3. **PHARMACEUTICAL EQUIVALENCE AND CLINICAL INTERCHANGEABILITY BETWEEN LAMIVUDINE AND EMTRICITABINE**

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

**Key messages**

- Overall, the available evidence supports the clinical equivalence of 3TC and FTC in terms of efficacy and safety.
- Evidence with regards to drug resistance is inconclusive, with differences appearing to be small, and their clinical importance unclear.
- Currently, 3TC is available in more fixed-dose combination formulations than FTC.

**Context**

The WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection consider lamivudine (3TC) and emtricitabine (FTC) as clinically equivalent, recommending either drug to be used as part of first-line once-daily triple drug therapy. However, early *in vitro* studies have suggested that there may be pharmaceutical differences between the two drugs, such as differences in binding affinities and drug half-life, that confer advantages to FTC. This review critically assesses these preclinical studies and summarizes findings from a systematic review and meta-analysis of comparative efficacy. This review also considers access issues such as patent barriers, drug pricing and the availability of 3TC and FTC as part of fixed-dose combination drug regimens.

**Introduction**

Lamivudine (3TC) and emtricitabine (FTC) are nucleoside reverse-transcriptase inhibitor (NRTI) antiretroviral drugs with similar chemical structures (Fig. 3.1) (1,2). The latest antiretroviral therapy guidelines of the United States Department of Health and Human Services and WHO consider 3TC and FTC as clinically equivalent, recommending either drug to be used as part of first-line once-daily triple drug therapy (3,4).

Fig. 3.1. Molecular structures of lamivudine (3TC) and emtricitabine (FTC)
3TC has been pivotal to all first-line ARV regimens in high-income as well as in resource-limited settings since the beginning of triple combination ART. It is safe, has an excellent toxicity profile, is non-teratogenic and is effective against hepatitis B virus (5,6). It is widely available in fixed-dose combination regimens. FTC shares the same efficacy against hepatitis B virus, has the same toxicity profile and is available in fixed-dose combinations (7). However, laboratory studies suggest that FTC may have a longer half-life than 3TC and that FTC favourably interacts with tenofovir (TDF), further extending FTC’s half-life, which could be advantageous (8,9).

Although both 3TC and FTC are associated with the emergence of the M184V resistance mutation, the most common NRTI mutation, it has been suggested that 3TC has a relatively low genetic barrier, meaning that specific resistance to 3TC evolves more frequently (10,11). However, the clinical consequences of this mutation are unclear. While the M184V mutation is generally problematic for treatment, conferring resistance to 3TC and FTC and therefore reducing their antiretroviral activity, the mutation has also been shown to be beneficial in terms of increased reverse-transcriptase fidelity (reducing the chances of spontaneous mutagenicity of HIV) and lowered viral fitness (12). Further, although in vitro M184V/I mutations cause high-level resistance to 3TC and FTC, and low-level resistance to didanosine (ddI) and abacavir (ABC), the mutation increases susceptibility to other drugs such as zidovudine (AZT), stavudine (d4T) and TDF (13). These considerations informed the decisions to retain 3TC in second-line regimens in the 2010 and 2013 revisions of WHO guidelines on ART (4,14).

However, pharmaceutical data are limited, particularly among adolescents, children and infants, and usually come from studies in high-income countries. Different genetic backgrounds, epidemiological settings, comorbidities and the balance between desired and undesired effects may not be comparable with populations in resource-limited settings.

In making a determination about the pharmaceutical equivalence and clinical interchangeability of 3TC and FTC, this technical update considered the following issues:

- evidence from preclinical and in vitro studies;
- clinical efficacy and safety data from randomized controlled trials;
- the development of resistance; and
- the relative availability of preferred fixed-dose combinations for use in resource-limited settings, including the existence of patents or other barriers.

**Preclinical and in vitro data**

There are several measurements used in virology to assess the potential potency of antiretroviral agents (15,16). The EC_{50} (half maximal effective concentration), measures the concentration of a drug required to inhibit 50% of viral growth. The binding affinity of an agent measures a drug’s ability to bind itself to the target enzyme. The intracellular half-life of a drug is the time taken for a drug’s intracellular concentration to halve. In order for an agent to be potent, it must bind to the target enzymes and enter and remain in the cell for a long enough period of time to exert its action, the inhibition of viral growth. It is also important that single drug agents be optimally combined with other drug agents to use the most effective triple combination drug regimen.

**Binding affinity**

The binding affinities of the active metabolites of FTC for reverse transcriptase are 10 times larger than those of 3TC, suggesting greater potency of FTC (18). Further, the binding affinity of FTC for human mitochondrial DNA polymerase – associated with host toxicity (22–24) – was found to be lower than that of 3TC in one study (21).

Two studies examining the effects of 3TC and FTC on mitochondrial structure or function in HepG2 cells (22–24) found no deleterious impact with either drug alone or in combination with TDF. It is thought that, although 3TC inhibits polymerase more than FTC, this inhibition occurs at such low levels that clinical differences are not apparent or important and that there are other factors other than mitochondrial disruption that play a part in toxicity (21,25).

**Intracellular half-life**

The intracellular half-life of FTC’s active metabolites (39 hours) – based on a once-daily dose of 200 mg – is longer than those of 3TC (15–22 hours) and is similar to that of TDF (26–29). Further, the intracellular half-life of 3TC has been shown to be independent of the dosing regimen, with similar results obtained when the drug was administered twice daily (150 mg) or once daily (300 mg) (15,29).

**Inhibitory potency**

On average, the EC_{50} of FTC is lower than that of 3TC, suggesting an 11-fold greater potency of FTC (30). Dual HIV-1 infection/competition assays estimate that FTC has a 3-fold greater potency than 3TC (31).

**Synergy with TDF**

With similar intracellular and plasma half-lives, it has been suggested that FTC and TDF make ideal companions as part of a combination drug regimen. For example, if two drugs with considerably different half-lives are used as part of the same dosing regimen and one drug’s concentration falls to low levels before the other drug, the dual drug regimen would effectively become a single drug regimen, with potential

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implications for the onset of drug resistance (15). One in vitro study (32) suggested that FTC and TDF in combination had an additive to synergistic effect against HIV replication (9). FTC in combination with TDF has also been shown to have a significantly superior inhibition of viral replication in vitro compared with a 3TC + TDF combination (P < 0.0005).

Clinical data: efficacy and safety

To date, three clinical trials have directly compared the clinical efficacy of 3TC and FTC among individuals with a baseline viral load <100 000 cells/ml (35–37). In one double-blinded randomized trial, 468 treatment-naive people living with HIV were randomized to receive either 3TC or FTC, in combination with stavudine and nevirapine or efavirenz (35).

At 48 weeks, 65% and 60% of those taking FTC had an HIV RNA load of ≤400 copies/ml and ≤50 copies/ml, respectively, which was comparable to the 3TC arm, of whom 71% and 64% had an HIV RNA load of ≤400 copies/ml and ≤50 copies/ml, respectively. Another trial of 440 people living with HIV-1 initially stable on a twice-daily 3TC regimen who were randomized to either continue their regimen or switch to a once-daily FTC regimen also found no differences in outcomes at 48 weeks (36). The rate of viral failure at 48 weeks was 7% for the FTC arm and 8% for the 3TC arm.

The third trial, an open-label, randomized non-inferiority trial, randomized 664 treatment-naive individuals to receive either FTC or 3TC in combination with TDF and EFV (37). Viral suppression was achieved by 90.1% of those taking a FTC regimen and 85.3% of those taking a 3TC regimen at 48 weeks, suggesting comparable efficacy between the two drugs. Two of these three trials reported on adverse drug events (35,36) and found equivalent rates of severe adverse drug events between the FTC and 3TC arms.

A recent systematic review and meta-analysis (38) pooled the data from these three trials and found no significant differences overall between 3TC and FTC in terms of achieving treatment success (relative risk (RR) 1.03, 95% confidence interval (CI) 0.96–1.10). This result was maintained regardless of whether the pooling was carried out using a fixed-effects or random-effects model. This systematic review and meta-analysis also performed analyses on data from nine other trials – for a total of 12 trials – where the partner drugs could be considered to be comparable. When data from all 12 trials were combined, for a total of 15 direct comparisons, there were no differences in treatment success between 3TC and FTC arms (RR 1.00, 95% CI 0.97–1.02) (Fig. 3.2) (38).

<table>
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<tr>
<th>Study</th>
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<th>Relative risk (95% CI)</th>
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<th>Events, Control</th>
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Source: Ford et al. (38).
Evidence on the development of resistance

The mechanisms for the development of resistance are similar for FTC and 3TC. Resistance to both drugs is usually caused by a single point mutation at position 184 of reverse transcriptase, causing methionine to be replaced by either valine or isoleucine, M184V or M184I mutations, respectively (7).

Several studies infer a lower rate of resistance mutations (M184V) with FTC-containing regimens compared with 3TC-containing regimens (32–36,43). The reasons cited were the greater potency or longer half-life of FTC compared to 3TC or potential pharmacokinetic differences, but no definite conclusions were reached.

The data from trials assessing the prevalence of M184V resistance mutations among those failing treatment where 3TC and FTC are directly compared or where 3TC and FTC were used with a comparable background regimen are inconclusive (34–36,43). A systematic review and meta-analysis (38) pooled the results from these four trials, using a random-effects model, finding the overall pooled estimate of viral failure with the M184V mutation to be higher among people receiving 3TC (RR 1.41, 95% CI 0.6–33), but this was not statistically significant. The results should be interpreted with caution due to high heterogeneity between studies and due to the selective reporting of two of the four trials (38).

Availability

A biowaiver⁵ monograph for 3TC was published in 2011 (44). Literature relevant to the decision to allow a waiver of in vivo bioequivalence testing for the approval of immediate-release solid oral dosage forms containing 3TC as the only active pharmaceutical ingredient was reviewed. The solubility and permeability data of 3TC as well as its therapeutic index, its pharmacokinetic properties, data indicating excipient interactions and reported bioequivalence and bioavailability studies were considered. A biowaiver was recommended for new 3TC multisource immediate release products and major post-approval changes of marketed drug products. This process is included in the WHO Prequalification of Medicines Programme and is detailed in the report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (45). This mechanism allows for the simplified approval of generic 3TC, thereby possibly making 3TC more readily available commercially. As of November 2011, FTC was identified by WHO Prequalification of Medicines Programme to be eligible for Biopharmaceutics Classification System (BCS)-based biowaiver applications (46). The current WHO Prequalification of Medicines Programme (http://apps.who.int/prequal/default.htm) contains many approved 3TC formulations (with AZT, ABC, TDF, with AZT + ABC, AZT + EFV, d4T + EFV and d4T + NVP,⁶ but a far more restricted list of FTC formulations (with TDF and with TDF + EFV).⁷

Access

The patent status of 3TC and FTC may be relevant to access. Access to patent information in relation to medical products has a major and growing importance for public health, to design access strategies, to assess for which products generic versions can be produced and marketed without infringing patents, and to determine with whom and the extent to which licenses have to be negotiated (47).

Assessing the patent status of medical products is not always easy. The Medicines Patent Pool Patent Status Database for Selected HIV Medicines provides information on the patent status of selected antiretroviral medicines in many low- and middle-income countries.⁸ It enables users to search by country and region, and by medicine, to obtain information on the key patents relating to each medicine.

The original patent covering both 3TC and FTC (EP0382526) expired in February 2010. A United Kingdom patent on the crystal form of 3TC (WO9111186) expired in June 2012 and a patent on FTC held by Emory University (WO9111186) expired in January 2011. However, there are patents on certain combinations of FTC or 3TC with other ARV drugs. The patent on the combination of abacavir (ABC) with 3TC (WO9630025) expires in 2016 and has been granted in many low- and middle-income countries. Combination patents have also been granted on TDF + FTC, TDF + FTC + RPV and TDF + FTC + EFV in several jurisdictions, which expire in 2024, 2024 and 2026 respectively. Voluntary licences on ABC + 3TC, TDF + FTC and TDF + 3TC + RPV have been issued that enable sale of generic versions of these combinations in many low- and middle-income countries.⁹

Data on global access and pricing can be found in the Médecins Sans Frontières report Untangling the web of antiretroviral price reductions (48). The best prices for 300 mg of 3TC remain lower than for 200 mg of FTC. An oral liquid formulation of 3TC is available, but no similar formulation of FTC has been prequalified by WHO.¹⁰ Combinations with 3TC are still less expensive than those containing FTC. However, the current best price for first-line combination regimens with either 3TC or FTC has declined considerably during the past five years (Fig. 3.3).

5. A biowaiver is a document or process that demonstrates the bioequivalence by in vitro instead of more expensive and time-consuming in vivo pharmacokinetic studies for the simplified approval for immediate release generic solid oral products, allowing companies to forgo clinical bioequivalence studies, provided that their drug product meets the specification detailed in the guidance (http://apps.who.int/prequal).
6. The use of d4T is no longer a recommended first-line option. However, many people are well controlled on d4T combinations and do not have an option to switch. The use of d4T will therefore continue for some time.
7. The United States Food and Drug Administration approved FTC + TDF + rilpivirine (Complera®) in August 2011.
9. Voluntary licences on ABC + 3TC cover 69 countries for adults and 118 for children. Licences on TDF + FTC and TDF + FTC + RPV cover 112 countries.
Conclusions

Despite limited direct comparisons, the available data support the clinical and programmatic interchangeability of 3TC and FTC. The current edition of the WHO Model List of Essential Medicines (April 2013) (49) states that 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretroviral medicines. This supports the latest guidance provided by WHO and the United States Department of Health and Human Services\textsuperscript{11,12} stating that 3TC may be substituted for FTC and vice versa.

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11. Available at: http://www.who.int/hiv/pub/guidelines/en
4. USE OF EFAVIRENZ DURING PREGNANCY AS PART OF FIRST-LINE ANTIRETROVIRAL THERAPY: A PUBLIC HEALTH PERSPECTIVE

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Key messages
Overall, the available data and programmatic experience continue to provide reassurance that exposure to EFV in early pregnancy has not resulted in increased occurrence of congenital anomalies or other significant toxicity. In addition, evidence suggests that EFV is clinically superior to NVP, since it provides better long-term viral suppression and has fewer adverse reactions and less risk of resistance. Finally, the cost of EFV has decreased considerably, and it is now increasingly available as part of once-daily fixed-dose combinations. From a public health perspective and based on the available data and programme experience, this technical update summarizes the rationale for choosing EFV as the preferred NNRTI option in first-line treatment for adults and adolescents, including among pregnant women and those of reproductive age.

Background
The WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, published in July 2013 (1), recommend efavirenz (EFV) as the preferred option for a non-nucleoside reverse-transcriptase inhibitor (NNRTI) in optimized first-line antiretroviral regimens for adults, including pregnant women and those of child-bearing potential. Concerns referenced in previous guidelines about EFV safety in early pregnancy had resulted in more complex treatment algorithms for women living with HIV who might become pregnant and for women in early pregnancy (2) and confusion regarding when to use EFV and when to use nevirapine (NVP). Recent evidence from systematic reviews provides reassurance regarding the safety of EFV in pregnancy and shows that EFV is superior to NVP in terms of safety and efficacy. The WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) emphasize simplification, harmonization and optimization of antiretroviral therapy, for a public health approach. There are multiple clinical and programmatic benefits of a switch to a harmonized one pill per day regimen for all adults, including pregnant women and those of childbearing potential. Switching to alternative and more complex antiretroviral regimens in pregnancy is no longer necessary, and the management of tuberculosis (TB) coinfected is simplified – unlike NVP, there are no clinically significant drug interactions between anti-TB drugs and EFV. Programmatic benefits include the simplification of treatment guidelines for health care providers and greater efficiency for drug procurement.

This section is a revised version of the technical update issued in 2012 (3) and summarizes the latest available data on the safety, tolerability and efficacy of EFV up to January 2014.

Introduction
In an effort to simplify and optimize HIV treatment and reflect the best available evidence, the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) recommend a once-daily simplified triple drug regimen – tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) + EFV – for all pregnant and breastfeeding women living with HIV for preventing mother-to-child HIV transmission, in accordance with the recommended first-line ART regimen for non-pregnant adults and adolescents. Further, the guidelines recommend that ART be continued for life after pregnancy or breastfeeding either for all women (option B+) or for those who meet eligibility criteria for their own health (option B).

Previous WHO guidelines for the treatment of HIV had recommended either NVP or EFV for adults (4) and that pregnant women or those planning pregnancy avoid EFV (2,4), due to concerns about its safety in pregnancy (specifically the risk of neural tube defects) if taken early in the first trimester of pregnancy. Until recently, most people receiving ART in resource-limited settings have initiated NVP-based regimens (5). The use of EFV is increasing in resource-limited settings as a result of its widespread availability as part of once-daily fixed-dose combinations, considerable reductions in drug price and the publication of the recent WHO guidelines recommending its use in preference to NVP.

This technical update summarizes the currently available evidence and experience that provided the basis for favouring EFV as the preferred NNRTI option in first-line therapy, including for pregnant women, and examines the broader anticipated benefits of this change in policy.
Rationale for this update

The 2013 WHO consolidated guidelines recommend a TDF-based first-line regimen in conjunction with 3TC (or FTC) and EFV as the preferred first-line treatment regimen for adults and pregnant women for treatment as well as for preventing mother-to-child transmission, as well as for adolescents, due to its more favourable clinical profile and programmatic advantages; a recent systematic review (6) showed that this combination has a better viral and treatment response compared with other once- or twice-daily regimens. EFV is now available in simplified formulations as part of a generic, fixed-dose, once-daily regimen (triple ARV regimens with NVP are available only in twice-daily formulations). This update provides current information regarding the safety and efficacy of EFV, including during pregnancy to present:

- an accumulation of evidence indicating that EFV has superior efficacy and tolerability compared with NVP, including when combined with TDF + 3TC (or FTC) as a once-daily regimen;
- substantial reductions in the price of EFV and increased availability of EFV as part of once-daily fixed dose combinations;
- updated data providing further reassurance about the safety of EFV during the first trimester of pregnancy;
- WHO-recognized benefit of using an EFV-based regimen for preventing mother-to-child HIV transmission harmonized with that for first-line adult ART (7) after programmatic experience highlighted the complications associated with switching pregnant women living with HIV and women living with HIV who may become pregnant from EFV to NVP; and
- increasing recognition of the benefits of initiating treatment among adults earlier, at higher CD4 counts (≤500 cells/mm³) and for pregnant women to remain on lifelong ART after pregnancy.

Comparative data on the efficacy profiles of regimens containing EFV and NVP

In the 2010 WHO ART guidelines for adults and adolescents (4), NVP and EFV were considered to have comparable clinical efficacy when administered in combination regimen and were recommended in combination with either zidovudine (AZT) or TDF plus either 3TC or FTC. This recommendation was based on a systematic review of seven randomized trials that concluded that there was no difference in clinical efficacy at 48 weeks; however, this analysis also noted a higher risk of non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance mutations among people taking NVP (8). A more recent analysis of these trials over a longer period of follow-up together with consideration of cohort data suggested clinical superiority of EFV over NVP in terms of suppression of viral load and length of time to treatment failure; people taking an EFV-based regimen were also more likely to achieve viral success (9).

Comparative data on the toxicity profiles of regimens containing EFV and NVP

EFV and NVP have different toxicity profiles, and both require clinical monitoring (1,11). The main concern of EFV is central nervous system toxicity (such as depression or mental confusion (1,12)), which typically resolves after two to four weeks. However, in some cases it can persist for months or not resolve at all. Thus, EFV should be avoided for people with a history of depression or other mental disorders. NVP is associated with rash and with life-threatening reactions such as Stevens-Johnson syndrome and hepatic toxicity (12), and there have been concerns that these risks are higher for women, particularly pregnant women with a higher CD4 cell count (1,13,14).

A systematic review and meta-analysis of randomized controlled trials and prospective observational cohorts conducted in support of the WHO consolidated guidelines providing toxicity data on more than 26 000 adults receiving EFV or NVP drug regimens (12) found that those receiving taking NVP were more than twice as likely as those taking EFV to discontinue treatment because of any adverse event. Those taking NVP were more likely to experience any grade of hepatotoxicity and skin toxicity, severe hepatotoxicity and skin toxicity as well as severe hypersensitivity reactions compared with those taking EFV. The review also found that people receiving EFV were more likely to experience central nervous system–related adverse events, although these were mostly mild and rarely resulted in drug discontinuation.

Another systematic review specifically assessing the safety of NVP for pregnant women according to CD4 cell counts found a significantly higher risk of severe skin toxicity at CD4 cell counts above 250 cells/mm³ (14). The association between NVP-associated toxicity and higher CD4 counts led to a more complex “lead-in” dosing strategy for initiating NVP and recommendations urging caution when prescribing NVP to pregnant women and women who might be pregnant, using the drug only after the risks, benefits and available alternatives have been considered (1).

Although the evidence supporting the association between NVP toxicity and CD4 count is not entirely clear, routine monitoring of people with higher CD4 counts receiving NVP is recommended (1). This, along with the complex lead-in strategy and the fact that NVP is unavailable as a once-daily triple drug regimen, favours the use of EFV in resource-limited settings (1).
Managing adverse events is a challenge in resource-limited settings, since the capacity for clinical and laboratory monitoring may be limited. In addition, adverse events are a risk factor for poor adherence (15) and treatment interruptions initiated by the person living with HIV (16) and lead to more frequent regimen changes.

On balance, EFV appears to be better tolerated and has much less risk of severe adverse reactions than NVP. In addition, recent evidence shows that viral suppression with EFV is superior to that with NVP.

**Cost and availability of EFV and NVP as fixed-dose combinations**

The 2013 consolidated guidelines (1) have chosen a TDF-based first-line regimen in conjunction with 3TC (or FTC) and EFV as the preferred first-line treatment regimen due to its more favourable clinical profile (6,17). The costs of both TDF and EFV have fallen substantially in recent years due to increased demand, improvements in the synthesis of the active ingredients and availability of generic formulations. In parallel with the decreasing cost of EFV as a separate compound (which is approaching the cost of NVP), the one-year treatment cost of generic formulations of once-daily TDF + 3TC (or FTC) + EFV has decreased to as low as US$ 112 (18), close to the US$ 100 annual cost of twice-daily AZT + 3TC + NVP. However, access to affordable generic versions, particularly as fixed-dose combinations, remains a problem for some countries, where current drug patent laws and licensing agreements restrict purchasing options (19).

**Safety of EFV use during pregnancy**

Although concerns persist about the safety of using EFV during pregnancy, particularly during the first 28 days, an analysis of all available data up to January 2014 provides reassurance of no evidence of increased harm. When the 2013 consolidated guidelines were developed, the evidence was considered sufficient to rule out more than a three-fold increase in risk. The overall prevalence of congenital anomalies reported in association with EFV is similar to that reported for other widely used ARV drugs and is consistent with rates reported in congenital anomaly registries from the general population (20–22).

In practice, the likelihood of a newly diagnosed pregnant woman living with HIV being initiated on ART during the first trimester is relatively low. A report from Kenya and Malawi, for example, showed that 12–15% of women attended antenatal care within the first trimester of pregnancy (23). Inadvertent exposure to EFV is more common, since the number of pregnancies among women living with HIV already receiving ART is increasing in both high-income (24) and low- and middle-income countries (25), and a large proportion of pregnancies among women receiving ART may be unplanned (26).

The latest systematic review and meta-analysis of congenital anomalies in infants with first-trimester EFV exposure, updated to January 2014 (27), found no overall increased risk of congenital anomalies associated with EFV exposure during the first trimester of pregnancy (Fig. 4.1). Across 22 studies, women receiving first-trimester EFV had 44 birth defects (of any kind) among 2026 live births (1.63%, 95% confidence interval (CI) 0.78–2.48%), which is similar to that reported for women exposed to other, non-EFV-based regimens in the United States Antiretroviral Pregnancy Registry (2.6%) and in the general population (6%) (20). The relative risk of congenital anomalies overall when comparing women on EFV-based and non-EFV-based regimens was 0.78 (95% CI 0.56–1.08%) (27).

A recent unpublished report from France suggested an increased risk of nervous system defects (none of which were neural tube defects) among infants born to women receiving EFV during the first trimester of pregnancy (28). However, no neural tube defects were reported in this cohort registry, and when these data were considered together with other available data in the latest systematic review, there was still no evidence of an increased risk of congenital anomalies associated with first-trimester exposure to EFV compared with exposure to other antiretroviral drugs (22).

Among the study populations included in the meta-analysis, there is only one reported case of neural tube defect (myelomeningocele), yielding an incidence of 0.05% (95% CI <0.01–0.28%). Thus, the estimated pooled prevalence of neural tube defects among women living with HIV exposed to EFV during the first trimester of pregnancy was lower than that reported in the general population in the United States (0.04–0.06% before regular folic acid fortification (29)), United Kingdom (0.14% (30)) and South Africa (0.36% (31)). However, the low background incidence and the small number of events reported in available studies necessitate a larger sample size to definitively rule out a doubling of risk for this rare event (22,27).

Congenital anomalies have not been consistently monitored in most low and middle-income countries, and in many resource-limited settings, the baseline risk of congenital anomalies remains unknown. Determining the additional risk due to the use of EFV or other ARV drugs cannot be established without prospectively following up a large number of pregnancies, both with and without the exposure of interest. To achieve this, WHO supports and encourages countries to implement a toxicity surveillance system and register the outcomes of drug use in pregnant women. A WHO technical brief was recently published (32) to provide technical guidance on the various approaches for the surveillance of ARV drug
toxicity during pregnancy and breastfeeding, which cover a prospective pregnancy-exposure registry, a congenital anomalies surveillance programme and a prospective monitoring of cohorts of mother–infant pairs during the breastfeeding approach. A joint manual has recently been produced that provides a method to implement a congenital anomalies surveillance system (33). In addition, UNAIDS, WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria are producing a technical brief note on toxicity surveillance of antiretroviral medicines within ART and programmes for preventing mother-to-child transmission to encourage standard procedures and integrating ARV toxicity surveillance into HIV funding proposals (34). As part of the effort to detect any increased signal of birth-related or maternal-related toxicity, WHO is also promoting the development of a targeted spontaneous reporting for monitoring the toxicity of ARV drugs (35).

While emphasizing the need for better data on congenital anomalies, the WHO Guidelines Development Group considered that the risk of increased congenital anomalies associated with EFV use was considered to be very low, the programmatic advantages and the clinical benefit of EFV in preventing HIV infection in infants and for the mother’s health outweighed any potential risk of EFV when recommending EFV as part of first-line therapy among pregnant women and those of childbearing age (1).

**Programmatic benefit of favouring EFV as part of first-line treatment regimen in pregnant women**

Recommending the use of EFV as part of first-line therapy in pregnancy is expected to result in a wide-range of programmatic benefits.

**Decreased frequency of regimen changes with benefit for health-care workers and patients**

A systematic review carried out in support of the WHO 2013 consolidated guidelines (12) compared the rates of switching regimens among the non-pregnant population and found that people taking NVP are more than twice as likely to switch regimens due to adverse events as those taking EFV. In settings where task-shifting strategies for managing HIV have been implemented, guidelines usually recommend referral to a higher-level health facility when managing severe side effects or when switching a person’s regimen. This may increase the burden on health systems in terms of personnel and costs. Management of drug side effects and difficulties associated with regimen switches may increase the number of clinic visits; more travel may be required for more frequent monitoring, perhaps to a more distant facility. A regimen change may

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**Fig. 5.1. Relative risk of birth defects with EFV versus non-EFV regimens**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Relative risk (95% CI)</th>
<th>Events, treatment</th>
<th>Events, control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral pregnancy registry</td>
<td>2013</td>
<td>0.79 (0.49, 1.28)</td>
<td>18/766</td>
<td>183/6160</td>
</tr>
<tr>
<td>Floridia et al</td>
<td>2013</td>
<td>0.74 (0.18, 3.10)</td>
<td>2/80</td>
<td>21/622</td>
</tr>
<tr>
<td>Bera et al</td>
<td>2010</td>
<td>0.90 (0.11, 7.43)</td>
<td>5/184</td>
<td>1/33</td>
</tr>
<tr>
<td>Townsend et al</td>
<td>2010</td>
<td>0.75 (0.30, 1.87)</td>
<td>5/204</td>
<td>48/1478</td>
</tr>
<tr>
<td>Machado et al</td>
<td>2010</td>
<td>6.22 (0.41, 95.10)</td>
<td>1/18</td>
<td>1/112</td>
</tr>
<tr>
<td>Gonzales-Tome et al</td>
<td>2010</td>
<td>0.65 (0.33, 1.26)</td>
<td>7/31</td>
<td>93/266</td>
</tr>
<tr>
<td>Bussmann et al</td>
<td>2010</td>
<td>0.75 (0.07, 7.78)</td>
<td>1/22</td>
<td>2/33</td>
</tr>
<tr>
<td>Patel et al</td>
<td>2010</td>
<td>1.33 (0.08, 21.51)</td>
<td>0/19</td>
<td>14/770</td>
</tr>
<tr>
<td>Cresssey et al</td>
<td>2012</td>
<td>(Excluded)</td>
<td>0/4</td>
<td>0/21</td>
</tr>
<tr>
<td>Ekouevi et al</td>
<td>2011</td>
<td>(Excluded)</td>
<td>0/147</td>
<td>0/102</td>
</tr>
<tr>
<td>Phanupak et al</td>
<td>2011</td>
<td>(Excluded)</td>
<td>0/6</td>
<td>0/180</td>
</tr>
<tr>
<td>Shwartz et al</td>
<td>2012</td>
<td>(Excluded)</td>
<td>0/9</td>
<td>0/58</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td>0.78 (0.56, 1.08)</td>
<td>39/1490</td>
<td>363/9835</td>
</tr>
</tbody>
</table>

The weights are from random effects analysis.

Source: Ford et al. (22).
result in a higher pill burden or more frequent dosing, both of which are inconvenient and could potentially lead to adherence problems (36). These factors have been shown to lead to resistance, requiring a switch to a second-line ART regimen, which adds to the burden on the health system, in terms of both human and financial resources.

**Simplifying and optimizing treatment for HIV and TB coinfection**

TB is the most common opportunistic infection for people living with HIV, particularly in sub-Saharan Africa, where most new TB cases are among people living with HIV (37). There are important drug interactions when NVP is given to people who are also receiving TB treatment. Unlike EFV, NVP concentrations are significantly reduced in the presence of rifampicin, which has been reported by many, but not all, studies (38–40) to reduce efficacy. Thus, EFV has been recommended as the preferred NNRTI for managing people with both HIV and TB (1). Up to 40% of people starting ART in sub-Saharan Africa have TB (41), and many of these are women of childbearing age (42). Therefore, there is practical benefit in recommending EFV in pregnancy considering that many women of childbearing age are also coinfected with HIV and TB.

**Potential decrease in the number of pregnancies terminated**

Despite a clear statement in the 2010 WHO ARV guidelines for preventing mother-to-child transmission (2) that terminating pregnancy for first-trimester exposure to EFV is not recommended, in some settings there has been an increase in the number of pregnancies terminated among women exposed to EFV during pregnancy. A pooled analysis of three studies reporting the frequency of induced abortion among women living with HIV exposed to EFV- and non-EFV-based regimens (22) showed a nearly three times higher risk of induced abortions among women exposed to EFV. These studies suggest that the termination of pregnancy may have been based on concerns among providers and pregnant women of potential birth defects rather than on any confirmation of birth defects. WHO recommending the use of EFV in pregnancy is expected to alleviate some of the concerns health care providers and pregnant women taking EFV may have and may reduce the number of unnecessary terminations of pregnancy.

**Simplifying and harmonizing treatment guidelines**

Uncertainty about the safety of EFV in pregnancy resulted in increased complexity of previous guidelines and practices related to ART and preventing mother-to-child transmission (2,4). These included the following.

- Which first-line ART regimen should be used for women who are unable or choose not to access contraception?
- Which first-line ART regimen should be used for women who are already pregnant, either during or after the first trimester?
- What guidance is appropriate for women already receiving an EFV-based first-line regimen who become pregnant and present to a health facility either during or after the first trimester of pregnancy?

Access to contraception in resource-limited settings is limited and, even when available, cultural barriers may prevent uptake. In sub-Saharan Africa, most people (approximately 60%) initiating ART are women, predominantly of childbearing age (43,44). The proportion of unintended pregnancies among women living with HIV in sub-Saharan Africa ranges from 50% to 90% (45).

These special considerations have prevented, until recently, one simplified and harmonized approach to first-line ART and prophylaxis for preventing mother-to-child transmission.

In an attempt to simplify and harmonize first-line therapy, the WHO 2012 technical update on the use of EFV in pregnancy (3) and the 2013 consolidated guidelines (1) recommended a once-daily fixed-dose combination regimen, with EFV as the preferred NNRTI for pregnant and breastfeeding women, in harmony with the recommendations for non-pregnant adults. This first-line regimen – TDF + 3TC (or FTC) + EFV – was chosen due to its relatively low cost, availability as a fixed-dose combination, safety for pregnant and breastfeeding women and their infants, good tolerability, low monitoring requirements, low drug-resistance profile and compatibility with other drugs in clinical care (1). Recommending a harmonized treatment regimen is easier for programmes to implement and ensures that the programmes that do not have access to CD4 cell testing can initiate ART among pregnant women without delay, which benefits the mother and her infant.

**Simplifying supply chain management**

Previous guidelines had recommended that countries intending to use an EFV-based first-line regimen needed to maintain NVP as the preferred option for women of childbearing age who are planning to become pregnant, or who may become pregnant. As summarized in this update, the latest evidence, as well as important programmatic considerations, suggests that this is not necessary. Eliminating this requirement will simplify programmatic drug procurement and enable more unified supply chain management between ART and programmes for preventing mother-to-child transmission for first-line ARV drugs. NVP needs to be stocked only in small amounts for those (whether pregnant or not) who need to switch from EFV.
Summary comparison of EFV and NVP

Table 4.1 compares the key characteristics of EFV and NVP reviewed in this technical update. EFV has a more favourable profile than NVP for the first five of these characteristics: safety and tolerability, drug interactions, convenience, efficacy and drug resistance. Although EFV and EFV-containing fixed-dose combinations are still more expensive than NVP, the price gap has closed considerably.

Table 4.1. Summary of clinical characteristics of efavirenz and nevirapine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and tolerability</td>
<td>Central nervous system adverse events, which usually resolve after 2–4 weeks</td>
<td>Hepatotoxicity, particularly among women with CD4 counts &gt;250 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>Potentially very low risk of congenital anomalies still cannot be ruled out</td>
<td>Severe skin rash and hypersensitivity reaction (Stevens–Johnson syndrome)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>No significant interactions</td>
<td>NVP concentrations are reduced in the presence of rifampicin and complicate TB treatment</td>
</tr>
<tr>
<td>Convenience</td>
<td>Available as a once-daily, fixed-dose combination (with TDF and 3TC or FTC)</td>
<td>Twice-daily regimen (with AZT- or TDF-containing regimens)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires lead-in dosing (use of half dose in the first two weeks of treatment)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Comparable efficacy in early clinical trials</td>
<td></td>
</tr>
<tr>
<td>Drug resistance (robustness)</td>
<td>Higher risk of NNRTI resistance mutations with NVP</td>
<td></td>
</tr>
<tr>
<td>Cost (generic, annual, per patient)§</td>
<td>Single drug US$ 39</td>
<td>US$ 29</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>US$ 134 (TDF + 3TC + EFV once-daily fixed-dose combination)</td>
<td>US$ 101 (AZT + 3TC + NVP, twice-daily fixed-dose combination)</td>
</tr>
</tbody>
</table>

§Data from Médecins Sans Frontières (46).

Conclusion and future directions

This technical update has reviewed the latest data relating to the use of EFV during pregnancy that form the basis of WHO’s increased confidence in recommending EFV as the preferred NNRTI in the recommended first-line antiretroviral regimen, including in pregnant women and those of childbearing age.

EFV is an important, effective and relatively safe and well-tolerated drug and is currently the best available NNRTI to be included as part of combination first-line ART. Regarding the risks and benefits of using EFV in pregnancy, evidence supports the benefits of EFV against the known risks and complexities of alternatives such as NVP. The 2013 consolidated WHO guidelines recommend that EFV-based treatment no longer be avoided among pregnant women or those who want to conceive.

More countries are adopting TDF-based regimens that can be combined with 3TC (or FTC) and EFV in one tablet as a once-daily fixed-dose combination, in accordance with WHO’s consolidated guidelines, which emphasize simplification, standardization and optimization of ARV regimens. This simplified regimen should facilitate improved adherence (36) and provide important programmatic advantages for use across different populations and in different settings (47). Despite the development of second-generation NNRTIs such as rilpivirine (RPV), the recently demonstrated superior viral suppression with EFV will probably mean that EFV will remain the preferred first-line NNRTI for some time to come (48,49).

The current data review of safety of EFV in pregnancy is reassuring. Additional research and ongoing surveillance through pregnancy registries are needed, both to prospectively collect more data on congenital anomalies and other severe adverse reactions resulting from exposure to EFV and other ARV drugs and to better assess programme, provider and patient perspectives on the true risks and benefits of EFV use, especially in low- and middle-income countries.

WHO recognizes and emphasizes a public health approach for treating HIV and for preventing mother-to-child transmission of HIV. A simplified, harmonized and optimal treatment regimen results in substantial clinical and programmatic benefits. This translates into better health and improved survival for mothers and their infants.
5. OPTIMIZING ANTIRETROVIRAL DRUGS FOR CHILDREN: MEDIUM- AND LONG-TERM PRIORITIES

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Background

Antiretroviral therapy (ART) for children living with HIV is associated with a host of pharmaceutical, clinical, service delivery and supply chain challenges, particularly in low- and middle-income countries. Global, regional, and national efforts are contributing to the scaling up of ART for children, with a sustained improvement in ART coverage for children. Nevertheless, the gap in treatment between children and adults persists, including in the 21 Global Plan priority countries in sub-Saharan Africa.

To support these efforts, reliable delivery of high-quality, affordable ART in doses and formulations appropriate for children is critical, as is the further development of child-friendly fixed-dose combinations.

Since 2010, a series of meetings has sought to address ways to optimize drug development and to harmonize regimens from childhood into adulthood. In June 2013, WHO issued consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Chapter 7, “Clinical guidance across the continuum of care: antiretroviral therapy” included new guidance and recommendations on when to initiate ART for infants, children and adolescents as well as new recommendations regarding infant prophylaxis with ARV to prevent mother-to-child HIV transmission.

The Paediatric Antiretroviral Drug Optimization Conference was held in October 2013 to identify medium- and long-term priorities for the development of antiretroviral drugs for infants and children. The key outcomes of the meeting were as follows.

1. All stakeholders agree that accurate forecasting of demand for ARV drugs for children and quantification of drug needs are critical to ensuring adequate supply.

2. Accelerating the approval of new drugs and formulations suitable for children (such as shortening the gap between drug approval for adults and children) is essential.

3. Patent-sharing agreements are needed for dolutegravir (DTG), tenofovir alafenamide fumarate (TAF),

13 lopinavir/ritonavir (LPV/r) and ritonavir (as a stand-alone drug), in particular for development of fixed-dose combinations.

4. In the medium term, developing a triple fixed-dose combination of ABC + 3TC + EFV for use among children 3–10 years old should be given priority.

5. In the long term, DTG and TAF should be given priority, particularly in fixed-dose combination formulations.

6. Innovative ways need to be explored to generate age-appropriate pharmacokinetic data to extend antiretroviral indications for children to the neonatal period in order to facilitate earlier treatment initiation among infants and more potent postnatal prophylaxis regimens.

Collective engagement between researchers, manufacturers, funders and policy-makers will be critical in driving innovation in HIV treatment that meets the unique needs of infants and children and maximizes individual and public health benefits.

Context

Despite progress in scaling up the prevention of mother-to-child transmission of HIV under the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (1), an estimated 260 000 children were newly infected with HIV in 2012 (2). Most of this transmission occurred in sub-Saharan Africa, where more than 90% of all children infected with HIV currently live. Of particular concern, the treatment gap between adults and children is widening, with latest estimates indicating that only 34% of children younger than 15 years eligible for ART (based on the 2010 WHO eligibility criteria) were receiving treatment compared with 61% ART coverage for adults. Moreover, the pace of scale-up in 2012 was slower for children than for adults – 14% compared with 21%. Scaling up treatment for children

13. TAF (formerly GS-7340) is an NRTI and a novel pro-drug of tenofovir.
living with HIV in low- and middle-income countries is challenging for several reasons, including poor access to early infant diagnosis, weak links between programmes for preventing mother-to-child transmission and ART programmes and the shortage of specialized providers. In addition to these programmatic challenges, the lack of appropriate ARV formulations for children remains a critical bottleneck.

In June 2013, WHO released consolidated guidelines on the use of ARV among adults, children and pregnant women for both prevention and treatment (3). These guidelines incorporate important new treatment recommendations, including a recommendation that all children living with HIV younger than 5 years should initiate ART irrespective of CD4 count or WHO clinical stage. In addition, the consolidated guidelines advocate several new treatment approaches, including the use of protease inhibitor–based therapy for first-line treatment among all children younger than 3 years, the possibility to replace LPV/r with an NNRTI after viral suppression is sustained and once-daily treatment using tenofovir disoproxil fumarate (TDF) as a preferred regimen for children over 10 years (Table 5.1). Although first-line ART for children has been simplified, further simplification and harmonization between age groups remains challenging. Urgent efforts are needed to develop suitable formulations to make these recommendations easier to implement.

Table 5.1. Preferred and alternative first-line regimens for children according to the 2013 WHO consolidated guidelines

<table>
<thead>
<tr>
<th>Age group</th>
<th>Preferred first-line regimens</th>
<th>Alternative first-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &lt;3 years</td>
<td>ABC or AZT + 3TC + LPV/r</td>
<td>ABC or AZT + 3TC + NVP</td>
</tr>
<tr>
<td>Children 3–9 years and adolescents</td>
<td>ABC + 3TC + EFV</td>
<td>ABC or AZT or TDF + 3TC (or FTC) + NVP or EFV</td>
</tr>
<tr>
<td>Adolescents (10–19 years) ≥35 kg</td>
<td>TDF + 3TC (or FTC) + EFV</td>
<td>ABC or AZT or TDF + 3TC (or FTC) + NVP or EFV</td>
</tr>
</tbody>
</table>

Fixed-dose combinations facilitate adherence to treatment and simplify prescribing and supply chain management and have long been used for adults. Fixed-dose combinations have been developed for use among younger children, including some dual NRTI scaled-down versions of adult formulations and dispersible formulations designed to dissolve in water. A triple-drug NVP-based fixed-dose combination was first developed and licensed by the United States Food and Drug Administration in 2007. Despite these improvements, there are still fewer ARV drugs and fixed-dose combinations approved for use in children compared with adults, and typically, the development and approval of indications for children lag many years behind adult indications. In addition, challenges arise from the slow transition by national programmes to adopt improved child-friendly fixed-dose combinations, thereby limiting the number of children able to benefit from them and threatening ongoing production and supply due to low demand.

The ARV landscape for children has to take into account the following factors:

- ARV metabolism in children is generally higher than in adults, so dose reduction by scaled-down weight ratios – particularly in the youngest age groups – might not always be a useful optimization strategy.
- ARV formulations need to be tailored to infants as well as older children.

- Both children living with HIV and HIV-exposed and uninfected children need ARV drugs, so optimization strategies should consider both treatment of children living with HIV and the use of ARV drugs for prophylaxis among infants born to women living with HIV for the needs of HIV-exposed and uninfected children.
- Earlier initiation of ART in the context of lifelong treatment requires careful consideration of each drug’s toxicity and tolerability profile.
- The market for ARV drugs for children is fragmented, substantially smaller and will be virtually limited to low- and middle-income countries in the coming years.

Task shifting and integration of services have been identified as critical elements to enable the further scaling up of treatment and care. In this context, drug optimization should give priority to simplicity while ensuring efficacy, tolerability, robustness, cost-effectiveness, no overlapping resistance in treatment sequencing and convenience for both children and caregivers (4).

Recent consultations on ARV drug optimization

The WHO and UNAIDS Treatment 2.0 framework has re-energized the public health approach to ART, with a vision of generating innovation in drug optimization,
diagnostics and service delivery (5). To guide innovation in drug development, short-, medium- and long-term targets and milestones are being identified through a series of expert consultations. Discussions on drug development priorities have largely focused on adults, despite the recognition that the pharmaceutical needs of children differ (6).

In 2010, the Conference on Antiretroviral Drug Optimization set the stage for potential strategies for reducing drug costs, including (i) modification to the synthesis of the active pharmaceutical ingredient; (ii) use of cheaper sources of raw materials in synthesis of these ingredients; and (iii) innovations in product formulation to improve bioavailability thus needing less active pharmaceutical ingredient (7).

In 2011, a WHO meeting on short-term priorities for drug optimization further refined the dose optimization strategy and provided recommendations on solid formulations for children such as LPV/r pellets, AZT + 3TC dispersible tablets and TDF + 3TC + EFV dispersible and scored tablets (8). That same year, a meeting convened by Médecins Sans Frontières on ART sequencing identified a set of key principles for ART choice that included: simplicity, tolerability and safety, durability, universal applicability and affordability and heat stability (9). In May 2012, WHO convened a think-tank meeting on drug optimization that identified treatment simplification as a critical element for scale-up and raised the issue of potentially aligning sequencing of first- and second-line regimens across populations (4). Finally, in April 2013, the Second Conference on Antiretroviral Drug Optimization concluded with a set of recommendations that included the need for additional studies to examine the role of DTG and TAF in first-line therapy; greater research efforts to improve second-line therapy, particularly the role of dose-optimized ritonavir-boosted darunavir (DRV/r) (10) and continued research on oral and injectable long-acting formulations, nano-formulations and implantables is needed (Box 5.1).

Box 5.1. Conferences on Antiretroviral Drug Optimization

HIV Treatment Optimization, a collaborative project between the Clinton Health Access Initiative, the Johns Hopkins University School of Medicine and Pangaea Global AIDS Foundation, is funded by the Bill & Melinda Gates Foundation and has sponsored Conferences on Antiretroviral Drug Optimization in 2010 and 2013. These Conferences brought together process chemists, clinical pharmacologists, pharmaceutical scientists, physicians, pharmacists and regulatory specialists, and included participation of members of the WHO Department of HIV/AIDS. Although the Conferences were not specifically cosponsored by WHO, their deliberations and observations have been very helpful for the WHO guideline development process.

The first Conference in 2010 (http://www.who.int/hiv/pub/arv/short_term_priorities/en/index.html) focused on developing a research agenda to optimize the doses and combinations of existing approved drugs, including through role of process chemistry, and recommended a research development agenda for HIV drug optimization. The Conference identified a portfolio of projects with the potential to significantly optimize treatment while achieving major cost reductions. Projects included improvements in process and formulation chemistry and dose reductions as intermediate technologies with an imperative to focus future resources on developing better regimens and formulations.

The goals and objectives of the second Conference were to identify and facilitate the development of novel, affordable, optimized drug regimens in resource-limited settings, within a public-health approach. The participants looked further into the future, to review drugs in the development pipeline and to highlight gaps in the drug development programmes. Underpinning the meeting was the commitment to a single global standard for the equitable treatment of everyone, in both resource-rich and resource-poor settings.

The report and recommendations for the second Conference (http://hivtreatmentoptimization.org/sites/default/files/documents/2010-11/cado2meetingreportfinaljuly2013.pdf), while not specifically WHO-endorsed, are consistent with WHO work on drug optimization for adults and are complementary to the Paediatric Antiretroviral Drug Optimization. The second Conference recommended the following.

First-line treatment

Studies to determine fixed-dose combination regimens that are equally or more potent and more durable and affordable than TDF + XTC (either 3TC or FTC) + EFV including TAF + XTC + DTG and TAF + XTC + EFV.
Post-treatment failure

Studies to identify improved second-line regimens, particularly the role of fixed-dose boosted, dose-optimized DRV in replacing atazanavir or lopinavir as the protease inhibitor of choice.

A one-pill once-daily second-line regimen.
Studies of reduced-dose DRV/r, in combination with recycled nucleosides or an integrase inhibitor.

Enhancing trial participant criteria

Studies to reflect the characteristics of people in treatment access programmes, including girls and women of reproductive age, TB coinfection and comorbidity (such as hypertension).

Early engagement of private sector developers and manufacturers

To maximize pharmaceutical company expertise in drug development for global health priorities and to speed up the preparation for production, scale-up and incorporation of new regimens into global treatment programmes.

Longer-term research priorities

Continued research into the potential use of oral and injectable long-acting drugs (including GSK744) as well as nano-formulations and implantable devices (longer-term priority).

Paediatric ARV Drug Optimization Conference

Building on these drug optimization initiatives, the Paediatric ARV Drug Optimization Conference brought together a range of key stakeholders, including clinicians, scientists, funding agencies, representatives of health ministries from settings with a high burden of HIV, implementing partners, civil society and United Nations agencies. The main objectives of this consultation were:

• to provide an overview of the latest research on antiretroviral medicines for children with respect to market dynamics and the research and development pipeline;
• to identify medium- and long-term priority drugs and formulations for different age groups in light of the evolving HIV epidemic among children; and
• to develop a roadmap to streamline access to antiretroviral medicines for children by optimizing drugs.

Although the guidance described below constitutes expert opinion rather than WHO recommendations, it should nevertheless provide direction to industry and, over time, inform the development of WHO’s recommendations for optimizing treatment for children.

Market dynamics and forecasting future ART needs for children

Successful efforts by programmes for preventing mother-to-child transmission have greatly contributed to preventing infants from acquiring HIV infection; however, the risk of mother-to-child transmission remains high in many countries. With recent changes to WHO treatment recommendations and country policies for preventing mother-to-child transmission, future projections of the potential number of children living with HIV and the proportion of those who would be eligible for ART initiation, stratified by age, as well as the number of infants who will require ARV drugs for preventing mother-to-child transmission, remains critical for forecasting future drug supply needs.

WHO and UNAIDS have used Spectrum to develop scenarios to explore future changes in the numbers of children living with HIV and the overall number of children needing ART by 2020. A maximum scale-up scenario (95% ART coverage among adults, 95% coverage of services for preventing mother-to-child transmission and 100% ART coverage among children) was compared with a minimum scenario in which countries maintain their 2012 coverage rates. An intermediate scenario was also developed to reflect critical differences between countries in their current performance (Table 5.2).

14. Spectrum is a modular program used by a variety of agencies to examine the consequences of current trends and future program interventions in reproductive health. UNAIDS uses Spectrum to estimate key HIV indicators based on HIV surveillance and surveys, programme statistics and epidemic patterns. These indicators include the number of people living with HIV, the number of people newly infected, the number of people dying from AIDS, the number of people orphaned by AIDS, the number of adults and children needing treatment the need for services to prevent mother-to-child transmission and how antiretroviral therapy affects survival.
For the 21 sub-Saharan African priority countries, all three scenarios resulted in very similar projections. In 2020, there will be an estimated 1,931,768 children living with HIV (range 1,905,934–1,933,598) and an estimated 1,593,251 children needing ART (range 1,402,393–1,883,387) (Fig. 5.1 and 5.2) (11,12). These estimates demonstrate that, even with expansion of programming for preventing mother-to-child transmission, new and current infections will contribute to a significant number of children living with HIV who will continue to require treatment, highlighting the need to maintain attention on development of appropriate drugs and formulations for infants and young children. An increasing proportion of children living with HIV will be older, and attention will need to focus on appropriate service delivery models for older children and adolescents.

Table 5.2. Assumptions used for the intermediate scenario: expected coverage by 2020 based on current coverage

<table>
<thead>
<tr>
<th>ART for adults</th>
<th>Programmes for preventing mother-to-child transmission</th>
<th>ART for children</th>
</tr>
</thead>
<tbody>
<tr>
<td>If current ART w/coverage is:</td>
<td>Expected in 2020</td>
<td>If current ART coverage is:</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>95%</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>50–75%</td>
<td>90%</td>
<td>50–75%</td>
</tr>
<tr>
<td>25–50%</td>
<td>85%</td>
<td>25–50%</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>80%</td>
<td>&lt;25%</td>
</tr>
</tbody>
</table>

For the 21 sub-Saharan African priority countries, all three scenarios resulted in very similar projections. In 2020, there will be an estimated 1,931,768 children living with HIV (range 1,905,934–1,933,598) and an estimated 1,593,251 children needing ART (range 1,402,393–1,883,387) (Fig. 5.1 and 5.2) (11,12). These estimates demonstrate that, even with expansion of programming for preventing mother-to-child transmission, new and current infections will contribute to a significant number of children living with HIV who will continue to require treatment, highlighting the need to maintain attention on development of appropriate drugs and formulations for infants and young children. An increasing proportion of children living with HIV will be older, and attention will need to focus on appropriate service delivery models for older children and adolescents.

Fig. 5.1. Number of children living with HIV in 21 Global Plan priority countries in sub-Saharan Africa (likely scenario, based on current performance)
Fig. 5.2. Number of children living with HIV and eligible for treatment in 21 Global Plan priority countries in sub-Saharan Africa (likely scenario, based on current performance)

![Graph showing the number of children living with HIV and eligible for treatment from 2013 to 2020. The x-axis represents the years, and the y-axis represents the number of children. The graph indicates the number of children living with HIV and eligible for treatment in different age groups (0–2 years, 3–4 years, 5–9 years, and 10–14 years) for each year. The number of children living with HIV ranges from 0 to 2,500,000.]

Source: WHO and UNAIDS.

Global ARV forecasting data by the Clinton Health Access Initiative (13) up to 2017 similarly highlights that a significant market for children will persist. The Clinton Health Access Initiative forecasting of regimens (Fig. 5.3) is intended to inform industry planning and country-level procurement. Notably, NVP and EFV demand will continue, reflecting the time lag between global guidance changes and likely uptake in national policy and practice. EFV demand may increase given the preference of the drug for children older than three years in accordance with the 2013 WHO guidelines, along with demand for LPV/r, AZT and ABC.

Fig. 5.3. Clinton Health Access (CHAI) Initiative forecasting indicating that AZT and ABC use will continue to increase into 2017

![Bar chart showing the predicted use of different ARV regimens from 2012 to 2017. The chart compares the predicted use of regimens in WHO and CHAI forecasts. The regimens include AZT + 3TC + NVP, ABC + 3TC + NVP, ABC + 3TC + EFV, and ABC + 3TC + LVP.]

Source: CHAI Initiative.
Challenges in the development and uptake of drugs for children

Barriers to treating more children living with HIV include procurement and supply chain management systems, regulatory approval and intellectual property barriers. Drug forecasting, procurement and supply chain issues also need to be considered carefully to move new products and formulations more effectively from research and development to clinical practice.

Drug delivery

The ideal target product profile as well as user factors such as age and developmental stage have to be considered in designing and developing novel formulations and drug delivery systems. In addition, the technical difficulties of producing child-friendly fixed-dose combinations may be substantial.

Drug palatability is a well-recognized challenge in HIV treatment, particularly for younger children. Although palatability solutions (such as taste masking) generally are introduced as part of the drug formulation, they can also be included in the way a drug is delivered to a child, beyond the conventional use of oral tablets and syrups (such as spoons or straws with chemical changes that improve taste). Non-oral routes such as transdermal patches and long-acting ARV drugs are being explored and could play a role in improving adherence among children, especially adolescents. Currently, investigational long-acting injectable nanoformulations of rilpivirine and the integrase inhibitor GSK744 are in clinical development (14). A recent study found that adults were generally receptive to the idea of long-acting injectable drugs, but in children this remains unknown.

Regulatory issues

From a regulatory standpoint, there are concerns over the widespread use of unlicensed and off-label medicines in children, including neonates, and WHO has issued guidance (linked to the List of Essential Medicines for children) to address these concerns (15).

One key regulatory mechanism in place for drug developers is the paediatric investigation plan, serving as a development plan to ensure necessary study data are generated to support the approval of a medication for use in children. Pharmaceutical companies submit proposals for paediatric investigation plans directly to a stringent regulatory agency (the United States Food and Drug Administration or the Paediatric Committee of the European Medicines Agency).

Non-harmonized regulatory frameworks between countries create delays in accelerating the development of ARV drugs for children. In response to this, the Paediatric Medicines Regulators’ Network has been set up and includes representatives from national medicines regulatory authorities from all regions. The Network has been convening regulators in interactive training sessions, on trials involving children. Regulatory networks such as the Paediatric Medicines Regulators’ Network can also support companies in expediting drug trials in children and to address the extrapolation of data from adults to children, the modelling and simulation studies, and provide advice on specific ethical considerations.

Intellectual property

Intellectual property rights can be barriers for accessing affordable ARV drugs and developing fixed-dose combination. Innovative licensing models such as the Medicines Patent Pool are facilitating ARV access for children in resource-limited settings by soliciting voluntary licences from ARV patent owners and creating a pooled resource from which drug manufacturers and innovators can access the rights to manufacture or develop new and adapted formulations for sale in low- and middle-income countries.

Careful considerations of patent issues are important factors that may affect the availability of formulations for children. For instance, although the patent for LPV expires in 2017, formulation patents may last longer. RTV remains a top priority, as there is currently no voluntary licensing arrangement in place. Of note, the patents for DTG and TAF do not expire until 2026, challenging drug access; however, there are contingencies in place to address this issue.

Procurement guidance

Fragmentation of the market for ARV drugs for children, particularly for drug formulations, has been perceived as a disincentive to investment into the future development of drugs for children. Since children account for fewer than 7% of all individuals receiving ART (2), the market for children is smaller and more vulnerable to supply disruptions than the ARV market for adults (16).

With the goal of reducing market fragmentation and streamlining procurement of products for children, the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children developed an optimal list of ARV formulations for children in 2011 that serves as guidance to countries in procuring products that meet the needs of children within the context of WHO recommendations (17). A recent revision of this list addressed the process of rationalizing available formulations by removing redundancies and focusing on a smaller number of formulation products that should facilitate procurement.

The Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children defined the criteria for what constitutes an optimal formulation (Table 5.3) and then evaluated all available products for children against these criteria.
Of the more than 50 products reviewed at that meeting, 10 formulations were identified for inclusion on a list of optimal ARV products for children – this list would include all WHO-recommended first- and second-line regimens for children. Additional products were recognized to be of limited use, and remaining products were listed as non-essential. Limited-use\textsuperscript{15} products include formulations for children that may be needed in limited supply during transition periods and for special circumstances (such as didanosine). Non-essential products are formulations that are not recommended for procurement. Major implementing partners and procurement agencies have endorsed the optimized formulary list of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children. Procurement for ARV drugs for children has been transitioning from UNITAID and the Clinton Health Access Initiative to the Global Fund to Fight AIDS, Tuberculosis and Malaria, which is currently procuring an estimated 45% of these drugs, and this will rise to 60% by 2015. The Global Fund also has in place a market-shaping strategy, including the establishment of the Paediatric ARV Procurement Working Group, which provides market insight, coordinates ordering through a procurement consortium, engages with suppliers more directly and gives in-country support on forecasting and procurement planning.

### Table 5.3. Selection criteria for inclusion in the optimal formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meets WHO requirements</td>
<td>Included in latest WHO guidelines for treatment for children</td>
</tr>
<tr>
<td>Allows for widest range of dosing options</td>
<td>Allows for flexible dosing across multiple weight bands and ages</td>
</tr>
<tr>
<td>Approved by a stringent regulatory authority or WHO prequalification</td>
<td>Availability of at least one product approved by a stringent regulatory authority</td>
</tr>
<tr>
<td>“User friendly”</td>
<td>Easy for health care worker to prescribe</td>
</tr>
<tr>
<td></td>
<td>Easy for caregivers to administer</td>
</tr>
<tr>
<td></td>
<td>Supports adherence</td>
</tr>
<tr>
<td>Optimizes supply chain management</td>
<td>Easy to transport</td>
</tr>
<tr>
<td></td>
<td>Easy to store</td>
</tr>
<tr>
<td></td>
<td>Easy to distribute</td>
</tr>
<tr>
<td>Available for resource-limited settings</td>
<td>Product is being manufactured and can be supplied to resource-limited settings</td>
</tr>
<tr>
<td>Comparative cost</td>
<td>Cost should not be a deciding factor; however, comparative cost of formulations of the same drug or drug combination should be considered</td>
</tr>
</tbody>
</table>

#### Country perspective on service delivery challenges

The gap in treatment coverage among children is a concern in both high and low burden countries. Country experiences highlight the challenges of identifying and diagnosing infants living with HIV in a timely manner and early infant diagnosis implementation is one of the major challenges to achieve wider uptake of ART. New models of service delivery in scaling up treatment for children (such as nurse-initiated ART management), simpler treatment options, giving priority to fixed-dose combinations and harmonizing treatment recommendations for children with adult regimens are programmatic innovations that will facilitate scale-up. At the patient level, palatability and food requirements are critical characteristics.

#### Toxicity monitoring

Toxicity monitoring has long been challenging due to lack of resources and infrastructure. As countries adopt the most recent WHO treatment recommendations and provide ART to a larger number of children, mechanisms to ensure that these regimens are safe must be strengthened. Although anaemia related to AZT is relatively easy to monitor, toxicity monitoring for other drugs, in particular, predicting

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\textsuperscript{15} Limited-use formulations are categorized either as transition products (phasing in and phasing out of drugs, such as d4T) or products for use under special circumstances (specific to the person or situation, such as third-line formulations).
risk of ABC-related hypersensitivity reaction or monitoring TDF-induced bone toxicity, is currently not feasible in most settings. This challenge for monitoring has been reported as a significant barrier to the uptake of ABC (particularly in Asia) and TDF among children despite their well-recognized advantages in terms of sequencing and potential for harmonization. Although ABC toxicity was rarely observed in a large randomized control trial recently completed (18) in Africa, several studies (19,20) have described TDF-related reduction in bone mineral density, and more data to understand the clinical relevance of this and how to best monitor it are urgently needed. Giving priority to drugs with good tolerability and safety profiles and ensuring that systems to monitor toxicity are in place need to be carefully considered in the future strategies for optimizing drugs.

Recommendations of the Paediatric Antiretroviral Drug Optimization Conference

Considering both the critical barriers and the current pipeline of new drugs and formulations, the Paediatric Antiretroviral Drug Optimization Conference identified medium- and long-term priorities for drug and formulation development that can optimize drug delivery and treatment sequencing in children. Critical research gaps that will be essential to inform appropriate use of these products were also highlighted. Lastly, a roadmap to streamline both access and uptake of children-specific ARV in low- and middle-income countries was designed.

1. Medium and long-term priorities for children

Overarching criteria to set priorities for developing drugs and formulations have been identified, key elements to be included in a paediatric investigation plan, and the criteria for inclusion in the optimal list of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children should serve as a model for what an ideal drug or formulation should encompass (Table 5).

There is a need to explore more extensively the use of new products and formulations to the youngest age group (neonates), and innovative ways such as washout data (from babies being born to mothers taking ARV drugs) may be useful to collect when direct pharmacokinetic data for neonates cannot be obtained. Drugs with minimal food-related requirements that are suitable for alternative drug delivery systems and do not present chemical barriers for combination with other drugs should also be given priority. Further, ensuring a high genetic barrier and minimal drug–drug interactions, particularly with TB medications, is essential to guarantee adequate use of these drugs in low- and middle-income countries. Finally, harmonization with adult regimens should continue to be sought.

A. Formulations to be given priority

Given both the current WHO treatment recommendations for children living with HIV and the remaining gaps in products for children, the following formulations are to be given priority in the medium term (the next five years).

- **ABC + 3TC + EFV**
  A one-pill, once-daily formulation of the currently preferred regimen for children 3–10 years old would be highly desirable to enhance adherence and avoid unintentional mono- or dual therapy as a result of individual drug stock-out. EFV-based AZT-containing and NVP-based ABC-containing triple fixed-dose combinations may be of value but not a priority in light of the clear preference given to EFV and ABC by the new WHO guidelines and the potential limited market that these triple fixed-dose combinations may have.

- **AZT or ABC + 3TC + LPV/r**
  These formulations are needed to be able to offer fixed-dose combinations to children younger than 3 years who are prescribed one of recommended preferred regimens in this age group; this could also overcome palatability issues and remove supply chain barriers with the currently available formulation.

- **DRV/r**
  The current lack of a manageable alternative to LPV/r as part of a robust second-line regimen, particularly for children for whom a LPV/r-based first-line fails, make developing these formulations an urgent need.

- **RTV pellets**
  The possibility of a manageable alternative to the existing formulation to ease double-boosting in the context of a LPV-based regimen used as part of TB co-treatment.

Long term (beyond five years), given the existing formulations for children and dosing across the entire age spectrum for raltegravir (RAL), development of a fixed-dose combination containing RAL, 3TC with AZT or ABC should be encouraged. This would provide a second-line option in fixed-dose combination, particularly to the young children started on an LPV/r-based regimen that fail first-line therapy before the age of three years.

B. New drugs to be given priority

In consideration of the new molecules that are currently at advanced stage of development in adults or children (phase 3), and in light of key product characteristics, three new drugs for children were identified for which development should be given priority.
- **DTG**
  This integrase inhibitor has already been approved for use in adults and is currently under study for use from birth (P1093 trial). DTG does not require boosting and has so far shown good tolerability and high potency at doses as small as 50 mg for adults. Hence, there is growing interest in this drug for use in first- or second-line ART (21).

- **TAF**
  A safer first-line alternative to TDF is a drug development priority. Preliminary data suggest that TAF may have lower renal and bone toxicity; however, more children-specific data are needed to confirm the more favourable safety profile and enable wider use of this drug in children. The opportunity to offer an alternative to ABC and further harmonize with adult regimens is an additional advantage, particularly if co-formulated with EFV or integrase inhibitors (preferably DTG).

- **Cobicistat**
  Cobicistat may potentially be a more child-friendly booster that could be combined with any protease inhibitor, particularly for the drugs for which co-formulation in dosing for children is still unavailable, such as ATV and DRV. Studies investigating this drug in formulations for children are planned.

The current timelines for development and potential approval of these priority drugs means that they are unlikely to be a viable treatment option before 2017. Therefore, these drugs represent the long-term vision. Although additional compounds such as elvitegravir and rilpivirine may well have value, at present it may be wise to give priority to fewer options that are more likely to meet the needs of children and better align with optimization principles.

**C. Optimized sequencing**

Given the age indications, known resistance profiles, potential for co-formulation and expected timelines of approval for most of the compounds being discussed, medium-term and long-term visions were developed on how to best sequence the priority drugs and formulations.

Although the current sequencing for children 3–10 years old remains a valid option in the medium term, better approaches are urgently needed for the younger age group (0–3 years) initiating an LPV-based first-line regimen. These younger children may be able to use an RAL-based or DRV/r-based regimen interchangeably for second- or third-line treatment, depending on whether first-line treatment fails before or after the third year of age to account for the age indication of these two drugs.

The long-term vision remains the opportunity to provide a potent, once-daily first-line option formulated in a fixed-dose combination containing DTG and 3TC in combination with either ABC or TAF (assuming that the age indication for the latter will be extended to newborns). This approach would not only allow complete alignment across the different age groups in children, but would most likely align with adult preferred regimens, thus representing for the first time full harmonization across populations (Table 5.4).

<table>
<thead>
<tr>
<th>Table 5.4. Recommended sequencing options for younger and older children (medium and long term)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 0–3 years</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Medium-term</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> If first-line failure occurs before three years of age.
<sup>b</sup> If first-line failure occurs before six years of age.
<sup>c</sup> Cobicistat can be considered a potential alternative for boosting, particularly if the DRV/r co-formulation is still unavailable.

Source: adapted from the recommendations of the Paediatric ARV DrugOptimization Conference, Dakar, Senegal, 22–23 October 2013.
2. Research priorities

The Paediatric Antiretroviral Drug Optimization Conference identified the following research priorities to address further drug optimization:

- DTG: establish dose, safety and efficacy in children;
- LPV/r in malnourished children: pharmacokinetics and implications for use;
- TB co-treatment in children: pharmacokinetics of ABC and newer drugs;
- drug interactions between ABC and LPV/r: impact on pharmacokinetics, efficacy and use;
- DRV/r ratios: pharmacokinetics of co-formulations for use by children;
- pharmacokinetics of EFV-based triple fixed-dose combination according to weight-bands dosing among children 3–10 years old;
- TAF and long-term TDF toxicity in young children (0–10 years): better understanding and clinical relevance;
- Cobicistat: pharmacokinetics and potential for co-formulations;
- head-to-head comparison between TAF and ABC among children of different ages; and
- rilpivirine: pharmacokinetics and efficacy and toxicity at higher dose to provide a more robust long-acting option particularly for older children and adolescents.

3. Roadmap to streamline access and uptake

A roadmap of actions with the objectives of facilitating access to drugs and formulations for children and ensuring adequate uptake of ART was developed at the Paediatric Antiretroviral Drug Optimization Conference, concerning the following four areas.

Speeding up the development and approval of drugs and formulations

There is a need to minimize the gap between the approval of new drugs for adults and children and neonates by engaging more effectively with ethics committees and industry. Harmonization of regulatory approval requirements across countries is critical to minimize the steps required for approval (harmonization of age categories and weight-bands). Establishing model paediatric investigation plans for regulatory bodies may further standardize and streamline the development and submission of adequate information. Lastly, fast-tracking mechanisms for priority products exist, and these systems should be more effectively used for children living with HIV to obtain regulatory approval (European Medicines Agency Article 58). International agencies such as WHO should ensure that priority products are identified and clearly flagged and use for fast-track approval.

Sharing patents

Although several patent-sharing agreements have already been negotiated, additional agreements are urgently needed. Priority should be given to such drugs as DTG, TAF, new LPV/r and ritonavir (stand-alone) formulations. Other drugs identified as important by the group, such as RAL, should also be considered. There is a need to streamline clinical approval across age groups and to develop strategies that easily transition patent agreement from one age group to another. In addition, mechanisms should be put in place to ensure the continuity of coverage through adulthood in middle-income countries as much as in low-income countries.

Giving priority to procuring formulations for children

Coordination between health ministries, technical agencies, industry, procurement agencies and donors is essential to streamline the production and effective supply of formulations for children. Technical agencies and global partners should provide guidance on optimal drugs and formulations to be procured in alignment with WHO recommendations. Industry needs to be clearly informed on the selected priority formulations to best serve the needs of children living with HIV in the medium and long term.

Enhanced communication and adopting tools such as the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children optimal formulary list are expected to facilitate procurement, prevent stock-outs, reduce market fragmentation and ensure the necessary investment. Lastly, the role of donors and development agencies in securing the availability of low-volume products and encouraging the adoption of procurement tools on a global scale will be critical in ensuring the feasibility and sustainability of these changes.

Overcoming financial barriers

Since HIV infection among children is almost entirely a problem of low- and middle-income countries, alternative financial mechanisms need to be explored urgently at the global level, including the potential role of advanced market commitments and learning from other disease areas (such as polio) where efforts aiming to sustain a

16. Agreements to share patent information for other important drugs mentioned in this report, such as ABC + 3TC, ATV and COBI, have already been negotiated and are available through the Medicines Patent Pool.
diminishing market will be an important additional step. In this context, the group recommended that more accurate epidemic estimates be urgently sought to develop more reliable forecasting for ARV drugs for children and to ensure the mobilization of adequate and sustainable funding.

National governments should secure specific budgets for ARV drugs (for example, in South Africa, AIDS budgets are ring-fenced) and explore the potential for orders for children to be added on to orders for adults for drugs with the same active pharmaceutical ingredients.

Conclusions

Although programmes for preventing mother-to-child transmission continue to succeed in reducing vertical transmission globally, there are currently 1.2 million children living with HIV eligible for ART who do not receive it, and the number of children acquiring HIV infection will remain significant, with an estimated 1.8 million children living with HIV by the end of 2020. An urgent and appropriate response to the specific needs of children is therefore urgently needed.

More strategies will be required to tackle treatment-experienced children living with HIV and to address the challenges and needs of adolescents living with HIV. In addition, ongoing acquisition of HIV infection will continue to contribute a significant number of children eligible for treatment in the coming years. As the use of early infant diagnosis improves, more data will be required to fully inform the use of ARV among neonates and young children.

In addition to the need to improve currently available formulations, new drug delivery systems have the potential for further optimizing drugs, and this promising work needs to move beyond academic research and into drug development. Better alignment of first- and second-line treatment options for both younger and older children also will be critical to facilitate the scale-up of ART for children and to ensure that treatment optimization enables new models for service delivery, such as task-shifting and decentralization, to reach more children earlier. Finally, efforts in advancing the research agenda on treatment for children, particularly in the context of new formulations and drugs, will require coordinated efforts between stakeholders, including academe, funders, regulators, industry, civil society and the affected communities.
6. CHANGING ROLE OF CD4 CELL COUNTS IN HIV CARE AND TREATMENT

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Key messages

- Assessment of baseline CD4 cell counts continues to play a role in stratifying risk and guiding clinical decisions about starting prophylaxis and screening for opportunistic infections.

- Assessment of CD4 cell count is still necessary to guide initiation of ART outside of certain clinical situations.

- HIV viral load, when available, is a more reliable tool for monitoring adherence to treatment and efficacy of ART than CD4 cell counts.

- Recent evidence demonstrates that, once people living with HIV receiving ART are virally suppressed, their CD4 cell count does not decline over time, suggesting that, in situations in which viral load is available routinely, CD4 monitoring could be reduced or stopped altogether.

National HIV programme policies for ART monitoring

During the past decade, WHO guidelines on antiretroviral therapy (ART) in low- and middle-income settings have evolved towards recommending that countries phase in viral load for treatment monitoring, although it has been acknowledged that the complexity of the technologies and the cost have limited access (4). The latest guidelines, released in June 2013, recommend that countries use HIV viral load as the preferred approach to ART monitoring (5).

Current guidelines for ART monitoring vary from country to country. The Democratic Republic of the Congo, Guinea and several other countries currently rely on CD4 alone, whereas several countries including Kenya, Lesotho, Mozambique, Swaziland and Zimbabwe rely on routine CD4 cell monitoring and use viral load only in a targeted way to confirm treatment failure among people with immune or clinical failure, and Malawi and South Africa rely on viral load for long-term monitoring; in the case of South Africa, discontinuation of routine CD4 is now recommended after one year for people stable on ART unless continued CD4 results are needed for decisions regarding stopping opportunistic infection prophylaxis (6). Monitoring strategies can also differ between the public and private sectors; in India, for example, targeted use of viral load is provided in the public sector, whereas routine viral load monitoring is offered in the private sector. The frequency of both CD4 and viral load tests performed for ART monitoring also varies substantially between countries.

Purpose of this section

As reflected in the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO now recommends ART initiation regardless of CD4 cell count for a number of clinical or programmatic indications. WHO further recommends HIV viral load measurement as the preferred approach to treatment monitoring (7), and there is a concerted effort to support the scaling up of viral load capability in resource-limited settings.

With access to viral load becoming increasingly available, the role of CD4 monitoring is increasingly being questioned. Several studies have recently suggested that CD4 monitoring has little added value in situations where viral load is available and patients are virally suppressed (2,3). In September 2013, WHO held an expert consultation on the future role of CD4 testing for ART monitoring. This technical update summarizes the evidence to date and the key findings of this consultation and is intended for clinicians and programme managers to assist them in decisions about the relative priorities of CD4 testing in settings in which viral load capacity exists or is being phased in.

Prospects for increasing access to viral load monitoring

Several middle-income countries – notably Botswana, Brazil, South Africa and Thailand – were early adopters of HIV viral load monitoring. Viral load monitoring has been integrated into the guidelines of national HIV programmes in countries with a high burden of HIV more broadly since 2010, when WHO guidelines first recommended that countries should phase in viral load for routine treatment monitoring (7). In practice, however, access to viral load remains limited due to the complexity of current technologies and cost.
Currently, it is estimated that less than 20% of the people receiving ART in Africa receive routine viral load testing (8). The anticipated arrival of point-of-care technologies from 2014 onwards should help overcome some of the technological limitations to improving access to viral load, particularly in remote rural areas. As of June 2013, nine point-of-care technologies were in the pipeline, with six anticipated to receive market authorization by 2016 (9). Other approaches that have been taken to increase capacity and access include the use of dried blood spot sample collection and sample pooling (10,11).

An important barrier to scaling up viral load testing remains the cost, which can range from US$ 10 to more than US$ 50 per test. The African Society for Laboratory Medicine recommends several approaches to reducing the cost of viral load testing, including negotiating volume-based regional or country-wide pricing for test supplies, encouraging competition by using multiple suppliers to negotiate lower prices and using automated technology to improve test quality and increase test throughput (8).

A key approach to increasing resource availability for phasing in viral load testing is to decrease the overall cost of laboratory test monitoring by reducing the overall number of tests performed. Recent studies from South Africa (12) and the United States of America (13) have suggested that reducing the frequency of CD4 testing can substantially reduce costs; in resource-limited settings, these resources could be directed towards increasing access to viral load testing.

The value of baseline CD4 measurements

Consistent with the trend towards policies of earlier initiation of ART, the median baseline CD4 count at which people start ART has risen during the past decade in all WHO regions, and most markedly in the lowest-income countries; however, many people enter into HIV care late, with advanced immunosuppression. The proportion of people initiating ART with very low CD4 counts remains high, with more than one in four people starting ART at CD4 ≤100 cells/mm³ across all regions (14).

People first presenting to HIV care with a low CD4 cell count are at increased risk of death in both low- and high-income settings (15,16), and CD4 determination currently has an important role in decisions for screening and prophylaxis for major opportunistic infections. A low CD4 count predicts several diseases associated with higher mortality, including cryptococcal meningitis, Pneumocystis pneumonia, toxoplasmosis, Mycobacterium avium complex and disseminated cytomegalovirus disease. CD4 test results can help stratify the clinical care requirements for people presenting late to care and support diagnostic decision-making at baseline and among people for whom ART is failing or who are returning to care after a period of treatment interruption.

For example, cryptococcal meningitis remains a leading cause of mortality among people with HIV, contributing up to 20% of AIDS-related deaths in low- and middle-income settings (17), and WHO recommends systematic Cryptococcus antigen screening for everyone with CD4 ≤100 cells/mm³ and preemptive treatment for those with positive antigen test (18).

WHO recommends providing co-trimoxazole prophylaxis to everyone presenting to care with a CD4 count ≤350 cells/mm³ (as well as for those with WHO clinical stage 3 or 4). Co-trimoxazole improves survival by reducing the risk of death from a range of infections, including malaria, severe bacterial infections, Pneumocystis pneumonia and toxoplasmosis (19).

CD4 cell count and treatment initiation

The 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) recommend that ART be initiated for all patients with CD4 ≤500 cells/mm³, and initiated immediately regardless of CD4 for children up to five years old, people with active TB or coinfected with hepatitis B virus with severe chronic liver disease and people living with HIV in serodiscordant partnerships. The guidelines further recommend that ART be offered to all pregnant and breastfeeding women living with HIV (20).

Most countries with a high burden of HIV are in the process of adopting and adapting these new recommendations according to their epidemic setting and resource availability. While there is a trend towards an increasing number of CD4-independent ART initiation scenarios, ART for all irrespective of CD4 cell count remains the exception rather than the rule and, for most countries, CD4 measurements continue to play an important role in determining eligibility for ART.

Value of CD4 for ART monitoring

Recent evidence from randomized trials and observational cohorts suggests that, once people living with HIV receiving ART are virally suppressed, CD4 cell counts do not decline over time for most of them.

An analysis of data from the Artemis trial found that, of the 449 people with sustained HIV-1 RNA suppression and CD4 ≥200 cells/mm³ followed for 192 weeks, only 1% experienced reductions in CD4 count below 200 cells/mm³. These reductions were transient, with follow-up results >200 cells/mm³ (3). A cohort study from the United States found that, among 832 people followed for a median of 7.7 years, those with an initial CD4 ≥300 cells/mm³ and who were virally suppressed on ART had a 99.2% probability of a durable CD4 ≥200 cells/mm³ at year 5, after excluding non-HIV causes of lymphopaenia (2). Similar studies from the United Kingdom (22) support these findings. Unpublished data from resource-limited settings further confirm that CD4 declines are rare and mostly transient among people who are virally suppressed. Although data for children are lacking,
there is no reason to expect that these dynamics will differ substantially. A recent model-based algorithm (23) suggests that the frequency of CD4 cell count measures could also be reduced in children, using last CD4 count, last viral load and age to predict clinical disease progression risk.

Criteria for stopping CD4 for treatment monitoring

Although a CD4 cell count at baseline continues to be important for initial clinical management decisions, once ART is initiated and people have achieved viral suppression and stabilized on treatment, the additional value of CD4 testing in the presence of routine viral load monitoring is questionable. CD4 cell counts rarely decline over time once viral suppression is achieved, even for people presenting late for care. The extent of immune recovery depends on nadir CD4 count before treatment initiation (24), but most people can be expected to achieve a reasonable degree of immune recovery after several years of ART provided that viral load remains suppressed (25–27). A minority of people may fail to increase CD4 despite viral suppression (28,29), but if viral load is suppressed, this variability in CD4 recovery would not alter treatment decisions, as there is no evidence for changing ART among those with a discordant immune and viral response.

There is a growing consensus that CD4 monitoring adds little additional value to viral load monitoring once patients are stable on ART with viral suppression. Guidelines issued by the Southern African HIV Clinicians Society recommend that, for people being monitored with viral loads, once the CD4 count is >200 cells/mm$^3$ and viral load is suppressed (two consecutive undetectable viral loads), there is no need to continue CD4 testing. CD4 testing is recommended if viral or clinical failure occurs (6).

Community considerations

In addition to guiding clinical decisions, CD4 cell counts are a central part of current approaches to treatment literacy, and considerable emphasis has been placed on using CD4 as a way to explain to people why ART is needed, the importance of maintaining good adherence and as a measure of a positive response to treatment.

If viral load is to be used as the principal means of monitoring ART, treatment literacy efforts will be needed so that demonstration of viral suppression can take the place of rising and subsequently stable CD4 as the main way that people living with HIV understand how they are responding to ART. However, both clinicians and people living with HIV recognize that CD4 cell counts can fluctuate significantly due to both the inherent variability of CD4 levels and the inconsistency of results obtained by CD4 tests, and this can be an unnecessary source of anxiety for the people living with HIV (30). Successful pilot programmes have already shown that, with appropriate communication materials, the relationship between viral load and treatment success is easy to convey and readily understood (31), and groups of people living with HIV have expressed a willingness to support a reduction in or stopping of routine CD4 monitoring for people in stable condition provided that this is accompanied by clear messaging that they can understand.

Conclusions

CD4 cell counts have been the main tool for making decisions about ART initiation and monitoring the response to treatment and have had considerable value for both clinicians and people living with HIV. However, the utility of ongoing CD4 monitoring among people stable on ART whose viral load is also being monitored is increasingly being questioned.

More than 10 million people are currently receiving ART, and more than 1.5 million people were newly initiated on ART in 2012 alone. Life expectancy studies from both high-income (32) and low-income (33–35) settings have concluded that, with timely ART initiation, people living with HIV can expect near normal life expectancy. There is therefore a pressing need to identify the most rational and cost-effective way to provide laboratory monitoring of HIV treatment over time.

CD4 counts will continue to play an important role in initial decisions around ART initiation and clinical management, particularly for the people presenting late to care, and will remain an important tool for treatment monitoring in settings where viral load monitoring is limited. Although CD4 cell levels provide an important indication of disease progression and death among people living with HIV but not receiving ART, once treatment has been initiated, the key focus is ensuring viral suppression.

In settings where both CD4 and viral load testing are routinely available, countries should consider reducing the frequency of CD4 cell counts or eliminating them altogether from routine use for monitoring treatment response once people are stable on ART. Countries in the process of phasing in viral load monitoring capacity should consider reducing the indications for and frequency of CD4 cell measurements at the same time and redirect these resources towards expanding access to viral load monitoring.

When access to viral load testing is assured, the WHO consultation endorsed the move to reduce routine CD4 monitoring for adults who are on ART and are immunologically stable. For children, the decision to stop CD4 is more complex both due to risk of disease progression, particularly for younger children, and determination of immune recovery. A working definition of stability on ART for children may need to be age dependent, and this is an important area for further research.
7. SCALING UP VIRAL LOAD TESTING IN RESOURCE-LIMITED SETTINGS

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy.

Key messages

- HIV viral load testing is the preferred monitoring approach to diagnose ART treatment failure.
- Options for phasing in viral load testing are varied and will increase as new technologies become available.
- Viral load scale-up is context specific, and programme managers and laboratory experts need to collaborate closely at the national level.
- The selection of a viral load platform will be affected by cost, robustness, low threshold accuracy and the ability to ensure expeditious delivery of samples to the viral load laboratory.
- The availability of point-of-care technologies over the next several years may impact early infant diagnosis and treatment monitoring.
- More detailed technical guidance is forthcoming to complement this programme update.

Introduction

By the end of 2012, 9.7 million people were receiving ART in low- and middle-income countries. This increase in the number of people receiving ART during the past decade has been achieved through political commitment, community mobilization and significant domestic and international financial support. Despite this success, more needs to be done to reach the target of 15 million people receiving ART by 2015 set by United Nations Member States in June 2011. Further, with the introduction of the 2013 WHO guidelines recommending a higher initiation threshold of CD4 ≤500 cells/mm³ for everyone and ART for certain people living with HIV regardless of CD4 count (including pregnant women and members of serodiscordant couples), the number of people eligible for ART is now estimated to have risen to 25.9 million.

In addition to expanding access to ART for everyone eligible, it is important to ensure that those receiving ART remain in care and on effective therapy if treatment programmes are to continue to have a sustained impact on morbidity, mortality and the transmission of HIV. Viral load, the gold standard for monitoring ART response in high-income settings, is increasingly recognized as an important and accurate tool for managing ART in resource-limited settings as a way to diagnose poor adherence and treatment failure early (1). Guidelines for ART management issued by WHO have recognized the importance of viral load monitoring since 2003, and routine viral load monitoring is now strongly recommended as the monitoring strategy of choice (2).

Most countries with a high HIV burden and lower-income countries still rely on clinical and immunological criteria to define treatment failure. However, a recent systematic review concluded that clinical or immunological criteria for treatment failure have low sensitivity and positive predictive value for identifying individuals with viral failure, particularly for children, and people who are identified with immunological failure may in fact have adequate viral suppression and risk being misclassified and switched unnecessarily to second-line therapy (3).

There are a number of challenges to implementing viral load monitoring in resource-limited settings, including complex technical requirements to perform the test, logistics of sample transport and cost. Nevertheless, recent operational experience has demonstrated the feasibility of performing viral load monitoring in a range of resource-limited settings, and provides strategies to overcome these challenges. Interest in the use of dried blood spot samples for viral load testing and a robust pipeline of near-to and point-of-care technologies will likely provide further opportunities for increasing access to viral load testing, particularly in settings that do not have easily accessible referral laboratories. The first commercially available point-of-care viral load technologies are expected to become available before the end of 2014 (4).

This section outlines key considerations for national programme managers as they consult with laboratory services experts for phasing in routine viral load monitoring and for selecting HIV viral load testing platforms that will be best suited for their national or local contexts. Programme managers and laboratory experts will need to evaluate how they can increase access with currently available technologies and how expected increased numbers of newer technologies, such as point-of-care viral load testing, might affect current priority-setting. WHO is collaborating with several technical partners to issue a more detailed technical update on viral load platforms that will complement this programme update.
Viral load monitoring is increasingly recommended in policy, including by WHO (Box 7.1), but availability remains limited. A 2012 survey of 23 countries with a high burden of HIV found that, although 13 countries include viral load for routine monitoring in their national guidelines, only three of these (Botswana, Brazil and South Africa) had the capacity to implement this as a nationwide policy (4). These three countries have been able to institute efficient and regular specimen collection systems and have decentralized viral load testing to provincial level laboratories, usually relying on fully automated platforms.

Where viral load monitoring is not routinely available, national guidelines generally recommend CD4 testing every six months to monitor treatment efficacy, but in practice many programmes perform significantly fewer than half of the number of CD4 tests that would be expected based on treatment monitoring guidelines (5). The reasons for this range from inconsistent test-ordering practices among health care providers, lack of regular or reliable sample transport, stock-outs of sample reagents, inadequate throughput capacity and lack of maintenance for the laboratory equipment. National programme planners and laboratory experts will benefit from understanding the challenges in accessing CD4 testing as viral load testing is scaled up (5).

Developing a strategy for scaling up access to viral load testing

Based on recommendations that, if feasible, expanding viral load testing capacity will facilitate patient monitoring, a range of stakeholders will need to collaborate to develop a country-specific situational analysis that defines plans for scaling up viral load testing. The issues related to expanding viral load testing are complex but include choice of platform(s), degree of decentralization of laboratory equipment, scope and scale of viral load testing expansion, issues of sample type and collection, logistical and infrastructure needs, laboratory staffing requirements, training needs for clinicians, modification of clinical tools and elaboration of monitoring and evaluation systems. The choice of viral load testing platform will be affected by cost, robustness in country-specific conditions, accuracy at lower viral load thresholds, availability of maintenance contracts and ability to use different sample types. Annexes 7.1 and 7.2 describe the operational characteristics of the most common viral load platforms. Deciding which viral load platform is the most appropriate requires considering not only price but also servicing needs and availability, quality, subtype and ability to meet the technical and throughput needs of the local context. Harmonization of platforms should be defined by the health ministry in collaboration with clinicians, laboratory staff and policy-makers. Finally, plans to introduce new approaches to increase viral load capacity should also consider how best to use existing equipment to maximize capacity.

Simplifying sample transport for centralized viral load testing

An important limitation to scaling up viral load testing
in resource-limited settings has been the complexities of transporting samples. Plasma obtained from EDTA anticoagulated whole blood remains the preferred sample type (6); however, obtaining plasma in peripheral clinics is often not feasible due to the lack of electrical centrifuges and cold-chain storage. One possible alternative to EDTA is a plasma preparation tube, although this does require centrifugation within 6 hours. When blood is collected at a peripheral clinic without centrifugation capacity in an EDTA tube, or in a plasma preparation tube, samples can be transported at room temperature but must reach the district laboratory within 6 hours (7).

Once centrifuged, samples can be stored up to 5 days at room temperature with a plasma preparation tube and up to 14 days at 2–8°C from EDTA-derived tubes, and longer if frozen at −20°C or −80°C. Stability under these conditions can facilitate sample transport if testing is performed at referral laboratories. These cold-chain limitations for the different sample types will need to be factored into costing sample storage and transport (8).

The practical implications of these various requirements are that, if sample transport does not occur daily, patients are either asked to visit their clinic again on a specific specimen collection day or are required to travel to the nearest hospital with a laboratory with centrifugation and plasma specimen storage and transport capacity, to have blood drawn.

Use of dried blood spots for viral load testing

A strategy to simplify sample transport for early infant HIV diagnosis for using DNA qualitative testing assays for HIV DNA has been to prepare whole-blood samples on dried blood spots on appropriate filter paper. Dried blood spot samples offer multiple operational advantages: they can be stored and transported at room temperature for long periods without affecting nucleic acid stability (9); they can be prepared by non-laboratory staff with limited training, either from capillary or venous blood; and the small volume of blood needed to impregnate the filter paper reduces the biohazard risk related to sample collection (10).

For quantitative viral load monitoring, HIV RNA testing is needed. Both dried blood spots and dried plasma spots for quantitative viral load measurements have been extensively evaluated with different viral load assays (11). An important limitation of dried blood spots is the presence of cell-associated nucleic acids (DNA and RNA), particularly in samples with lower levels of viral load (≤5000 copies/ml), that, compared with plasma, can lead to elevated results when using methods relying on total nucleic acid extraction (DNA and RNA) reverse-transcriptase PCR methods rather than RNA-specific extraction methods.

Dried plasma spots have been proposed as an alternative to dried blood spots, with studies showing good correlation with plasma (12,13); however, its applicability in primary health clinics is limited owing to the need for centrifugation for plasma preparation.

Tradeoffs therefore exist with each sample type, and these should be balanced against clinical and operational considerations. For example, dried blood spots may allow decentralization of viral load testing, but this may restrict the type of viral load platform to be used and the applicable clinical thresholds. For use of EDTA-derived plasma rather than whole blood, small and inexpensive battery-operated centrifuges may be a solution but, where logistics for adequate sample transport to a laboratory do not exist, this will require dedicated staff at the clinic level trained in phlebotomy, sample processing, storage and transport as well as safety precautions associated with sample manipulation and waste management.

Rapid plasma preparation devices may in the future provide an alternative to obtaining plasma without the need for electrical centrifuges, but their applicability for viral load testing has not yet been evaluated (14,15).

The challenge of selecting a technique-specific, reliable threshold that is above the currently recommended lower limit of 1000 copies/ml to identify treatment failure (and higher transmission risk) can be overcome to some extent by using RNA-specific methods such as nucleic acid sequence-based amplification (NASBA). At present, the NucliSENS EasyQ HIV-1 v2.0 assay is the only commercially available RNA-specific NASBA-based viral load testing technology and the only viral load test with regulatory approval to use dried blood spots as a sample type. Other manufacturers are adapting their tests for use with dried blood spots. Fig. 7.1 outlines the sample transport considerations for the different sample types.

Reducing the cost of viral load testing

The cost of viral load testing per sample has declined in recent years. Programme managers must factor in many cost centres when evaluating the most cost-efficient testing platform and strategy. From a clinical and programmatic standpoint, several options may reduce the cost to the national programme.

Viral load pooling

Viral load pooling can reduce the total number of tests being performed by combining sample aliquots — for example, for five individual patient samples — and analysing them according to a standard operating procedure. A pool deemed negative — below the applicable threshold — does not require further testing, and all samples are considered

17. Some studies suggest that EDTA whole-blood samples can be stored at room temperature for up to seven days, with negligible impact on RNA stability. These results only apply to samples with high viral loads (≥5000 copies/ml); thus, further investigation is needed for samples with low viral loads (≤5000 copies/ml).
below the threshold. A pool deemed positive — above the applicable threshold — will require individual testing of each patient sample. The number of tests saved will therefore depend on the proportion of “detectable” samples found. Further operational and clinical research is required to evaluate the feasibility of pooling in resource-constrained settings, particularly in high-throughput settings. Although this approach requires further validation for routine monitoring, it is already being used in Malawi.

**Reduced frequency of testing**

The cost–effectiveness of viral load testing in comparison to clinical or immunological monitoring is sensitive to the frequency of testing, with annual viral loads being more cost-effective than six-monthly viral load testing (16). Current guidance recommends performing viral load monitoring routinely at month 6 following ART initiation and then yearly thereafter, and more frequent monitoring is not indicated. Currently, there is little evidence on the clinical impact of differing monitoring frequencies; however, as part of the phased approach to scaling up routine viral load testing, a decrease in frequency of monitoring may allow increased coverage (17).

**Reducing CD4 monitoring in the presence of viral load monitoring**

CD4 testing remains necessary for the staging of immune status and vulnerability to opportunistic infections, and this information is frequently used to guide initiation of prophylaxis for opportunistic infections. For people receiving ART, an increasing number of countries are considering reducing or stopping the use of CD4 testing for treatment monitoring as a way to free up funds for scaling up viral load testing. A growing body of evidence suggests that people who have achieved a degree of immune reconstitution and who maintain viral suppression are unlikely to experience a
subsequent drop in CD4 count (18). The latest ART guidelines issued by the Southern African HIV/AIDS Clinicians Society recommend that CD4 be checked initially and at 12 months after ART initiation; subsequent monitoring is through yearly viral load alone. This approach was endorsed by a recent WHO consultation on the changing role of CD4 cell counts in HIV care and treatment (19).

Pricing

The prices of viral load testing vary considerably. Although the market is very fragmented, with a wide range of prices paid both within and between countries, the recent prices for viral load tests quoted to low-income countries average US$ 15 per test (including all reagents and consumables) and may even include complimentary instrumentation. Price negotiations are usually subject to confidentiality agreements such that pricing information per country is not publicly available, and many additional costs may be added to this, including distribution costs, tax or duties and procurement overhead.

Comprehensive test price calculations should include laboratory overhead, human resource expenses, maintenance costs, consumables required for the test but not included in the kit, sample collection consumables, sample transport costs and data management costs. Some countries have been able to negotiate price decreases with manufacturers using a combination of competition between manufacturers and volume scale-up – to prices as low as US$ 10 per test (including all reagents and consumables) – volume discounts may increase as scale-up occurs, and preliminary work suggests that manufacturing costs can be further lowered through economies of scale (20).

Using early infant diagnosis to scale up viral load testing

Traditionally, early infant diagnosis has been performed using a qualitative virological test for HIV DNA. However, several molecular platforms are now available that are more automated and sensitive and can do DNA or RNA testing or total nucleic acid testing. The advantage of using reverse-transcriptase quantitative PCR is that the quantitative result will be more informative for clinicians since a baseline viral load in infants will be established as part of monitoring treatment efficacy. Although the same platform can be used for both quantitative and qualitative PCR, some platforms will require running different batches for each test type, since plasma and dried blood spot samples may not be able to be tested simultaneously in all platforms; for example, the Roche COBAS® AmpliPrep/COBAS® TaqMan® (CAP/CTM) version 2 allows simultaneous testing of plasma and dried blood spots, but the Abbott and other platforms do not. Similarly, the combined testing volume for HIV viral load and early infant diagnosis testing required on the same platform needs to be considered to maximize efficiency and the turnaround time of the results. For example, if viral load and early infant diagnosis samples must be batched separately, and early infant diagnosis testing is typically much lower throughput – although more urgent – than viral load testing, operational space will need to be made for early infant diagnosis testing in between batches of viral load samples while still trying to maximize the efficiency of processing. Alternatively, should a national programme have more than one instrument available, individual platforms could be dedicated to either early infant diagnosis or viral load testing.

Options for phasing in viral load testing

Several approaches for phasing in viral load testing capability can be considered depending on patient load, sample transport constraints, financial resources and equity considerations. Phase-in could be achieved in several ways, depending on the country-specific challenges to scaling up. Depending on the context, a mix of approaches may be used.

Confirming treatment failure

In situations in which sample transport concerns are not the prime factor and viral load capacity is limited, the first priority should be to confirm viral failure in patients with suspected treatment failure due to clinical progression or significant deterioration in immune status. WHO has put forward criteria for defining treatment failure based on clinical and immunological grounds but recognizes that these criteria have low specificity and sensitivity for predicting viral failure. Confirmatory testing using a viral load test is therefore important to avoid unnecessary switching to second-line treatment.

Routine viral load testing

Current WHO guidelines recommend that viral load be checked after six months on ART and yearly thereafter to enable earlier and more accurate detection of treatment failure (2). Challenges, particularly in sample transport, may lead to selecting specific populations for the initial roll-out of routine viral load testing, although a blend of strategies may be chosen in practice.

Geographical tiered approach

To establish laboratory capacity, specimen collection and result delivery, internal and external quality assurance and adequate training of clinical and counselling staff, a tiered
approach to phase-in may be chosen. Health facilities with easy access to laboratories with existing or easily implemented viral load testing capability could be chosen to implement routine viral load testing, with a gradual decentralization to peripheral sites once systems are established and practical implementation lessons learned. Such an approach will allow for a stepwise approach to training, sharing of experiences in implementation and avoid multiple facility-specific changes in messaging for health staff on viral load testing algorithms.

Phasing in according to target populations

An alternative approach to phasing in routine viral load testing could be to target specific populations at higher risk. Children, adolescents, pregnant or breastfeeding women and people identified as being at higher risk for early poor adherence might benefit selectively from receiving routine viral load testing if capacity does not exist for monitoring everyone receiving ART in the initial phases. Depending on the setting, a combination of approaches may be preferred.

Pregnant women. Higher maternal viral load is associated with elevated antenatal and postnatal transmission, with an estimated 29% greater transmission rate for every log
_10 unit increase in viral load (21).

Children and adolescents. Rates of viral failure tend to be higher among children and adolescents than among adults (22). Identifying the children with viral failure early would enable them to receive more targeted adherence interventions, or changes in regimen, early.

Identification of early poor adherence. Poor adherence soon after initiating ART has been found to predict short- and long-term viral failure (23). Early identification through viral load testing and intensive adherence intervention may prevent the future development of resistance and decrease the time before switching treatment.

Targeting specific populations still requires functioning sample transport systems for all sites, training and supervising all site staff members and clinical staff being able to systematically identify the subgroups requiring monitoring. Where ART care has been task-shifted to lower-level health workers and/or extensively decentralized, top-down roll-out may be the better option, since it does not add the programmatic complication for clinicians to triage access within a specific facility.

Emerging technologies – point-of-care viral load testing

Viral load testing has been confined so far to centralized laboratories and performed by trained laboratory technicians. Although some platforms are highly automated, the availability of point-of-care viral load technologies in the coming years will provide increased opportunities for viral load testing at the district or primary care level. Table 7.1 outlines the main issues for national programmes to consider when deciding whether to introduce point-of-care technologies, once available, for routine viral load testing, in addition to centralized testing. The decision-making will be affected by the specifications of the particular point-of-care platform that is chosen.

Point-of-care testing for early infant diagnosis could allow ART initiation for infants on the same day of HIV testing and diagnosis, a critically important issue because of the high risk of mortality associated with HIV infection among infants. Point-of-care testing can reduce the risk of loss to follow-up before diagnosis, whether exposed infants are tested at birth or at 4–6 weeks (24).

Once point-of-care testing is widely available and validated, programme managers will need to make judicious choices regarding the balance between point-of-care and more centralized laboratory viral load testing.

When a point-of-care technology is being considered, the total number of sites requiring viral load testing and the daily throughput of each individual site need to be assessed, including workload considerations for the clinical staff. If throughput at a given site is very low, it may not justify the investment required to install and maintain a point-of-care device. Similarly, in settings with a high prevalence of HIV infection, where a single point-of-care test at the clinic or district level is unlikely to meet daily throughput needs, and many instruments would place an undue burden on staff, a high-throughput laboratory-based instrument at provincial level may be the preferred choice. Policies to allow task shifting of laboratory tasks to nurses and lay workers will facilitate the use of point-of-care devices at the health facility level, accompanied by appropriate training and supervision.

Comparative costing studies should be undertaken to inform these decisions. The price per test is minimized when instruments are used efficiently; if a point-of-care test can be performed eight times per day but would only be used twice per day at clinic level, then it may be better to install the point-of-care test at the district level to process samples from several clinics per day.
Table 7.1. Programmatic considerations for different tiers of the health care system for viral load monitoring

<table>
<thead>
<tr>
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<th>Centralized or partly decentralized laboratory-based viral load testing</th>
<th>Point-of-care viral load testing</th>
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</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Provides high-throughput testing</td>
<td>• Same-day result for patient at time of testing</td>
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<tr>
<td></td>
<td>• Facilitates the storage and analysis of results in a centralized database</td>
<td>• No sample transport but a result delivery system required</td>
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<tr>
<td></td>
<td>• An existing sample collection and result delivery system could be used</td>
<td>• Simplicity allows task-shifting to low cadres</td>
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<tr>
<td></td>
<td>• A centralized approach simplifies quality assurance</td>
<td>More suitable in:</td>
</tr>
<tr>
<td></td>
<td>• Fewer machines mean fewer maintenance contracts and simpler supply chain for reagents and commodities</td>
<td>• Low-throughput settings</td>
</tr>
<tr>
<td></td>
<td>• Sample transport and result delivery system has to be established</td>
<td>• Restricted number of treatment sites</td>
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<tr>
<td></td>
<td>• No immediate result</td>
<td>• Sites that will be difficult to reach via sample transport</td>
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<tr>
<td></td>
<td>• Batch testing required</td>
<td>• Vulnerable groups for treatment failure (such as children and adolescents or populations at high risk of loss to follow-up)</td>
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<td></td>
<td>• Cost per test linked to the efficiency of testing (preferably using the instrument at least at 50% capacity)</td>
<td>• Widespread training, supervision, supply chain, quality assurance, maintenance and connectivity for central reporting are required</td>
</tr>
<tr>
<td></td>
<td>• Skilled laboratory staff required</td>
<td>• No experience with viral load point-of-care use to date</td>
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<tr>
<td></td>
<td>• Preventive maintenance may be costly</td>
<td>• Cost (not currently determined)</td>
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<td></td>
<td></td>
<td>• Increased workload for already overloaded health care workers due to task shifting</td>
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<td>• Limited number of tests per day</td>
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**Procurement**

Laboratory test quality relies on the availability of laboratory equipment, reagents and consumables that meet minimum quality standards as well as a quality assurance policy, including quality assurance policies established by funding agencies. In an effort to enhance quality and promote efficient resource use, equipment selection should be standardized wherever possible in a tiered laboratory network (25). The health ministry should define harmonization and procurement policies in collaboration with clinicians, laboratory staff and policy-makers. Standardizing the type of platform for viral load testing across different laboratory levels offers many benefits. Ideally, a list of prequalified vendors would be established based on WHO guidelines and/or the list of products from the WHO prequalification of diagnostics. A team of laboratory technicians should provide input, and along with procurement specialists, should develop technical specifications for equipment acquisition. It is advisable to include at least two different platforms on the national approved procurement list to avoid problems in case of quality or distribution issues, and to account for differences in capacity between laboratory tiers within a decentralized viral load testing network. Post-procurement, national quantification and forecasting should be performed to inform future budgeting and procurement.

A local service provider should be available to facilitate training and support, either in the form of local representatives of the company or a third party designated by the manufacturer for procurement, training and maintenance.
It is advisable to investigate whether a local or regional office is available for the product of interest and to negotiate a favourable maintenance contract with the manufacturer. If national and/or donor regulations permit, an instrument leasing option or reagent rental option may be preferable to purchasing expensive instrumentation outright. This option will also allow for end-user flexibility to adopt newer and more efficient technologies as they emerge in the market.

In settings in which molecular testing for multiple pathogens is required, a polyvalent platform may be the preferred choice. Most manufacturers of commercially available laboratory-based platforms (such as Abbott, bioMérieux, Qiagen, Roche, Siemens, Biocentric and Cavidi) offer multiple kits for different diseases: typically HIV DNA (for early infant diagnosis), hepatitis B and C, human papillomavirus, chlamydia and gonorrhoea, for use on their single molecular instruments (Annexes 7.1 and 7.2). Point-of-care instruments will initially be sold for single use, but there are plans to design additional test cartridges for other diseases, such as TB or hepatitis B and C. The GeneXpert instrument by Cepheid offers a substantial test menu already, with a robust pipeline for the future.

Open platforms can be used on various real-time PCR instruments, thereby allowing other tests to be run on the same platform. Open platforms offer the possibility for ordering reagents and instrumentation separately and from multiple manufacturers. This has the advantage of both sourcing the best-priced item and optimizing the test for best performance in the particular population where it will be used. For example, viral load testing must be able to detect all HIV subtypes and circulating recombinants that are present locally. A limitation of this approach is that, once optimized, the test must be standardized for routine use and for submission to a strict regulatory authority.

Although current real-time PCR technologies are comparable in terms of analytical performance (lower limit of detection, linear range and HIV subtype detection), they differ in terms of technology used, level of automation, throughput capabilities, costs, infrastructure and human resource requirements and ability to process different sample types. These differences are important considerations for implementing and scaling up of viral load testing nationwide.

Preparing for second-line ART as treatment failure is diagnosed

A major programmatic challenge associated with scaling up viral load monitoring is the likely increase in identification of treatment failure and the need to budget for more expensive second-line ART. Even in settings in which targeted viral load is used, programmes have not reliably switched those diagnosed with viral failure due to ongoing adherence concerns, poor implementation of the clinical algorithm or loss to follow-up (26). Establishing an effective decentralized approach to switching to second-line therapy should be part of any strategy for scaling up viral load testing. Job aids and training of clinicians on the use of second-line regimens for both adults and children are needed to ensure familiarity with second-line regimens.

Preparing health providers

Successfully rolling out routine viral load testing requires appropriate action by health providers, for which training and supervision are critical. User-friendly clinical algorithms and simple schematics are useful to assist health care providers in ensuring that people living with HIV are routinely tested for viral load and that the results are acted on appropriately. In addition, adequate supervision, through monitoring and evaluation and site visits, is needed to ensure that the treatment failure and second-line therapy algorithms are systematically implemented. Providing laboratory-generated lists of people receiving ART with viral load >1000 copies/ml to clinic coordinators and programme supervisors may aid follow-up to ensure that the people who will benefit from intensified adherence interventions or initiation of second-line therapy are being managed appropriately.

Preparing counsellors

The algorithm recommended in the WHO 2013 consolidated guidelines proposes that an adherence intervention be implemented for the people receiving ART with a viral load >1000 copies/ml. Although many countries have adopted this principle, the types, intensity and uptake of adherence interventions vary. The ART clinic team should clearly identify who is responsible for addressing adherence barriers for those patients who have detectable viral loads.

Principles of enhanced adherence counselling

Based on the workload of the staff providing adherence support and their competencies, the number of sessions, the mode and the content should be adapted. Adequate monitoring and supervision of the implementation of the enhanced adherence intervention are essential for effective roll-out. Adherence interventions are context-specific and need to be adapted to the local resources available (27). Enhanced adherence support interventions should aim to identify the behavioural, cognitive, socioeconomic or emotional problems affecting people’s adherence. At the same time, individualized strategies should be identified with the person to overcome these barriers. Ideally, follow-up counselling over a further one or two sessions should be provided to evaluate strategies implemented by the person living with HIV.
**Preparing people living with HIV**

Patient literacy on the need for and interpretation of viral load to monitor their treatment response is essential to support the demand for viral load and is likely to aid adherence. For many people, changes in CD4 values have been the way to understand treatment efficacy, and changing this paradigm will require concerted patient literacy and counselling, both within the clinic and from community-based awareness-raising. Visual tools to explain the concept of viral load may aid understanding as well as having clear written instructions on patient-held records as to when viral load should be tested (28).

**Establishing a viral load implementation plan**

Viral load testing may be scaled up nationally, regionally or within a specific referral hospital laboratory and primary health centre network. A situational analysis should be performed to identify existing capacity, utilization and need. There are key steps that programme planners, laboratory workers, clinical manager and other service providers can then follow to ensure that a comprehensive scale-up plan is developed and implemented (Fig. 7.2).

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**Fig. 7.2. Steps for rolling out viral load testing at the national level**

<table>
<thead>
<tr>
<th>Implementation plan for viral load testing</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Coordinate efforts and define priorities</td>
<td></td>
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<tr>
<td>Internal consultation within the health ministry and consultation with laboratory national strategic plan</td>
<td></td>
<td></td>
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<tr>
<td>Consultation with donors and partners: funders, suppliers, laboratories, clinicians and economists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establish working group, analyse prevalence for selecting sites and adapt clinical algorithm</td>
<td></td>
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<tr>
<td>Develop funding proposal</td>
<td></td>
<td></td>
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<tr>
<td>Develop a pilot and phased plan: analyse strengths, weaknesses, opportunities and threats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Develop a procurement plan and negotiate with suppliers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess the human resources required: laboratory and clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verify instruments when required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set up or improve systems for transporting samples and delivering results (SMS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepare sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepare training materials, standard operating procedures, external quality assessment and instrument interface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modify the database to handle viral load results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitize provincial and city hospitals about the viral load testing programme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot viral load accreditation criteria at provincial and city hospital laboratories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Select initial sites to begin routine viral load testing and enhanced adherence counselling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot enhanced adherence counselling at selected sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot viral load training at selected sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Install instruments and laboratory information system and verify instruments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-site training and parallel clinic training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Build capacity for training (laboratory and clinic) support resources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commence testing at sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport coordination and system for delivering results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biweekly meeting with the laboratory team and the supplier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring and evaluation framework Collect data and evaluate the project</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly monitoring and evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data analysis, instrument use and quality control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly and quarterly report and review of plans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale up viral load testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate routine viral load testing in more clinics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate further viral load testing laboratories</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### ANNEX 7.1.

Operational characteristics of the most common automated molecular HIV RNA viral load platforms

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbott</th>
<th>bioMérieux</th>
<th>Roche</th>
<th>Siemens</th>
<th>Biocentric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>RealTime HIV-1 assay</td>
<td>NucliSENS EasyQ HIV-1 v2.0</td>
<td>COBAS Amplicprep/COBAS TaqMan HIV-1 monitor v2.0</td>
<td>VERSANT HIV-1 RNA 1.0 assay (kPCR)</td>
<td>Generic HIV viral load assay</td>
</tr>
<tr>
<td>Principle</td>
<td>RT-qPCR</td>
<td>RT-qPCR</td>
<td>RT-qPCR</td>
<td>RT-qPCR</td>
<td>RT-qPCR</td>
</tr>
<tr>
<td>Storage of EDTA blood before testing</td>
<td>≤6 h (15–30°C) or ≤24 h (2–8°C)</td>
<td>≤24 h (15–30°C)</td>
<td>≤6 h (2–25°C)</td>
<td>≤6 h (15–25°C)</td>
<td>≤6 h (2–25°C)</td>
</tr>
<tr>
<td>BD plasma preparation tubes validated</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Storage of plasma preparation tubes before centrifugation</td>
<td>6 h (2–25°C)</td>
<td>Not applicable</td>
<td>6 h (2–25°C)</td>
<td>≤6 h (15–25°C)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Storage of plasma preparation tubes after centrifugation</td>
<td>Frozen in situ until testing</td>
<td>Not applicable</td>
<td>5 days at 25°C</td>
<td>5 days (4–8°C)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Extraction automation</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Amplification automation</td>
<td>++</td>
<td>+</td>
<td>+++ (with docking station)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Number of tests in one run</td>
<td>M2000sp: 96 M24sp: 24 M2000rt: 96 (93 test samples)</td>
<td>EasyMAG: 24; EasyQ: 48 (46 test samples)</td>
<td>Ampliprep: 21 test samples; Taqman 48; 48 (42 test samples); Taqman 96: 96 (84 test samples)</td>
<td>SP module: 96 (89 test samples)</td>
<td>Nordiag Arrow: 12Thermocycler: 96 (82 test samples)</td>
</tr>
<tr>
<td>Number of plasma tests in one day (8-h shift)</td>
<td>279</td>
<td>EasyMAG: 168 (lysis on board workflow) / 240 (lysis in tube workflow); EasyQ: 192</td>
<td>Taqman 48: 100; Taqman 96: 250</td>
<td>178</td>
<td>192</td>
</tr>
<tr>
<td>Regulatory approval</td>
<td>WHO PQ, CE-IVD, US-FDA-IVD, Canada-IVD (plasma)</td>
<td>WHO PQ, CE-IVD (plasma and EDTA DBS)</td>
<td>WHO-PQ, CE-IVD (not m24sp), Canada-IVD, Japan-IVD (plasma)</td>
<td>CE-IVD (plasma)</td>
<td>Commercialized but currently research use only (WHO PQ and CE mark in process)</td>
</tr>
<tr>
<td>Cost of the test in resource-limited settings</td>
<td>US$ 25, subject to negotiations</td>
<td>US$ 24</td>
<td>US$ 11–25 (applicable to all least developed countries or countries in sub-Saharan Africa with a high burden of HIV infection, otherwise US$ 35–90)</td>
<td>US$ 54–72</td>
<td>US$ 16</td>
</tr>
<tr>
<td>Approximate cost of equipment (extraction and amplification)</td>
<td>US$ 200 000</td>
<td>US$ 150 000</td>
<td>US$ 250 000</td>
<td>US$ 200 000</td>
<td>US$ 55 000 (US$ 70 000 with two automated nucleic acid extractors)</td>
</tr>
</tbody>
</table>
ANNEX 7.2
Polyvalency of currently available commercial viral load platforms

<table>
<thead>
<tr>
<th>Tests commercially available</th>
<th>Company</th>
<th>Abbott (m2000)</th>
<th>BioMérieux (EasyQ)</th>
<th>Qiagen (QS-RGQ)</th>
<th>Roche (CAP/CTM)</th>
<th>Siemens (VERSANT kPCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV quantitative RNA (viral load)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HIV qualitative (early infant diagnosis)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em> and <em>Neisseria gonorrhoeae</em></td>
<td>Yes</td>
<td>No</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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<sup>a</sup>In development.

<sup>b</sup>For chlamydia only.

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