reactions, severe acute renal failure associated with rhabdomyolysis and depression – have been reported only rarely. RAL has also been linked to instances of Stevens-Johnson syndrome, which can be accompanied by hepatic involvement. Preliminary data show that RAL could be used concurrently with TB treatment (rifampicin) with no drug interaction and few side-effects. However, because of the small size of the study, these results need further assessment (431). Evidence from the systematic review (411) showed that RAL is less likely to lead to dyslipidaemia than LPV/r and has less impact on bone mineral density than is observed with therapy containing EFV, DRV/r and ATV/r.

The toxicity profile of RAL in children and adolescents 2–18 years of age is comparable to that observed in adults (411). The profile of DTG has not been established in children younger than 12 years of age or weighing less than 40 kg, or in INSTI-experienced paediatric patients with documented or clinically suspected INSTI resistance.

There are limited data on the use of INSTIs (DTG and RAL) in pregnant or breastfeeding women. See section 4.6.6 “Special considerations for toxicity monitoring during pregnancy and breastfeeding”.

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

Monitoring the toxicity of abacavir

The use of ABC has been limited due to its toxicity profile, including an increased risk of hypersensitivity reaction (HSR) and myocardial infarction in adults (432). HSR, which is associated with the presence of the HLA-B*⁻⁵⁷⁰¹ allele, represents a main concern in children (433–435). An updated systematic review and meta-analysis conducted for these guidelines (331) reported adverse outcomes for 1769 children (age between 0 and 18 years) exposed to an ABC-containing regimen among 2546 patients treated. Despite heterogeneity between studies with regard to the incidence of adverse outcomes, the review found no increase in HSRs, treatment discontinuations due to toxicity, grade 3 and 4 reactions or death associated with ABC exposure compared to exposure to other ARV drugs. The estimated incidence of HSR from the systematic review among children exposed to ABC was low (2.2%), as was the number of reported deaths (3.3%), with none of the deaths reported as being associated with ABC toxicity.

Among adults, a strong relationship was reported between HSR related to ABC and HLA-B*⁻⁵⁷⁰¹ allele genotype (436), but this association has not been studied in children. The review included comparative data from two randomized controlled trials (437,438) conducted in one setting of high prevalence of the HLA-B*⁻⁵⁷⁰¹ allele before the introduction of any pre-treatment screening of this allele and one low-prevalence setting (318). The prevalence of the HLA-B*⁻⁵⁷⁰¹ allele genotype seems to differ significantly according to ethnicity, with a prevalence higher than 5% in people of Caucasian origin, intermediate in people of Asian origin (4.0% among Thais, 3.4% among Cambodians) but lower than 2% in people of African origin and 0.6% in people of Chinese origin. Screening for the HLA-B*⁻⁵⁷⁰¹ allele before initiating ABC therapy has been recommended in the drug label by the US FDA and United States paediatric ARV guidelines since 2008, as well as in the drug label by the European Medicines Agency. More evidence is needed to assess the prevalence of the HLA-B*⁻⁵⁷⁰¹ allele in Asian populations. In the meantime, because HSR remains rare, where screening is not feasible, appropriately trained clinical staff should manage patients clinically, with education provided to caregivers and older children.

Overall, the review found a high frequency of treatment discontinuation due to toxicities, including both severe adverse reactions and other milder reactions (grade 1 or 2, such as vomiting, nausea, fever, diarrhoea and rash) with paediatric drugs (ABC, AZT or d4T). Qualitative evidence synthesis highlighted caregivers’ concerns about adverse reactions, often resulting in children’s refusal to take ART (moderate confidence) (439). Clinical vigilance is required to be alert to adverse reactions in children and adolescents on ART.

Monitoring the toxicity of efavirenz

The main type of toxicity of EFV is CNS side-effects, which typically resolve after a few weeks. In some cases, they can persist for months or not resolve at all (440).

A recent systematic review comparing the risk of discontinuation due to adverse drug reactions associated with EFV compared to other ARV drugs in first-line therapy found that EFV was well tolerated, with over 90% of patients remaining on an EFV-based first-line regimen after an average follow-up time of 78 weeks. While the relative risk of discontinuation was higher for EFV compared to most other first-line options, absolute differences were less than 5%, and there was no difference in the risk of severe clinical adverse reactions. The rate of suicidal ideation was low (0.6%), and no suicides were reported (247). In children, CNS toxicity will need to be monitored more closely, as younger children may have more difficulty in characterizing symptoms.

A randomized trial comparing standard-dose EFV at 600 mg/day with the reduced dose of 400 mg/day in non-pregnant adults found that fewer EFV-related adverse reactions were reported with the lower dose, including fewer CNS symptoms, a finding that informs the new recommendation to use the lower dose as part of first-line ART (269) (see section 4.4.1 "First-line ART for adults").

Despite concerns about the potential risk of teratogenicity associated with the use of EFV during pregnancy, an update of a systematic review in 2015 found no overall increase in the incidence of birth defects with first-trimester EFV exposure compared with other ARV drugs (259). The safety of EFV among pregnant women is discussed further in section 4.6.6 "Special considerations for toxicity monitoring during pregnancy and breastfeeding".

Monitoring the toxicity of nevirapine

The laboratory measurement of liver enzymes has very low predictive value for adverse reactions to NVP-containing regimens. However, monitoring hepatic enzymes is recommended where feasible, especially for women with HIV who have CD4 counts above 250 cells/mm³ and people with HIV who also have HBV or HCV.

Monitoring the toxicity of zidovudine

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin should be considered before initiating ART, mainly among adults and children with low body weight, low CD4 cell counts and advanced HIV disease. Monitoring severe anaemia at baseline (haemoglobin <6.5 g/dL) and during treatment in adults and children is recommended, notably in those receiving AZT as part of first-line therapy (see section 4.6.2 "Major types of ARV toxicities").

4.6.6 Special considerations for toxicity monitoring during pregnancy and breastfeeding

Safety of efavirenz and tenofovir during pregnancy

In 2015, updated systematic reviews and meta-analysis showed that data on the safety of EFV and TDF during pregnancy were reassuring, confirming prior reviews conducted for the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (259,260,441).

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

of 0.02–0.2%, confirming studies reviewed for the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (259,441,442).

Review of the evidence showed no increased risk of abnormal pregnancy outcomes such as congenital anomalies, growth, bone health, low or mean birth weight, prematurity, pregnancy loss or miscarriage or other serious maternal adverse reactions with TDF-based ART compared with pregnant women receiving other triple-drug regimens without TDF. The evidence review is consistent with data from the Antiretroviral Pregnancy Registry (442), which now includes a sufficient number of first-trimester TDF exposures to be able to rule out at least a 1.5-fold increased risk of overall birth defects, with a prevalence of overall birth defects with first-trimester TDF exposure of 2.3%, comparable to the 2.7% prevalence in the general population of the United States. Current human data available suggest that TDF does not increase the risk of major congenital anomalies.

Data on maternal toxicity or infant growth and adverse bone effects associated with TDF exposure remain limited. Only one study directly measured bone mineral density in newborns and found a significant loss of bone mineral density in TDF-exposed newborns compared to those who were not exposed to the drug. However, longitudinal data were not available, and the clinical significance of this finding remains unclear (443). Although significant differences in anthropometric parameters have not been found in TDF-exposed compared to TDF-unexposed newborns at birth, one study reported slightly lower mean length-for-age-scores in TDF-exposed compared to TDF-unexposed infants at 1 year of age. However, in another study with a follow-up of two years, this difference did not persist (370,444).

Safety of dolutegravir and raltegravir during pregnancy

There is a lack of data on the safety of INSTIs during pregnancy and breastfeeding (411,442). The safety of DTG in pregnancy in particular is not well established, as there are no published safety or efficacy data on the outcomes of treating women with DTG during pregnancy. Furthermore, calcium or iron supplements frequently used during pregnancy could significantly reduce DTG drug levels (445). Although there are no animal data to suggest that any of the INSTIs have any fetal toxicity, the current update of the Antiretroviral Pregnancy Registry reports only 391 documented INSTI exposures during pregnancy (442). In the absence of well-controlled studies in pregnant women, DTG and RAL should be used only if the perceived benefits outweigh the risk. For practical purposes, in most settings, first-line therapy for pregnant women should continue to be based on drugs for which adequate safety data are available. For these reasons, EFV-based regimens are preferred over DTG-based regimens until more data become available.

Safety of nevirapine during pregnancy

Concerns about a higher risk of severe hepatic and skin reactions with NVP compared with EFV were addressed for the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. The systematic review conducted at the time suggested that the frequency was increased but no higher than in the general adult population and concluded that NVP needs to be used with caution in pregnant women or women who might become pregnant (294). The higher risk of hepatic and skin reactions with NVP in pregnancy and at higher CD4 counts led to the 2013 recommendation favouring EFV as a first-line NNRTI.

Specific considerations on the safety of ART prior to conception

Use of ART during pregnancy, particularly when it begins before conception, has been associated in some studies from both high-income and resource-limited countries with increased risk of adverse birth outcomes, such as preterm delivery and low birth weight (446–449). In 2015, a systematic review conducted for these guidelines to assess the safety of ART use in terms of pregnancy outcomes compared ART use prior to conception to starting ART during pregnancy (450). Evidence showed an increased risk associated with preconception ART for adverse pregnancy outcomes of preterm delivery (12 studies, low-quality evidence), low birth weight (three studies, moderate-quality evidence), stillbirth (one study, very low-quality evidence), miscarriage (one study, very low-quality evidence), and possible increased risk of pregnancy-induced hypertension and pre-eclampsia (two studies, very low-quality evidence). However, the severity of prematurity and low birth weight were not well delineated in the published literature, with no papers discussing the association of preconception ART with very preterm delivery (<34 weeks gestation) or very low birth weight (<1500 g), which would be expected to have more severe neonatal consequences compared to preterm delivery (34–37 weeks) and low birth weight (1500–2500 g). Although better data on magnitude and impact are needed, the clear benefits of ART use during pregnancy for both child and mother outweigh the risk of adverse reactions. In addition, because pregnancy-induced hypertension and pre-eclampsia have been identified as predictors of pregnancy adverse outcomes, active screening and management of pregnancy-induced hypertension should be prioritized for all high-risk women, including those receiving ART and particularly those receiving ART prior to conception.

Safety of recommended first-line regimens (TDF + FTC or 3TC + EFV)

The PROMISE randomized controlled trial (297) compared the prevention efficacy and safety of ART regimens given to women with healthy immune systems (CD4 cell count above 350 cells/mm³). It compared a prophylaxis regimen of AZT from 14 weeks followed by a single dose of NVP (sdNVP) during labour and two weeks of TDF + FTC after delivery with one of two triple-drug regimens (AZT + 3TC + LPV/r and TDF + FTC + LPV/r). The study reported a significantly lower risk of mother-to-child transmission with the triple-drug regimens (0.6%, compared to 1.8% with the AZT + sdNVP regimen). However, there was also a significantly higher risk of low birth weight (<2500 g) and preterm delivery (<37 weeks) with the triple-drug regimens compared to the prophylaxis regimen of AZT + sdNVP. Additionally, in a subanalysis comparing the two triple-drug regimens, the TDF + FTC + LPV/r regimen had a higher risk of severe preterm delivery (<34 weeks) and early infant death compared with the AZT + 3TC + LPV/r regimen. The most common reported cause of these deaths was prematurity. This subanalysis included only about a third of the patients enrolled in the study, and further analyses are in progress.

The WHO-recommended first-line regimen for pregnant women is distinct from the LPV/r-based regimens used in the PROMISE study. The results from other studies have not suggested that TDF or TDF + FTC is associated with excess adverse pregnancy outcomes. By contrast, PIs, including LPV/r, have been reported to be associated with prematurity and low birth weight. Additionally, there may be pharmacokinetic interactions between TDF and LPV/r, which could result in raised TDF levels. As LPV/r-based regimens are recommended in second-line treatment, toxicities associated with these regimens need further research. Although analysis is ongoing, the PROMISE study results to date support

the recommendation in these guidelines of lifelong ART for all pregnant women, as well as the preferred first-line regimen of TDF + 3TC or FTC + EFV (451).

Clinical considerations

Active screening and management of hypertension in pregnancy should be prioritized for all high-risk women, including those receiving ART and particularly those receiving ART prior to conception.

Research gaps

Better research evidence is needed on the association between clinically relevant renal disorders and exposure to TDF. The trends in renal function parameters among people exposed to TDF over time and the potential reversibility of renal impairments when stopping TDF need further surveillance. Studies are also needed to establish which laboratory test(s) reliably detect TDF-related renal disorders and can be used as reference tests. More accurate and affordable methods to monitor bone toxicity are needed for paediatric and adolescent populations. Research to optimize drug tolerability and safe use in children is crucially needed. Implementation research is needed to assess newly available point-of-care creatinine clearance tools.

Toxicity profiles of INSTIs need further exploration and surveillance in resource-limited settings, especially their association with hepatotoxicity, risk factors for severe reactions and use during pregnancy and breastfeeding. The risk of hepatotoxicity and adverse reactions when co-administered with other potentially hepatotoxic drugs to treat comorbidities needs further assessment.

More data are needed on the presence of the HLA-B*5701 allele associated with ABC HSRs, notably in children and in Asian populations.

There is a critical need for continuing active toxicity surveillance to accompany implementation of lifelong ART for pregnant and breastfeeding women. Further research is needed to assess the extent and consequences of adverse pregnancy outcomes with preconception ART, whether there are differences by type of ART regimen and the ultimate effects on neonatal and infant mortality and to better understand the pathogenesis and determine whether there are potential interventions to reduce these outcomes.

More data are needed on the effects of in utero TDF exposure on infant bone development and growth and maternal toxicity. More data are also needed to determine whether use of TDF during breastfeeding increases the normal bone mineral density loss observed during breastfeeding (lactation is associated with bone mineral density loss that stabilizes after lactation) and, more importantly, whether if accelerated loss of bone mineral density is found, it reverses when breastfeeding stops or persists. This is a key question because TDF use could result in excess bone fragility among women during breastfeeding or in the future.

4.6.7 Drug substitutions for ARV drug toxicity

Drug regimen or single-agent substitutions may be required to manage drug toxicity and to avoid drug interactions. Delaying substitutions or switches when there are severe adverse drug reactions may cause harm and may affect adherence, leading to drug discontinuation, resistance and treatment failure.

When drug interruptions are required, such as for severe and life-threatening adverse reactions, it is important to consider the various half-lives of ARV drugs. For example, when an NNRTI needs to be discontinued, a staggered approach should be followed, in which the use of the NRTI backbone is prolonged for two to three weeks. Alternatively, the NNRTI could be temporarily substituted with a boosted PI.

4.7 Key ARV drug interactions

Pharmacological interactions can reduce the efficacy of ART and/or increase ART-related toxicities. Major ARV drug interactions are summarized in Table 4.14 and described in more detail in Annex 13. Providers should be aware of all drugs that people are taking when ART is initiated, including alternative medicine products such as herbal remedies and dietary supplements as well as new drugs that are added during treatment maintenance.

Antituberculosis drugs

WHO *Treatment of tuberculosis guidelines* include key considerations for managing concomitant TB and HIV therapy (452). A key contraindicated drug combination is rifampicin with PIs. When people with HIV-related TB are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the boosting dose of RTV (see section 4.8.1 “Second-line ART for adults and adolescents”). For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered. For patients who are coinfecting with HIV and extensively drug-resistant or multidrug-resistant (XDR/MDR) TB, there is limited information on the drug interactions of ARV drugs with new drugs such as bedaquiline and delamanid. As bedaquiline is primarily metabolized by CYP3A4, concomitant use with EFV and PIs can interfere with drug concentrations and should be undertaken with extreme caution and close clinical monitoring; alternative ARV options should be considered (453). Rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule may be necessary, but there are very few studies and limited clinical experience with this combination, particularly in individuals living with HIV and active TB (see section 4.4.1 “First-line ART for adults”).

Drugs for hepatitis C

Potential drug interactions should be considered when using ARV drugs and DAAs for HCV infection. Simeprevir and the combination of ombitasvir + paritaprevir + ritonavir plus dasabuvir should not be co-administered with any PI or NNRTI. Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. Ledipasvir and sofosbuvir have shown reduced potential for drug interactions with ARV drugs due to their use of different metabolic pathways (454,455). Although access to DAAs is still limited in many settings, ribavirin and pegylated interferon alpha-2a are being less frequently used to treat HCV infection. Administration of both agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfecting with HCV and HIV who are using AZT may need to be switched to TDF. A complete list of drug–drug interactions is available at www.hep-druginteractions.org.

Antifungal agents

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

Antimalarial drugs

WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria (456). One such recommended artemisinin-based combination therapy is artesunate and amodiaquine. EFV increases the concentrations of amodiaquine and has been associated with significant increase in liver transaminases. Halofantrine and lumefantrine should not be used with PIs. Alternative artemisinin-based combination therapies (such as artestunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine) could be used to prevent severe toxicity in people with HIV.

Opioid substitution therapy

WHO recommends methadone and buprenorphine for treating opioid dependence (457). Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People taking methadone and NNRTIs should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

Hormonal contraceptives

ARV drugs have the potential to either decrease or increase the levels of steroid hormones in hormonal contraceptives (458). There may be drug interactions between some NNRTIs and RTV-boosted PIs with hormonal contraceptives, which can reduce the effectiveness of both the hormonal contraceptive and the ARV drug. There are generally fewer concerns regarding interactions of hormonal contraceptives with NRTIs and newer NNRTIs (see Annex 13). The contraceptive efficacy of injectable formulations of either intramuscular or subcutaneous depot medroxyprogesterone acetate (DMPA) is unaffected by ARV drugs and can be used without restriction (459). There is a potential for reduced efficacy of long-acting progestogen-only implants when a woman is also on ART containing EFV. If women receiving ART decide to initiate or continue using hormonal contraceptives, consistently using condoms and other contraceptive methods is recommended both to prevent HIV transmission and unintended pregnancy. WHO recommendations released in 2014 on the use of hormonal contraception by women receiving ART are available at www.who.int/reproductivehealth/publications/family_planning/MEC-5/en.

Antihistamines

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

Statins

WHO recommends statins for people with a 10-year cardiovascular risk exceeding 30% (460). Boosted PIs may lead to increased concentrations of lovastatin and simvastatin,

which may increase the risk of serious adverse events such as myopathy, including rhabdomyolysis. Alternative cholesterol-lowering agents should be used to prevent severe toxicity in people with HIV.

Other interactions

DTG should not be simultaneously administered with cation-containing antacids, laxatives and multivitamin or mineral supplements because of the risk of chelation. If combined, DTG should be administered two hours before or six hours after taking medications containing polyvalent cations (445).

Table 4.14. Key ARV drug interactions and suggested management

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

This table was developed using the University of Liverpool's drug interaction charts, which can be found online at www.hiv-druginteractions.org and www.hep-druginteractions.org. A more comprehensive table of ARV drug interactions is available in Annex 13.

AZT zidovudine, ATV atazanavir, DAA direct-acting antiviral (agent), DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, TDF tenofovir.

4.8 What ART regimen to switch to (second- and third-line ART)

Table 4.15. Preferred second-line ART regimens for adults, adolescents, pregnant women and children

Population		Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP)	2 NRTIs ^b + ATV/r or LPV/r	2 NRTIs ^b + DRV/r ^c
		2 NRTIs + DTG		
Pregnant or breastfeeding women		2 NRTIs + EFV (or NVP)	2 NRTIs ^b + ATV/r or LPV/r	2 NRTIs ^b + DRV/r
Children	Less than 3 years	2 NRTIs + LPV/r	2 NRTIs ^b + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs ^b + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs ^b + LPV/r	2 NRTIs ^b + RAL ^d
	3 years to less than 10 years	2 NRTIs + LPV/r ^a	2 NRTIs ^b + EFV	2 NRTIs ^b + RAL ^d
		2 NRTIs + EFV (or NVP)	2 NRTIs ^b + LPV/r	2 NRTIs ^b + ATV/r ^d

^a ATV/r can be used as an alternative PI for children older than 3 months of age.

^b If ABC+ 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa.

^c RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

^d DRV/r can be used as an alternative PI option in special situations.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, RAL raltegravir.

4.8.1 Second-line ART for adults and adolescents

Table 4.16. Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen ^a	
Adults and adolescents	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r ^{b,c}
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r ^{b,c}
Pregnant or breastfeeding women	Same regimens as 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) ^d
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r) ^b	

^a ABC and didanosine (ddI) can be used as NRTI back-up options but add complexity and cost without clinical advantages.



^b DRV/r can be used as an alternative PI option.

^c RAL + LPV/r can be used as an alternative second-line regimen (conditional recommendation, low-quality evidence).

^d Standard LPV/r and RTV-boosted saquinavir (SQV/r) doses with an adjusted dose of RTV (that is, LPV 400 mg/ RTV 400 mg or SQV 400 mg /RTV 400 mg twice daily) can be used as alternative options.

3TC lamivudine, ATV atazanavir, AZT zidovudine, d4T stavudine, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, TDF tenofovir.

Recommendations

- Second-line ART in adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus 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).
- **Heat-stable fixed-dose combinations of DRV/r can be used as an alternative boosted PI option for second-line ART (conditional recommendation, low-quality evidence).** 
- **A combination of RAL plus LPV/r can be used as an alternative second-line ART regimen (conditional recommendation, low-quality evidence).** 

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that second-line adult ART regimens should include two NRTIs and a boosted PI (9). Those guidelines placed a high value on using simpler second-line regimens, ideally as heat-stable formulations and FDCs. The preferred PI/r options for second-line ART were the heat-stable FDCs of ATV/r or LPV/r. RTV-boosted darunavir (DRV/r) could be used in special situations, but was recommended as a preferred third-line drug, as it was not available as a heat-stable FDC boosted with low-dose RTV at that time and because of its higher price compared with other options. The drugs used in first-line therapy should determine the choice of NRTI backbone in second-line regimens.

Since 2013, several studies exploring different strategies for second-line ART have been published, including those focused on the use of drug classes other than PI and NRTI, NRTI-sparing regimens and PI dose-optimization strategies (461–465).

As 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 has been used for second-line therapy in high-income settings (466,467). However, several factors precluded DRV/r being recommended as a preferred option in the WHO

2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. These included limited comparative studies on its use as a second-line option, the high cost compared with other PI drugs and limited availability as an FDC. As a result, DRV/r has more frequently been used in third-line regimens in resource-limited settings (468).

Rationale and supporting evidence

As in the case of first-line ART, WHO emphasizes a public health approach to second-line ART with a limited number of preferred regimens that can be used across different populations, including adults, adolescents, children, pregnant or breastfeeding women and people coinfecting with TB, HBV and HCV. Less toxic, more convenient, tolerable, durable and efficacious heat-stable FDCs are also needed (469).

The recommendations on second-line regimens for people with HIV and TB and with HIV and HBV remain unchanged from 2013.

NRTI backbone for second-line ART in adults and adolescents

Choice of second-line regimens should be consistent with ART-optimizing principles, in particular, availability as FDCs, tolerability and resistance mutation risk, based on the NRTIs used in the first-line regimen (9). 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 (TDF), AZT should be used in the second-line regimen. Other NRTI drugs such as ABC and ddl are acceptable as potential back-up options in special situations but are not recommended as preferred alternatives, as they have no specific advantage and add complexity and cost.

PI options for second-line ART in adults and adolescents

A systematic review and network meta-analysis was undertaken to determine whether DRV/r-based regimens are comparable to currently recommended boosted PI options in second-line regimens with respect to safety and efficacy (470). The analysis was restricted to patients failing NNRTI-based first-line regimens. Four randomized controlled trials (464,471–473) and two observational cohort studies (474,475) showed low- to very low-quality evidence that a DRV/r-containing regimen is not distinguishable from ATV/r- or LPV/r-containing regimens in terms of viral load suppression, mortality and grade 3/4 adverse events. However, there were no direct or indirect comparisons involving DRV/r-containing regimens with other outcomes.

The analysis also evaluated whether once-daily DRV/r regimens were equivalent to twice-daily DRV/r regimens, but no comparisons of frequency of administration and dosage were found in the studies with patients for whom NNRTI-containing regimens are failing. When the definition of study population was expanded to include treatment-experienced patients for whom any ART regimen fails (i.e. including patients on third-line regimens), five randomized controlled trials (476–480) showed that the estimated virological efficacy of DRV/r 800 mg/100 mg once daily was comparable to DRV/r 600 mg/100 mg twice daily (moderate-quality evidence), but the confidence intervals were too large to determine equivalence. For all other outcomes, the estimated effects favoured once-daily dosage, but the statistical analysis was not significant (low-quality evidence). Despite limited data, lower once-daily doses of DRV/r were found to be inferior

in terms of viral suppression and treatment discontinuation, though not statistically significant (low-quality evidence).

Considering the body of evidence in the review, there is inadequate new information to support a change in the recommendations on preferred boosted PI options and DRV/r dosing established in the WHO 2013 guidelines. Additional research in this area is required. DRV/r continues to be recommended as an alternative option to LPV/r or ATV/r for second-line ART.

INSTIs for second-line ART in adults and adolescents

In the same network meta-analysis, two randomized controlled trials investigated the comparative efficacy of RAL + LPV/r and 2 NRTIs + LPV/r (464,465). The review showed moderate- to low-quality evidence supporting the equivalency of the NRTI-sparing regimens (i.e. INSTI + PI/r) when compared to 2 NRTI + ATV/r or LPV/r regimens. Apart from higher increases in CD4 cell counts in patients using RAL + LPV/r, there were no statistically significant differences in the evaluated outcomes. However, credible intervals tended to be narrow enough to suggest equivalency. No comparisons between RAL + LPV/r and 2 NRTI + DRV/r were available.

While evidence in the review allowed for inferences to be drawn about the use of NRTI-sparing regimens for second-line ART, it did not allow for inferences on the use of 2 NRTI + INSTI second-line regimens. The absence of such evidence can be explained by the low threshold for viral drug resistance with this regimen (263), limiting the use of currently available INSTIs with simple NRTI backbones in patients for whom ART is failing.

Considerations for second-line regimens in TB and hepatitis B coinfection

For people with active TB disease taking rifampicin, all boosted PIs in standard doses are contraindicated because of drug interactions with rifampicin and significant reductions in PI plasma concentrations (481–484). In these circumstances, rifabutin can be used in place of rifampicin and concomitantly administered with all boosted PIs in their standard doses. Rifabutin can be taken at an adjusted dose of 150 mg once daily or 300 mg three times a week (485); careful monitoring is important for the occurrence of adverse events, particularly neutropaenia (486). If rifabutin is not available, LPV/r may be used by doubling the daily dose (i.e. LPV/r 800 mg/200 mg twice daily) or with an adjusted, super-boosted dose of RTV (i.e. LPV/r 400 mg/400 mg twice daily), but this is frequently associated with high levels of toxicity and requires close clinical and laboratory monitoring (483,487,488). The recommendation to use LPV/r 800 mg/200 mg twice daily is based on low-quality evidence and is associated with similar to slightly lower levels of toxicity when compared with LPV/r 400 mg/400 mg twice daily (486,487). However, the double dosing option may be less complex and more feasible, as LPV/r is widely available as a single heat-stable formulation, whereas RTV is not.

For people 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 (489).

There are limited studies on the efficacy and safety of INSTI-containing second-line regimens in patients with TB and HBV coinfection. Despite the overall lower potential of

Table 4.17. 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	2–4
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	±	+	±
Accessibility in countries (registration status)	Moderate	High	Low
Availability of generic formulations	Yes	Yes	No

^a Approved only for children older than 3 months.

^b Approved only for children older than 3 years.

^c Can be used with dose adjustment.

^d A generic heat-stable FDC of DRV/r (400/50 mg tablet) is expected to be available in late 2016.

INSTIs for drug interactions compared with PIs, rifampicin can significantly reduce the levels of RAL and DTG, and dose adjustments may be necessary (275,490,491).

Implementation 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 with boosted PI and NRTI components (such as TDF + 3TC [or FTC] + ATV/r) should be used. If a TDF-based regimen is failing, twice-daily dosing with boosted PI and NRTI components (such as AZT + 3TC + LPV/r) should be used.

Use of DRV/r as a boosted PI option and NRTI-sparing regimens such as RAL + LPV/r increase the cost of second-line ART and have not shown better performance when compared with the current standard of care (i.e. 2 NRTI + ATV/r or LPV/r). Heat-stable FDCs of DRV/r are expected to be available only in late 2016, but with good potential for price reduction through generic competition (281). For these reasons, these options are recommended as alternative choices for second-line ART.



Key research gaps

Additional research is required to better understand choice and sequencing strategies for PI options in second- and third-line ART. Several ongoing studies comparing various drugs and ARV classes will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches. The different drug toxicity profiles of ATV/r, DRV/r and LPV/r, the contraindication of using ATV/r and DRV/r with rifampicin and the lack of WHO approval for the use of ATV/r and DRV/r in younger children are highlighted in Table 4.17. Further investigation is needed of the role of boosted DRV in second- and

third-line regimens, including optimal dosing in adults and children, FDCs with other boosting agents and INSTIs, and sequencing strategies. Several trials are under way to examine induction and maintenance using PI/r monotherapy or in combination with 3TC as maintenance therapy. The potential of including rifabutin as part of FDCs for TB treatment also needs to be explored.

4.8.2 Second-line ART for children

Recommendations

- After failure of a first-line LPV/r-based regimen, children younger than 3 years should be switched to a RAL-based second-line regimen (conditional recommendation, very low-quality evidence). 
- After failure of a first-line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus EFV or RAL (conditional recommendation, very low-quality evidence). 
- After failure of a first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r are preferred (conditional recommendation, very 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).

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

Of the 1.5 million children estimated to be in need of ART by 2020, up to 20% are expected to experience virological failure at some point (355). Recommending potent and effective second-line regimens for infants and children is difficult because of the current lack of experience in resource-limited settings and the limited formulations available. This challenge highlights the importance of choosing potent and effective first-line regimens and the need for optimal adherence to ensure their durability and effectiveness (492).

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend a PI boosted with RTV and combined with two NRTIs as the second-line treatment for children for whom a regimen of two NRTIs plus an NNRTI fails (9). For infants and young children who had used a first-line, PI-based regimen, a new NRTI backbone and an NNRTI were recommended for second-line ART, as NNRTIs were the only new drug class available. In addition, data from randomized controlled trials among older children (314) provided indirect evidence supporting the safe

Table 4.18. Summary of recommended first- and second-line ART regimens for children

	Children (including adolescents)	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	AZT or ABC+ 3TC + RAL ^a
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV or RAL
		AZT + 3TC + LPV/r	ABC or TDF ^b + 3TC + EFV or RAL
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + ATV/r or LPV/r ^c
		TDF ^b + 3TC (or FTC) + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC ^c (or FTC) + ATV/r or LPV/r ^c

^a If RAL is not available, no change is recommended unless in the case of advanced clinical disease progression or lack of adherence specifically due to poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on 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 be given only to children older than 2 years.

^c ATV/r can be used as an alternative to LPV/r in children older than 3 months. However, the limited availability of suitable formulations for children younger than 6 years, the lack of an FDC and the need for separate administration of the RTV booster should be considered when choosing this regimen.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, RAL raltegravir, TDF tenofovir.

use of an NNRTI-based second-line regimen. However, concerns remain about the effectiveness of this approach, given the potential for re-emergence of archived resistance as a result of NNRTI exposure during breastfeeding and postnatal prophylaxis.

Since 2013, safety and dosage trials have been completed for RAL, which is now approved by stringent regulatory authorities for use in children older than 4 weeks (336,353). In addition, while a DRV co-formulation with RTV is not commercially available for either adults or children, a single-entity paediatric DRV formulation that can be used in children 3 years and older has become available in a few countries in sub-Saharan Africa through a limited donation programme (493).

Rationale and supporting evidence

A systematic review undertaken to assess clinical outcomes for drugs used in second- and third-line ART (494) identified 13 cohort and seven single-arm studies. All drugs under consideration were reported to be effective and well tolerated. However, it was not possible to establish a clear preference based on efficacy due to a lack of comparative data.

After reviewing the data for adults and children and considering factors such as the availability of a heat-stable FDC, optimal daily dose, regimen harmonization with adults, cost and availability of alternatives, the main recommendations of the WHO 2013 guidelines were maintained. RAL-based regimens have been added as a second-line option when an LPV/r-based first-line regimen fails for infants and children.

For children for whom a first-line PI-based regimen fails, INSTIs offer advantages over

NNRTIs, including the possibility of potent, palatable formulations without pre-existing resistance that can be used from 4 weeks of age. However, due to the current limited availability of RAL, it is important to strengthen adherence and maintain EFV as a viable option for children who are 3 years and older, as NNRTIs are the only new drug class that can be introduced. Data from a randomized controlled trial among older children (314) provides 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, the limited data available to inform the use of EFV in children younger than 3 years (339,340) and the potential re-emergence of archived NNRTI-resistant HIV, second-line NNRTI-based regimens are expected to have limited durability in this age group (495).

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 (346,496–499). In this context, and if RAL-containing regimens are unavailable, children younger than 3 years of age with treatment failure should be maintained on LPV/r until the age of 3 years. However, a more rapid switch should be considered in situations where failure results from poor adherence because of the poor palatability of LPV/r or in cases of advanced HIV disease. In these cases, children younger than 3 years should be switched to an NVP-based regimen and close monitoring provided to ensure adequate adherence.

For children for whom a first-line NNRTI-based regimen fails, PI-based regimens remain the recommended choice for second-line therapy, as they are less costly and more broadly available than newer drugs such as RAL and DTG. LPV/r and ATV/r are the preferred options.

Reviews of clinical trials and observational and pharmacovigilance studies did not provide any direct comparison between LPV/r, ATV/r and DRV/r. Despite its side-effect profile and limited role in TB and HIV coinfection, ATV/r is likely to be a good alternative to LPV/r for children older than 3 months due to less frequent gastrointestinal side-effects, a more favourable lipid profile, the potential for once-daily dosing and lower cost. However, acceptability may be lower due to ATV-related hyperbilirubinaemia, which – although usually mild and transient – is found in 50% of cases (500) as well as the lack of co-formulated FDCs containing ATV/r. Validation studies are urgently needed to develop appropriate paediatric ATV/r formulations.

DRV/r may be appropriate, given its efficacy, high genetic barrier to resistance and good safety profile (500). However, there is no suitable co-formulation with RTV, it is significantly more expensive in the absence of a donation programme (493) and it is contraindicated in children younger than three years. For these reasons, DRV/r is not recommended for second-line use but could be considered in the future should a generic paediatric formulation become available. DRV/r can be considered for third-line therapy where it is available.

Because unboosted PIs such as fosamprenavir (FPV), DRV and ATV and other PIs such as indinavir (IDV)/r, SQV/r, FPV/r and tipranavir (TPV)/r are associated with reduced viral suppression, high pill burden and/or a higher frequency of side-effects, their use is discouraged (9).

The sequencing of NRTIs was assessed for both PI and NNRTI failures, based on

optimizing principles for ARV drugs and the need to maximize antiviral activity in the context of 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 NRTI drug (ABC or TDF) was used in the failing first-line regimen, AZT should be used in the second-line regimen. The use of ddI in second-line regimens is no longer recommended; continuation of 3TC even where 3TC resistance is likely is the preferred option. HIV harbouring 3TC resistance with the M184V mutation may have reduced viral replication capacity and may induce some degree of resensitization to AZT or TDF based on in vitro data (354,501).

Key research gaps

More evidence is needed to inform the choice of second-line regimens, particularly for young children for whom an LPV/r-based first-line regimen fails. Validation studies to assess simplified dosing for ATV/r and DRV/r FDCs are critical to ensure the availability of effective alternatives. Innovative second-line strategies such as using a PI combined with INSTIs or induction and maintenance approaches using boosted PI monotherapy should also be investigated among children. Further studies to examine the role and feasibility of genotyping to inform second-line choice in the context of a public health approach would also be of value.

4.8.3 Third-line ART

Recommendations

- 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 INSTIs and second-generation NNRTIs and PIs (conditional recommendation, low-quality evidence).
- Patients on a failing second-line regimen with no new ARV drug options should continue with a tolerated regimen (conditional recommendation, very low-quality evidence).

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/arv2013/download/en>).

Background

In 2010, WHO made recommendations on third-line ART in a context of limited evidence to guide treatment of patients for whom second-line therapy fails (65). Although there were few studies with newer agents, cohort data showed high mortality among people for whom second-line ART had failed (502). Salvage regimens were recommended with new drugs such as DRV/r, etravirine (ETV) and RAL with or without previously used ARVs that potentially maintained residual virological activity, particularly from the NRTI class (503–505). These recommendations were maintained in 2013 based on additional trial data (506–509), but the need for more clinical and operational research to guide the

establishment of strategies and public health policies on third-line ART was emphasized (9).

Rationale and supporting evidence

Recent data from several randomized controlled trials and observational cohorts are available for DRV/r-, ETV-, DTG- and RAL-containing regimens in treatment-experienced adults, but most studies have been conducted in middle-to-high or high-income settings (430,510–515). Many of these ARV drugs were effective in prospective studies in children and adolescents (494). Taken together, the data support the efficacy of new agents such as INSTIs, second-generation PIs and NNRTIs in people for whom second-line ART fails. However, in ART-experienced patients for whom first- and second-line regimens have already failed, multiple resistance to NRTI agents with reduced virological efficacy is common, and there is some uncertainty about whether maintaining or recycling previously used NRTIs provides clinical benefit through reduction in viral fitness and/or in vitro enhancement of susceptibility caused by some mutations, combined with some residual antiviral activity of these drugs (516–518). Furthermore, as NRTI agents are often associated with cumulative toxicity, their maintenance in third-line ART may not be optimal and may involve increased pill burden and risk of drug interactions. Avoiding NRTIs in third-line regimens is now more feasible due to the increasing availability of new ARV drug classes with a different resistance profile.

A systematic review and network meta-analysis was undertaken to determine whether NRTI-sparing new regimens (i.e. regimens that do not include NRTIs and that contain new drugs with a minimal risk of cross-resistance to previously used regimens) are comparable to NRTI-containing new regimens in those for whom first- and second-line therapy has failed (470). Three comparative studies were relevant and included NRTI-sparing and NRTI-containing new regimens for patients for whom both NNRTI- and PI-containing regimens had failed. One study was a phase III, open-label trial with 360 patients (519). The other two studies were prospective observational cohorts with 122 patients and 689 patients, respectively (520,521). Only limited data are available on third-line ART for children, adolescents or pregnant women. In the absence of data among these populations, it is reasonable to extrapolate from adult studies, but pharmacokinetic and safety data on new drugs are particularly critical for children and pregnant women.

The analysis showed that NRTI-sparing and NRTI-containing regimens were comparable with respect to viral suppression. Efficacy with respect to change in CD4 cell count favoured NRTI-containing regimens, but this difference was not statistically significant. For other outcomes such as mortality, AIDS-defining illnesses, serious adverse events, serious treatment-related adverse events, treatment discontinuation, discontinuation due to adverse events and risk of drug resistance, all estimates favoured NRTI-sparing regimens but also failed to do so in a statistically significant manner. The data suggest that NRTI-sparing regimens may have better tolerability but that further evidence with highly treatment-experienced patients is needed.

Because there is limited evidence to show that NRTI-sparing regimens are as effective as NRTI-containing salvage regimens, the WHO 2013 recommendations for third-line use are maintained in 2015. Further data on the pharmacokinetics, safety and efficacy of salvage regimens in children, adolescents and pregnant women are needed. Countries must strike a balance between the need to develop policies for third-line ART and the continued

expansion and optimal use of first-line and second-line ART. Many countries also face financial constraints that limit the adoption of third-line regimens. Table 4.19 summarizes potential options for third-line regimens depending upon the preferred options used previously in first- and second-line therapy.

Table 4.19. Summary of sequencing options for first-, second- and third-line ART regimens in adults, adolescents, pregnant women and children

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (>10 years)	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r ^a 2 NRTI + DRV/r ^b	DRV/r ^b + DTG ^c (or RAL) ± 1–2 NRTIs
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r 2 NRTI + DRV/r	DRV/r ^b + 2 NRTIs ± NNRTI Optimize regimen using genotype profile
Pregnant or breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r ^a 2 NRTIs + DRV/r ^b	DRV/r ^b + DTG ^c (or RAL) ± 1–2 NRTIs
Children (0–10 years)	2 NRTI + LPV/r	If less than 3 years: 2 NRTIs + RAL ^d If older than 3 years: 2 NRTIs + EFV or RAL	RAL (or DTG) ^f + 2 NRTIs DRV/r ^g + 2 NRTIs
	2 NRTI + EFV	2 NRTIs + ATV/r ^e or LPV/r	DRV/r ^g + RAL (or DTG) ^f ± 1–2 NRTIs

^a RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

^b In PI-experienced patients, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

^c Safety and efficacy data on the use of DTG in adolescents younger than 12 years and pregnant women are not yet available.

^d If RAL is not available, 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 approval of the use of EFV in children less than 3 years of age, 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 (see Table 4.18).

^e ATV/r can be used as an alternative to LPV/r in children older than 3 months of age. However, the limited availability of suitable formulations for children younger than 6 years of age, the lack of an FDC and the need for separate administration of RTV booster should be considered when choosing this regimen.

^f RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been used in a previous regimen. DTG is currently approved only for children 12 years and older; however, studies are ongoing to determine dosing in younger children, and approval for lower age groups is expected in the near future.

^g DRV/r should not be used in children younger than 3 years of age.

ATV atazanavir, DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir.

Implementation considerations

WHO estimates that less than 1% of people taking ART globally are using third-line regimens, but the demand for third-line regimens will increase as access to viral load monitoring and use of first- and second-line ART continue to expand (239). The cost of third-line drugs is either higher than first- and second-line regimens or has not been established, which may limit the adoption of third-line regimens in many countries with limited resources. Although developing a policy on access to third-line ART is desirable, it should not compromise access to first- and second-line ART.

Special considerations for children, adolescents and pregnant women

There have been limited studies on the use of many newer ARV drugs as part of third-line regimens in children and adolescents and during pregnancy and breastfeeding; pharmacokinetic and safety data are particularly lacking. As a result, strategies that balance the benefits and risks need to be explored when second-line treatment fails.

A systematic review and network meta-analysis conducted to inform these guidelines showed overall good efficacy and tolerability of newer drugs in treatment-experienced patients (494). However, no head-to-head comparison was identified to fully assess the clinical advantages of one drug over others. Given the limited evidence available, DRV and DTG are recommended for use in third-line regimens for children (355). There is uncertainty about whether these drugs should be used in combination or as part of a standard NRTI-backbone regimen. DRV cannot be used in children younger than 3 years and is provided as a single drug through a donation programme only to selected countries (493). In addition, no paediatric FDC of DRV with RTV is available. DTG is currently approved for adolescents from 12 years, but the availability of this drug is expected to be limited. A safety and dose-finding trial (IMPAACT 1093 study) is under underway, and its completion in 2016 is expected to support paediatric registration by stringent regulatory agencies. RAL provides an alternative option in children for whom PI-based second-line ART fails and should be considered when DTG cannot be used (Table 4.18).

Children for whom a second-line regimen fails with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, attention should be paid to preventing OIs, symptom relief and pain management.

There are limited data on the use of newer third-line drugs in women who are pregnant or breastfeeding. The current edition of the Antiretroviral Pregnancy Registry reports only 200 documented in-utero exposures to any of the INSTIs, although this is likely to increase with expanded use of DTG as a first-line therapy (442). There are no animal data to suggest fetal toxicity with any of the INSTIs, but in the absence of well-controlled studies in pregnant women, as well as pharmacokinetic data to inform dosing of INSTIs during pregnancy, DTG should be used in pregnancy only if clearly indicated. For DRV, sufficient numbers of first-trimester exposures have been reported to detect at least a twofold increase in risk of birth defects, no such increases have been reported to date. In the case of a pregnant woman needing third-line ART, it may be warranted to use both DRV and DTG, as the benefits are likely to outweigh any potential risks (Table 4.19).

Research gaps

Further research into a range of areas is needed to guide third-line ART strategies for resource-limited settings. Priorities include the monitoring of critical outcomes for people taking second-line ART, once-daily dosing for DRV/r and RAL as alternatives to NRTI-based regimens in second-line ART, developing heat-stable formulations of DRV/r and evaluating the pharmacokinetics, safety and efficacy of new drugs in children, adolescents and pregnant women. The need to assess the pharmacokinetics and safety of DTG in pregnant women is particularly urgent. Pharmacovigilance research is also needed, including studies on the long-term safety of and potential interactions with drugs used for TB, malaria, hepatitis and opioid substitution therapy. As the epidemic matures in resource-limited settings, pilot studies are urgently needed on implementing third-line ART in settings with limited capacity and resources.

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