



Photo: Eric Bond, 2018

Accelerating Access to Optimal Child-Friendly Antiretroviral Formulations for Children Living with HIV:

Lessons Learned from Eight Sub-Saharan African Countries

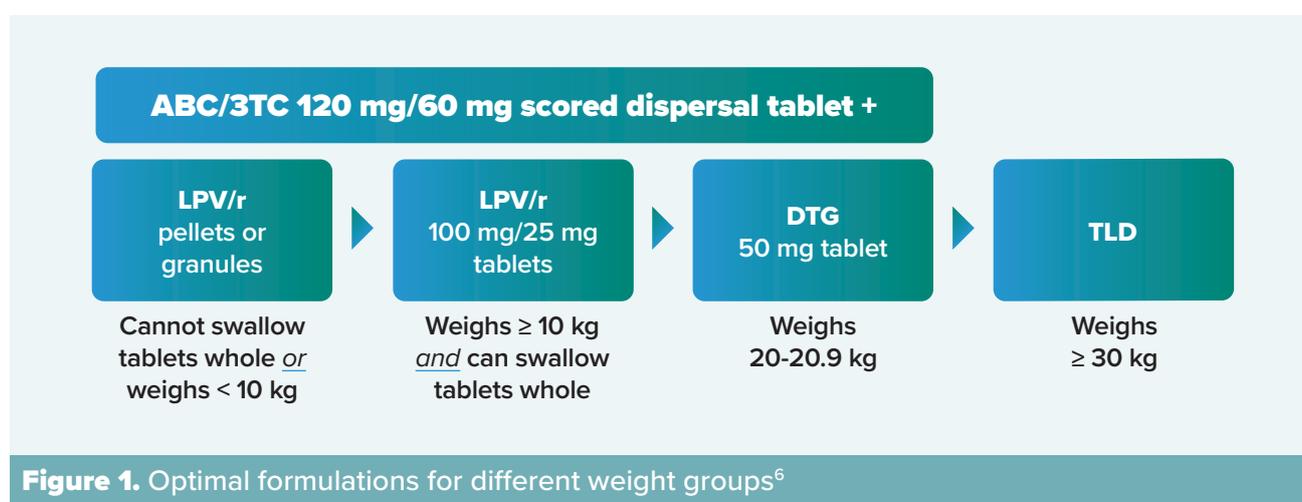
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1. Background

To improve health and save lives, children living with HIV must have access to timely diagnosis and effective, child-friendly antiretroviral (ARV) treatment and care. Yet in 2018, only 63% of 1.1 million HIV-exposed infants in 23 UNAIDS focus countries were tested for HIV by the age of 2 months, and just 54% of HIV-positive children ages 0–14 years were receiving antiretroviral therapy (ART). Treatment disparities were especially stark in western and central Africa, where ART coverage among children was only 28%.¹ Although children ages 0–14 years represented 5% of the people living with HIV in the 23 focus countries, they accounted for 15% of those dying from AIDS-related causes.²

In 2018, the majority of children on ART were receiving suboptimal ARV formulations, and viral suppression rates were low across most of the 23 focus countries. Countries with available data—Côte d'Ivoire, Botswana, Malawi, Tanzania, Uganda, South Africa, Kenya, Lesotho, Zambia, Eswatini, and Namibia—reported viral suppression rates among children ranging from 24% in Côte d'Ivoire to 67% in Namibia.³ More than half of all children on ART were still receiving suboptimal formulations, such as nevirapine (NVP), efavirenz, and lopinavir/ritonavir (LPV/r) solution. The World Health Organization (WHO) no longer recommends NVP-based regimens due to the increased risk of drug resistance and inferior clinical outcomes. Although clinically superior to NVP, LPV/r solution is foul tasting and poorly tolerated by children as well as difficult to store due to its cold chain requirement. WHO therefore recommends LPV/r solution only as an alternative when a suitable solid form of LPV/r is not available.⁴ The use of suboptimal formulations negatively affects treatment adherence and viral suppression and ultimately increases HIV-related morbidity and mortality.

In December 2018, WHO released updated guidelines recommending regimens based on dolutegravir (DTG) as the preferred first- and second-line regimens for children for whom approved DTG dosing was available. Children weighing 20 kg or more could be given regimens containing DTG 50 mg tablets. Children weighing 30 kg or more should be given TLD—tenofovir + lamivudine (3TC) (or emtricitabine) + DTG. However, due to the absence of an appropriate DTG formulation and/or dosing for children weighing less than 20 kg, WHO recommended LPV/r-containing regimens until child-friendly DTG formulations and dosing became available.⁵ Figure 1 illustrates how ARV formulations available in late 2018 could be combined with an abacavir (ABC) / 3TC backbone to deliver optimal regimens for different weight groups.



- 1 UNAIDS. Start Free, Stay Free, AIDS Free. Geneva, Switzerland: UNAIDS; 2019. https://www.unaids.org/sites/default/files/media_asset/20190722_UNAIDS_SFSAF_2019_en.pdf.
- 2 Ibid.
- 3 UNAIDS. UNAIDS Data 2019. Geneva, Switzerland: UNAIDS; 2019. <https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data>.
- 4 World Health Organization. The 2019 Optimal Formulary and Limited-Use List for Paediatric ARVs. Geneva, Switzerland: World Health Organization; 2018. <https://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/>.
- 5 World Health Organization. Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV: Interim Guidelines. Supplement to the 2016 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Geneva, Switzerland: World Health Organization; 2018. <https://apps.who.int/iris/handle/10665/277395>.
- 6 World Health Organization. Considerations for Introducing New Antiretroviral Drug Formulations for Children: Policy Brief. Geneva, Switzerland: World Health Organization; July 2020. <https://www.who.int/publications/i/item/9789240007888>.

2. Project Overview

In 2019, the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) began supporting the national governments of eight African countries in their efforts to transition children living with HIV to new, optimal pediatric ARV formulations. This work began in August 2019 under the Unitaid-funded Securing Pediatric ARV Access Now (SPAAN) project in Côte d'Ivoire, Eswatini, Lesotho, Mozambique, and Zimbabwe, and in November 2019 in Kenya, Tanzania, and Uganda under the REACH project led by the Drugs for Neglected Diseases Initiative and funded by a grant from the Agence Française de Développement. Representing diverse regional and health systems contexts, the eight project countries together comprised more than two-fifths of the total burden of pediatric HIV in the 23 priority focus countries and approximately 35% of the total pediatric HIV burden globally in 2018.

Although several new child-friendly ARV formulations and regimens had received stringent regulatory authority (SRA) approval, and others were on the horizon, significant quality, demand, and supply barriers hindered their rapid and sustainable uptake. Quality barriers consisted of difficulties in obtaining national approval of new formulations and weak pharmacovigilance systems to support rapid roll-out with a safety net. Demand barriers included challenges in quantifying pediatric ARV needs as well as national HIV program concerns about product availability, feasibility, and affordability. Finally, the capacity of manufacturers to supply sufficient quantities of new products was uncertain, and transitioning to several new formulations for a low-volume market posed challenges in maintaining adequate stocks of new ARVs in the context of fragile supply chains.

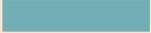
Both projects sought to streamline and accelerate the quality introduction of new pediatric formulations as well as reduce the proportion of children on suboptimal formulations such as NVP. The projects focused on an immediate transition to available LPV/r solid formulations, such as LPV/r 2-in-1 pellets and granules, for children weighing less than 20 kg, and to DTG 50 mg tablets for children weighing more than 20 kg. They also supported advanced planning for the uptake and roll-out of DTG dispersible tablets and ABC / 3TC / LPV/r fixed-dose combination granules, which were expected to receive U.S. Food and Drug Administration approval by January 2021.

EGPAF tailored project activities to each country's context, with the following overarching objectives:

- Update national guidelines and essential medicines lists to include new pediatric ARV formulations
- Develop and/or adapt materials and tools on new formulations for clinicians and caregivers
- Build the capacity of health care workers to prescribe new formulations and of caregivers to administer them
- Generate demand and sustainable funding for optimal pediatric ARVs
- Increase the number and percentage of children on ART who receive optimal regimens
- Ensure alignment of ARV commodity supply plans with the pediatric ARV optimization agenda
- Collect and disseminate evidence from and lessons learned in the adoption and roll-out of optimal regimens to inform future transitions

Table 1 lists the key steps taken across all project countries to transition to SRA-approved LPV/r solid formulations and indicates the overall progress by October 31, 2020, after approximately one year of implementation.

Table 1. Key steps and achievements for SRA-approved LPV/r solid formulations by 31 October 2020

| Activity | Number of countries completing by 31 October 2020 |
|---|---|
| 1. Rapid landscape assessment of potential barriers to introducing new optimal pediatric ARVs | 8  |
| 2. Updating national treatment guidelines and essential medicines lists to include SRA-approved LPV/r solid formulations | 8  |
| 3. Assessing existing stock of sub-optimal legacy formulations | 8  |
| 4. Completing quantification and forecasting of SRA-approved LPV/r solid formulations | 8  |
| 5. Developing national transition and roll out plans for SRA-approved LPV/r solid formulations | 7  |
| 6. Fully implementing the national transition and roll out plan for SRA-approved LPV/r solid formulations | 6  |
| 7. Developing and/or updating job aids and educational materials on SRA-approved LPV/r solid formulations for use by healthcare workers and caregivers | 8  |
| 8. Training all healthcare workers at EGPAF project sites on SRA-approved LPV/r solid formulations | 7  |
| 9. Offering multi-month dispensing to eligible children aged 5 years and above at all EGPAF project sites | 6  |
| 10. Updating ARV stock management tools and training of staff to ensure timely ordering and accurate consumption monitoring of optimal pediatric ARV formulations | 7  |
| 11. Updating adverse drug reaction reporting forms and training healthcare workers in pharmacovigilance for optimal pediatric ARVs | 6  |
| 12. Developing and/or adapting information systems to actively monitor the implementation of pediatric ARV transition plans | 6  |

This brief shares key lessons learned from project implementation across the eight countries in order to guide the rapid uptake of new pediatric ARV formulations in the future. It includes key barriers to rapid, quality, and sustainable transition to new pediatric formulations and actions taken to overcome those barriers. In addition to summarizing the lessons learned, it also proposes recommendations to inform future transitions to optimal pediatric ARV formulations.

3. Common Challenges to Pediatric ARV Optimization and Actions Taken to Overcome Them

Most project countries adopted a phased approach to introducing new pediatric ARV formulations while phasing out suboptimal legacy formulations. Many countries had large stocks of legacy formulations to use and/or had limited capacity to implement a national scale-up all at once. While no major differences were reported between what had been planned and what was actually implemented, COVID-19 hindered the progress of country optimization activities and required some activities to be implemented differently. For example, in all project countries EGPAF moved training sessions and national technical working group meetings from in-person events to virtual events, or followed a modified approach, such as convening small in-person group meetings or training sessions with social distancing and masks, in accordance with national COVID-19 protocols.

During implementation, project countries encountered various challenges and implemented country-specific actions to overcome them. Challenges clustered thematically across nine areas:

1. National guidelines, essential medicines lists (EMLs), and authorization of WHO-recommended pediatric ARV regimens
2. National transition strategy or roll-out plan for new pediatric ARVs
3. Quantification, supply planning, and stock management of pediatric ARVs
4. Materials for health care workers and caregivers
5. Health care worker capacity to transition eligible children and counsel their caregivers on new pediatric ARVs
6. Caregiver capacity to administer new pediatric ARV formulations
7. Multimonth dispensing (MMD) for children 5 years and older
8. Pharmacovigilance and reporting of adverse drug reactions (ADRs)
9. Data and information systems to support quantification and to monitor the transition of children living with HIV to new pediatric ARVs

Appendix A lists the challenges faced, by country. In the section below, these challenges and solutions to address them are presented and discussed in detail.



Photo: Eric Bond, 2018

National guidelines, essential medicines lists (EMLs), and authorization of WHO-recommended pediatric ARV regimens

Six project countries experienced challenges in updating national guidelines and EMLs and registering new pediatric ARVs. These challenges were primarily due to slow national processes as well as COVID-related disruptions.

Solutions to these challenges included the following:

- Issuing government circulars to provide guidance on ART optimization while awaiting the official release of updated national treatment guidelines
- Releasing a memo with additional guidance on transitioning eligible children to supplement current national guidelines
- Securing special authorization from the national pharmaceutical authority to permit the use of new ARV formulations prior to the official updating of the national EML
- Using virtual platforms to disseminate guidelines and/or orient relevant staff to the new guidelines

Country Spotlight: Zimbabwe

In Zimbabwe, EGPAF supported the Ministry of Health and Child Care in updating the national HIV treatment guidelines to recommend a DTG-based regimen for all clients living with HIV, including children weighing less than 20 kg, as soon as an appropriate formulation was SRA approved and WHO released dosing guidance. The revised guidelines also recommended solid formulations of LPV/r for infants and children. Early engagement of key stakeholders, including the Pediatric HIV Technical Working Group, facilitated the acceptance of DTG 10 mg dispersible tablets prior to their receiving SRA approval and will ensure timely implementation once the product is available on the market. It also allowed the country to quantify for and include DTG 10 mg in the 2021 national ARV forecast and supply plan.

National transition strategy or roll-out plan for new pediatric ARVs

Five countries reported difficulties with developing and/or implementing a national strategy or roll-out plan for new pediatric ARVs. Challenges included a lack of guidance for transitioning children under different scenarios; inaccurate assumptions in the transition plan about the age at which children can swallow whole tablets, which led to an overstock of LPV/r 100/25 mg tablets in some countries; Ministry of Health (MOH) reluctance to dispose of existing stocks of suboptimal formulations; and delays in developing and/or implementing the plan due to COVID-19.

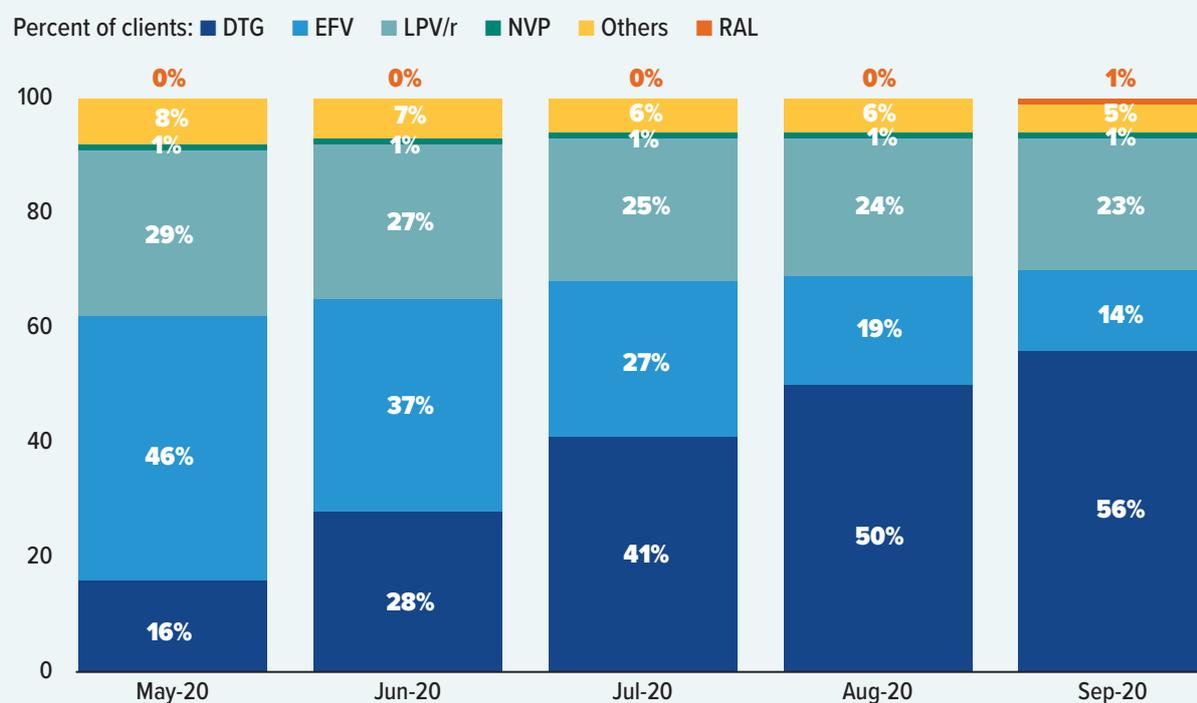
Solutions to common challenges included the following:

- Developing standard operating procedures with different scenarios to guide health workers on transitioning children to optimal formulations
- Providing enhanced clinical and psychological support for children and their caregivers via phone calls and/or home visits to ensure treatment continuity and retention in care during the transition
- For countries experiencing delayed delivery of optimal ARV orders, guiding health care facilities on how to temporarily transition children from regimens in short supply to those with larger supplies
- Dispensing LPV/r 100/25 mg tablets to older children who were receiving LPV/r 200/50 mg to avoid wastage, and adjusting assumptions on the age when children can swallow tablets for future orders

- Advocating with the MOH and donors to allow for wastage/disposal of suboptimal legacy formulations after adequate supplies of optimal pediatric ARVs arrived in country
- Continuing to engage stakeholders through virtual consultations to maintain momentum for transition and optimization work during the COVID-19 pandemic

Country Spotlight: Kenya

In Kenya, EGPAF supported the MOH, through the Division of National AIDS and STI Control Program (NAS COP), in its efforts to develop and implement a transition plan that aimed to phase out NVP, LPV/r solution, and efavirenz for children under 15 years and transition them to LPV/r solid formulations or DTG. In Phase 1, the rapid response initiative transitioned almost 6,000 children off NVP-based ART. In Phase 2, the plan targeted another 32,000 children on efavirenz and 16,000 on LPV/r solution for transitioning to DTG or LPV/r 2-in-1 pellets. All children under 15 years who were newly initiating on ART were henceforth started on a DTG-based first-line regimen if weighing more than 20 kg and a solid LPV/r-based regimen if weighing less than 20 kg. All children and adolescents with zidovudine in their first-line nucleoside reverse transcriptase inhibitor backbone were switched to ABC as the backbone. EGPAF also assisted NAS COP in monitoring the plan's implementation. The table below shows progress over time in implementing Phase 2 of the transition plan, with the proportion of children on efavirenz decreasing from 47% in May 2020 to 15% by September 2020, while the proportion on DTG increased to 56%. Over the same period, nearly all children weighing less than 20 kg were transitioned from suboptimal LPV/r solution to optimal LPV/r solid formulations.



DTG = dolutegravir; EFV = efavirenz; LPV/r = lopinavir/ritonavir; NVP = nevirapine; RAL = raltegravir
 Data source: Kenya Health Information Systems, October 16, 2020

Quantification, supply planning, and stock management of pediatric ARVs

All eight countries reported challenges with quantification, supply planning, and stock management of pediatric ARVs. These were the most common challenges reported across project countries. Recurring challenges included surpluses of suboptimal legacy formulations (e.g., NVP, LPV/r 80/20 suspension formulation), which delayed the transition to new formulations; shortages and stock-outs of key optimal pediatric ARVs at various levels of the health system; insufficient stock at the facility level to transition patients as planned; delays in shipping and/or distribution of new products; and a temporary decrease in manufacturer production capacity of LPV/r pellets, granules, and 100/25 mg tablets. From March 2020 onward, these challenges were further amplified due to the COVID-19 pandemic, which led to interruptions in manufacturing and shipping of optimal ARV products as a result of plant closures, flight cancellations, border closures, and other measures to prevent the spread of the virus.

Solutions to these challenges included the following:

- Applying a phased approach to transitioning to optimal ARV regimens in conjunction with active monitoring of pediatric ARV stocks at the national level and tracking of stock and consumption at the health facility level
- Actively participating in pediatric ARV quantification exercises, including with other implementing partners, to share information and provide additional sources of data for improved quantification
- Using consumption and stock management tools for pediatric ARVs with regular reporting from health care facilities to help monitor stocks and prevent stock-outs
- Supporting the emergency distribution of ARVs from central warehouses to health care facilities and/or redistribution of ARVs from health care facilities with excess stocks to those with shortages
- In health care facilities with product shortages or stock-outs, supporting the temporary transitioning of children from one regimen to another to avoid interruptions in treatment
- Advocating with the MOH, central medical stores, donors, and manufacturers to facilitate expedited delivery of ordered stock (for example, some shipments were delivered by air instead of by land, which increased the final price but prevented stock-outs)
- Advocating through the pediatrics technical working groups to discontinue use / dispose of legacy formulations and support the transition to optimal formulations

Country Spotlight: Lesotho

In Lesotho, LPV/r 2-in-1 pellets arrived at the national warehouse. However, they were not delivered immediately to health facilities because the national push system had not been updated with the new formulation, and the MOH also wanted facilities to first be trained on pellet administration. EGPAF worked with the MOH and Baylor to train all facilities on pellet administration. EGPAF supported the use of a temporary manual system for ordering the formulation and worked closely with the MOH and Chemonics to fast-track the updating of the informed push system to ensure delivery of pellets to all health care facilities. From January 2020 onward, health care facilities could place orders of LPV/r pellets through the updated online system, and the MOH recalled all stocks of NVP that were still in health care facilities. EGPAF also participated in monthly bilateral supply chain meetings with partners, including Baylor, mothers2mothers, and Chemonics, to address supply chain issues and monitor transition plans. These efforts included providing support for early quantification of DTG 10 mg dispersible tablets and LPV/r 4-in-1 granules, ahead of their U.S. Food and Drug Administration approval. The group also discussed the option of converting some pending orders of LPV/r 2-in-1 pellets to LPV/r 4-in-1 granules, because Cipla produces both products.

Materials for health care workers and caregivers

Six countries reported challenges with materials developed for clinicians and for the caregivers of children on ART. These challenges included the following: materials had been developed prior to the initiation of the pediatric ARV optimization work and therefore did not reflect new guidelines and/or dosing charts; there were vendor-caused delays in finalizing and printing materials for clinicians and patients (e.g., flip charts, dosing wheels, job aids, posters, pamphlets, informational and educational materials, pharmacovigilance booklets, reporting forms, etc.); there were delays in finalizing and validating materials due to restrictions on gatherings posed by COVID-19; and not all materials were translated into local languages for caregivers.

Solutions to these challenges included the following:

- Using online platforms to convene stakeholders for adapting, developing, and/or validating materials for health care workers and caregivers
- Producing and distributing a range of materials and tools on new optimal regimens, such as training materials, videos, job aids, pediatric dosing charts, and caregiver counseling cards or flip charts
- Printing and disseminating provisional dosing charts for use at health care facilities (so as not to delay pediatric ARV optimization) while awaiting updated materials
- Translating English-language materials into local languages

Country Spotlight: Uganda

In Uganda, EGPAF supported the MOH in creating a comprehensive pediatric ARV optimization package for health care workers and caregivers that covers the full portfolio of WHO-recommended ART regimens, including formulations pending SRA approval, such as LPV/r 4-in-1 granules and DTG 10 mg dispersible tablets. The package contains standard operating procedures for transitioning a child from one ART regimen to another (i.e., different scenarios to guide health care workers on transitioning children). It also provides training materials for health care workers, counseling cards for caregivers, and stickers for use in patient files to guide decision making on the initiation of new treatment. At the health care facility level, children due for ARV optimization were line listed and their patient files were labeled with stickers that guide next steps, such as viral load monitoring and subsequent ART transition when the beneficiaries return to the facility.

Health care worker capacity to transition eligible children and counsel their caregivers on new pediatric ARVs

Five countries reported challenges with health care worker capacity to transition eligible children and counsel caregivers on new pediatric ARVs. These challenges included a lack of health care worker knowledge of or training on updated guidelines for transitioning children to optimal treatment regimens, including supporting caregivers in administering new formulations correctly; a lack of confidence among health care workers in transitioning children and providing counseling to caregivers; confusion among clinicians due to frequent changes of guidelines and formulations/regimens (e.g., confusion on what to prescribe children); health workers not being trained on communication, counseling, and support of caregivers on new formulations; caregivers not bringing children on ART to health facilities when picking up medications, so the children could not be weighed and transitioned to optimal formulations; service interruptions and delays in training on updated treatment guidelines associated with COVID-related lockdowns and travel restrictions, such that children could not be transitioned to optimal formulations; and health care worker reluctance to prescribe DTG to children because of reported ADRs in adults.

Solutions to these challenges included the following:

- Orientation, training, and capacity building of health care workers and pharmacists on the new guidelines and the administration of optimal pediatric ARV formulations
- On-site coaching and mentorship for health care workers and community workers
- Training health care workers on communication, messaging, counseling, and support of caregivers for infants and young children on ARVs
- Labeling patient files to facilitate prompt switching to optimal treatment, noting both the current and new proposed optimal regimen in advance
- Calling caregivers to inform them that the children in their care should be present at their next appointment so they can be weighed and transitioned to optimal formulations
- Developing case-based standard operating procedures to cover most likely transition scenarios to guide and support clinical decision making
- Continuous mentorship on regimen transitions and ADRs via continuing medical education
- Engaging health care workers and caregivers, including through survey tools, to capture the challenges they face, and developing literacy materials to address identified challenges
- Implementing quality improvement activities to identify root causes of delays in transitioning children and defining corrective actions to be implemented
- Conducting training virtually until COVID-19-related national restrictions on public gatherings were lifted and training sessions could safely be convened in person



Photo: Eric Bond, 2018

Country Spotlight: Mozambique

In Mozambique, EGPAF completed at least one quarterly monitoring visit to all 31 project sites in Gaza and Inhambane provinces. After each visit, EGPAF met with the health facility director and clinicians to present the main findings and orient them on how to improve in areas with gaps. In addition, the project clinical officer sent a report to the provincial HIV supervisor for further follow-up. During the visits, EGPAF noted that several patients were not present when their caregivers came to the clinic to pick up their prescriptions. As a result, several patients were not switched to a new formulation, or they were switched but prescribed an incorrect dosage. In addition, EGPAF found some errors in the doses prescribed according to the child's weight, which contributed to stock-outs at the health facility level and to inadequate reported consumption based upon real needs. Sites where gaps were identified during monitoring visits received mentoring from EGPAF on how to improve the implementation of new pediatric ART recommendations. EGPAF also organized some in-service training for pharmacists to improve the use of register tools for monthly ARV delivery. Due to COVID-19, EGPAF conducted monitoring visits by phone from March to July 2020.

Caregiver capacity to administer new pediatric ARV formulations

Five countries reported challenges with caregiver capacity to administer new pediatric ARV formulations. These challenges included insufficient guidance from clinicians and lay counselors to caregivers on how to prepare granules and pellets for administration; a lack of customized caregiver literacy material for the administration of LPV/r 2-in-1 and tablet swallowing; limited caregiver understanding of new optimal regimens; challenges in administering LPV/r pellets due to bitter taste, leading to poor adherence (e.g., children refusing treatment); complexity in preparing and administering LPV/r granules; and low acceptability of use of granules and ABC/3TC 60/30 mg due to the bulkiness of the ARVs to be carried, especially with multimonth dispensing.

Solutions to caregiver capacity challenges included the following:

- Training lay counselors and mentor mothers on how to teach caregivers the correct administration of LPV/r granules and pellets to children, including reinforcing correct administration during home visits
- Developing customized literacy materials, including videos, for caregivers to address administration of LPV/r 2-in-1 and tablet swallowing
- Adapting the caregiver engagement curriculum and tools to include sensitization of caregivers on optimized formulations (e.g., caregiver counseling flip charts), including orienting health care workers on the tools
- Enhanced counseling during clinical consultations about the importance of administering the correct ARV dose
- Translating caregiver literacy materials into local languages to support counseling sessions
- Counseling caregivers on how to mask the bitterness of LPV/r formulations with food or drink to improve adherence
- Providing bags for caregivers with children on granule formulations to facilitate carrying multiple refills
- Enhancing clinical and psychological support to beneficiaries through phone calls or home visits to ensure treatment continuity and retention in care and treatment

Country Spotlight: Tanzania

In Tanzania, almost two-thirds of children ages 0–4 years receiving LPV/r tablets who were assessed on their swallowing ability could not swallow the tablets whole. As a result, caregivers of these children reported crushing, cutting, and/or dissolving the tablets in water for hours before administration. These practices are discouraged because they reduce the effectiveness of the treatment. In response, EGPAF used a differentiated service delivery model to build the capacity of caregivers to address the identified challenges. The inability to swallow whole tablets forced health care providers to increase the minimum age/weight for prescribing LPV/r tablet. This led to a temporary surplus of LPV/r 100/25 mg tablets and a shortage of LPV/r granules in some regions immediately after initiating the transition. The new age/weight range and ability to swallow whole tablets will be taken into consideration in the future quantification of LPV/r tablets and granules.

Multimonth dispensing (MMD) for children 5 years and older

Although some countries were already offering MMD to children ages 5 years and above, donors, such as the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), encouraged MMD as a mitigating measure in all countries in order to continue the provision of essential HIV services during the COVID-19 pandemic. However, six project countries reported challenges with implementing MMD for children. The issues included not enough stocks of commodities, especially LPV/r solid formulations, to give more than a one-month supply of ARVs to each child; delays in regimen optimization caused by MMD, due to infrequent visits to health care facilities; criteria for MMD applied to adults only; and limited guidance on how to implement MMD for children on pediatric ART.

Solutions to common challenges included the following:

- Supporting the revision of differentiated service delivery (DSD) guidelines to include more comprehensive guidance on DSD models for children, including MMD, as well as incorporating DSD models into health worker training
- Facilitating the redistribution of pediatric ARVs from facilities with sufficient stocks to facilities with low stocks
- Contacting clients on suboptimal regimens through phone calls and home visits to request that they return for regimen optimization if their scheduled return dates were far in the future due to MMD
- Orienting provincial supervisors on the eligibility criteria of children on ART who can be included in MMD and providing follow-up support and monitoring
- Providing financial support for MMD (e.g., transportation fees) to community workers to support picking up ARVs at the facility and delivering them to the community level

Country Spotlight: Zimbabwe

In Zimbabwe, EGPAF supported the revision of the DSD section of the national Operational and Service Delivery Manual for the Prevention, Care and Treatment of HIV. The revisions incorporated MMD for children above the age of 2 years, who are eligible for three-month MMD once they have been on ART for at least six months. Children who are now on adult doses, have a viral load under 1,000 copies/ml, and are fully disclosed are eligible for six-monthly reviews with three-month MMD, while adolescents meeting the same criteria are eligible to receive six-month MMD if medicine stocks are adequate. Training on MMD in addition to family-centered DSD models was integrated into the roll-out of LPV/r 2-in-1 granules. There are still some challenges with stocks of formulations at some health care facilities being insufficient to permit dispensing of three months of ARVs (e.g., LPV/r 100/25 mg tablets).

Pharmacovigilance and reporting of adverse drug reactions (ADRs)

Seven countries reported challenges with pharmacovigilance and reporting of ADRs. These challenges included delays in developing pharmacovigilance policy and tools with content specific to infants and children; insufficient capacity of health care workers and caregivers to identify ADRs in children; inconsistent and/or suboptimal collection and reporting of pharmacovigilance data, including clinicians reporting only severe side effects; weak pharmacovigilance systems to track and quantify events; and a lack of mechanisms to provide feedback to health care workers who do report ADRs.

Solutions to pharmacovigilance challenges included the following:

- Training clinicians and pharmacists on monitoring and reporting ADRs in infants and young children on optimal formulations, including highlighting the importance of reporting all drug side effects, both minor and severe
- Providing post-training supportive supervision and/or mentoring health care workers on monitoring ADRs in infants and children
- Introducing health care workers to electronic methods of reporting to improve reporting rates and shorten the feedback loop to health facilities
- Facilitating on-site caregiver engagement sessions on LPV/r granules, including advising caregivers to be vigilant and promptly report any adverse reactions
- Advocating and providing technical support to the MOH for the revision of pharmacovigilance tools to address the specific needs of pediatrics, and to integrate those tools into the national client management information system
- Establishing a collaboration with the national pharmaceutical regulatory authority to implement an operational pharmacovigilance system at the health facilities level
- Developing a national program to strengthen pharmacovigilance, including through selecting sites for laboratory monitoring of ADRs



Photo: Eric Bond, 2018

Country Spotlight: Côte d'Ivoire

In Côte d'Ivoire, EGPAF supported the MOH in updating the ADR reporting forms, trained health care workers in their use, and signed a memorandum of understanding with the national pharmaceutical regulatory authority to (1) build the capacity of health workers and other providers on spontaneous reporting of ADRs, (2) track the safety profile of new pediatric ARV formulations through pharmacovigilance plans, and (3) create and operationalize a National Commission for Pharmacovigilance. EGPAF and the commission will focus on strengthening the system of ADR notifications by creating sentinel pharmacovigilance sites, increasing the ADR notification rate through e-notification and/or other data collection tools, identifying a pharmacovigilance focal person at each health facility to improve reporting, monitoring ADR occurrence, and coordinating pharmacovigilance activities.

Data and information systems to support quantification and to monitor the transition of children living with HIV to new pediatric ARVs

Seven countries reported challenges with national data and information systems to support transitioning to optimal pediatric formulations. These challenges included the following: national reporting systems do not capture weight data, making it difficult to both forecast and monitor the uptake of optimal weight-based regimens and formulations; data discrepancies and errors at the facility level in the reporting of pediatric ART optimization lead to inaccurate forecasting; the data categories in the DHIS2 health management information system do not include new pediatric ARV formulations; and there is a lack of national data disaggregated by age and/or specific ARV regimens and formulations to inform quantification.

Solutions to data and information challenges included the following:

- Revising electronic medical record forms to make weight data submission mandatory, such that data will not be submitted if the forms miss this element, and also engaging implementing partners to capture weight data through their electronic medical records, as applicable
- Implementing training, supervision, and mentorship to improve pediatric ARV data reporting and quality
- Convening weekly monitoring meetings with implementing partners to identify and rectify data discrepancies, track children whose ARV formulations are being optimized, and improve local forecasting for new pediatric ARVs
- Engaging subnational focal points to provide mentorship to health facilities on reviewing data prior to submission to ensure accurate and quality data
- Advocating with the MOH and health management information system to revise the national data reporting system to correctly capture new pediatric formulations
- Supporting the updating of the national reporting system to include new optimal pediatric ARV formulations, including incorporating DTG and LPV/r 2-in-1 pellets within DHIS2
- Using monitoring tools, including online dashboards, to track children transitioning from suboptimal to optimal pediatric ARV formulations
- Supporting the development of a patient-level electronic database to capture HIV testing and the initiation of children living with HIV on improved pediatric ARV formulations

Country Spotlight: Eswatini

In Eswatini, EGPAF provided technical assistance to the Eswatini National AIDS Program at the MOH for the adoption of the WHO-recommended pediatric formulary in the client management information system and the health management information system to enable reporting by weight, formulation, and regimen and to consequently improve pediatric quality of care. By July 2020, the system had been updated and a national roll-out of the new system as well as data capture was underway.



Photo: Eric Bond, 2018

4. Recommendations to Inform Future Transitions to Optimal Pediatric ARV Formulations

The following recommendations summarize the lessons learned across the eight project countries and aim to inform future pediatric ARV optimization efforts.

- 1. Strong coordination and leadership from MOHs through existing technical working groups are critical in ensuring a smooth transition from legacy regimens to optimal pediatric ARV formulations.** Proactively aligning key stakeholders and processes under the leadership of the MOH will limit challenges in key areas, such as revising national guidelines, updating materials and tools for health care workers and caregivers, and quantifying new pediatric ARVs.
- 2. The transition to optimal pediatric ARV formulations should be planned well in advance.** Discussions can be initiated while awaiting SRA approval, at least six months in advance of implementation. This preparation includes assessing available stocks of suboptimal pediatric ARVs as well as manufacturing capacity and average lead times for new pediatric ARV formulations, to inform transition planning and meet country demands. It also includes identifying specific strategies to address overstock of suboptimal or legacy formulations, balancing wastage with patient benefit. Moreover, procurement must take place early enough to ensure that sufficient quantities of new optimal formulations are in country before the transition to optimal formulations is initiated.
- 3. It is critical to ensure the consistent and continual availability of optimal ART formulations so infants and children can be transitioned effectively and maintained on optimal pediatric ARV formulations.** This requires strengthening stock management and reporting at all levels of the health system, as well as working closely with MOH departments such as national AIDS control programs, central medical stores, and national ARV quantification task forces, as well as key stakeholders, to track and monitor ARV stocks, consumption, orders, and deliveries. It also includes strengthening national capacity for forecasting and quantification for pediatric ARVs. It is especially important to capture data on the number of children on each ARV regimen, disaggregated by weight and age. National reporting systems do not generally capture children's weight, making it difficult to both forecast need and monitor the uptake of optimal weight-based regimens and formulations. Timely reporting on pediatric ARV consumption by weight and formulation would help improve forecasting and quantification and contribute to better stock management. Lastly, as stock-outs and shortages are common challenges, risk mitigation measures should be identified and integrated into transition planning and project implementation.
- 4. Training health care workers, especially on the administration of newer formulations, should be prioritized and well timed with transition plans.** Many countries reported significant challenges with health care worker capacity to transition eligible children and counsel caregivers on new pediatric ARVs as well as caregiver capacity to administer new pediatric ARV formulations. Health care workers require strong early training and job aids as well as ongoing capacity building, mentorship, and on-site coaching to effectively implement guidelines and support families with the transition to new pediatric ARV formulations. Case-based clinical mentorships are a good way to improve the quality of care for children on ART, especially in the scenario of drug transitions.

- 5. Caregiver education should be provided before transitioning children to optimal formulations and reinforced during the transition process.** Caregivers must be prepared in advance of the transition, which will help increase treatment literacy as well as promote demand. It is also critical to provide structured follow-up caregiver literacy sessions on the administration of newer formulations to provide support as well as address any questions or challenges. Engaging communities and peer support groups, including mothers and people living with HIV, in advocacy efforts will also help with buy-in and demand creation.
- 6. There must be a greater emphasis on pharmacovigilance and active monitoring of ADRs as part of transition planning, health care worker capacity building and post-training mentorship, and caregiver education.** This effort includes strengthening and/or developing pharmacovigilance systems and tools to monitor and report ADRs among infants and children on pediatric ART, including those transitioned from suboptimal to optimal ARV formulations. It also includes developing and implementing feedback mechanisms, such as data dashboards, to allow health care workers who report ADRs to have greater visibility into commonly reported ADRs as well as to promote better reporting and data use at the facility level.
- 7. Establish a system to monitor the progress of pediatric ART optimization.** Transition plans should include clear timelines and indicators of success (e.g., proportion of children on each formulation) that can be monitored over time to track progress in implementing the plan and provide an early alert in the event that course corrections are needed.
- 8. Incorporate learning from COVID-19 into future transitions to optimal pediatric ARV formulations.** Due to the challenges and movement restrictions posed by COVID-19, all countries had to quickly adapt to new ways of working and providing training, support, and services. Adaptations included convening virtual stakeholder consultations, intensifying clinical and psychosocial support to beneficiaries through phone calls and home visits, providing online health care worker training and mentorship, and supporting multimonth dispensing for children stable on pediatric ART. These necessary and innovative adaptations should be considered for continued use in future transitions to optimal pediatric ARV formulations.

As new pediatric ARV formulations enter the market, the lessons learned from the eight project countries can inform, streamline, and accelerate their introduction and roll-out so that all children living with HIV have access to optimal, WHO-recommended treatment and care.

Appendix A

Table A.1 lists the challenges faced by each country and also summarizes the frequency of each challenge across countries.

| Table A.1. Frequency of Challenges Across Project Countries, by Country | | | | | | | | | |
|---|-------------------------|-----|-----|-----|-----|----------------------|-----|-----|--|
| CHALLENGE | Unitaid SPAAN COUNTRIES | | | | | DNDi REACH COUNTRIES | | | TOTAL NO. OF COUNTRIES REPORTING CHALLENGE |
| | CDI | ESW | LES | MOZ | ZIM | KEN | TAN | UGA | |
| 1. National guidelines, essential medicines lists, and authorization of WHO-recommended pediatric ARV regimens | X | | X | X | | X | X | X | 6 |
| 2. National transition strategy or roll-out plan for new pediatric ARVs | X | X | | | | X | X | X | 5 |
| 3. Quantification, supply planning, and stock management of pediatric ARVs | X | X | X | X | X | X | X | X | 8 |
| 4. Materials for health care workers and caregivers | X | X | | X | | X | X | X | 6 |
| 5. Health care worker capacity to transition eligible children and counsel their caregivers on new pediatric ARVs | X | X | X | X | | | | X | 5 |
| 6. Caregiver capacity to administer new pediatric ARV formulations | | X | | X | | X | X | X | 5 |
| 7. Multimonth dispensing for children 5 years and older | X | | X | X | X | X | X | X | 6 |
| 8. Pharmacovigilance and reporting of adverse drug reactions | X | X | X | X | X | X | | X | 7 |
| 9. Data and information systems to support quantification and to monitor the transition of children living with HIV to new pediatric ARVs | X | | X | X | X | X | X | X | 7 |

CDI = Côte d'Ivoire; DNDi = Drugs for Neglected Diseases Initiative; ESW = Eswatini; LES = Lesotho; MOZ = Mozambique; ZIM = Zimbabwe; KEN = Kenya; SPAAN = Securing Pediatric ARV Access Now; TAN = Tanzania; UGA = Uganda

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