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), 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.

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 Spectrum14 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). 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.

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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 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>

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)

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.

Source: WHO and UNAIDS.
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 formulations by removing redundancies and focusing on a smaller number of formulation 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\(^\text{15}\) 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>
<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...

\(^\text{15}\) 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>Age 0–3 years</th>
<th>Age 3–10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option 1</strong></td>
<td><strong>Option 2</strong></td>
</tr>
<tr>
<td>Medium-term</td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>ABC + 3TC + LPV/r</td>
</tr>
<tr>
<td>Second line</td>
<td>AZT + 3TC + DRV/r</td>
</tr>
<tr>
<td>Third line</td>
<td>Optimized background regimen + RAL</td>
</tr>
<tr>
<td>Long-term</td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>TAF + 3TC + DTG or ABC + 3TC + DTG</td>
</tr>
<tr>
<td>Second line</td>
<td>AZT + 3TC + LPV/r or ATV/r&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Third line</td>
<td>DRV/r&lt;sup&gt;c&lt;/sup&gt; + ETR or EFV</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 Drug Optimization 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,16 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.