Paediatric HIV Research to inform future initiatives in Southern, East and West Africa

aidsfonds

Executive Summary

Children living with HIV are not getting the rapid diagnosis and linkage to quality treatment they need to live long and healthy lives. In 2018, Aidsfonds launched the 'Paediatric HIV Initiative' in Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe to close the large gap in paediatric HIV care. Aidsfonds is dedicated to find missing children living with HIV quickly and consistently, and enroll them in HIV care, before it is too late. Furthermore, Aidsfonds works on advocacy for an increase in funding for community paediatric HIV care, for remaining affordability in paediatric treatment and for child-appropriate HIV treatment and care. SAPAM has undertaken this Paediatric HIV Research to inform future initiatives in Southern, East and West Africa. The main objective for this research for Aidsfonds was to generate evidence to better understand the state of affairs in Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe on access to paediatric HIV treatment.

Conclusions:

- About 90% of the infants who are HIV positive, acquire it from their HIV-positive mothers either during pregnancy, delivery, or through breast-feeding (mother-to-child transmission, MTCT).
- Research tells us that without treatment, one-third of infected children die in their first year of life, half by the age of two, and four-fifths by five years of age.[1] For. For those who manage to receive HIV treatment, their life journey remains precarious due to sub-optimal paediatric HIV treatment. HIV drug resistance is also a growing problem in paediatric HIV.
- The main driver of HIV Drug Resistance (HIVDR) seems to be lack of access to routine viral load testing. Other factors identified included pre-treatment HIVDR because majority of mothers are on Combination Antiretroviral Therapy (cART) as part of the Prevention of Mother-to Child Transmission (PMTCT) programmes. The second being acquired HIVDR, which is caused by resistance to first- and second- line treatment used in Infant prophylaxis (either Nevirapine (NVP) or NVP/ Atazanavir (AZT).
- The key contributing factors to the success of (PMTCT) HIV programmes at national level included greater appreciations of the benefits of early initiation of anti-retroviral therapy (ART), prompt linkages to care and access to services. There has been an appreciation that these interventions are only effective within an eco-system of strong public health infrastructures, committed political leadership, coordinated engagement of multiple partners, sufficient funding, and robust monitoring systems.[2]
- The research found that access to paediatric HIV diagnostic and treatment varies across countries.
- The procurement landscape identified numerous barriers, such as: lack of transparency, lack of competition for products in the market, gaps in information from country to country; and the lack of collaboration (even where countries belong to a common Regional Economic Community (REC).
- Key structural interventions are required to promote integrated approaches by multiple stakeholders to achieve reduction of paediatric HIV and to improve paediatric HIV scenario in these countries.

This research aimed to contribute towards a better contextual understanding of the key paediatric HIV diagnostic and treatment access constraints, as well as existing opportunities in some focal countries sampled in Southern, East and West Africa. The objective of this work was to inform future initiatives both nationally or regionally, to scaled up access to paediatric HIV diagnostics and treatment.

1 DNDi, Ending the Neglect of Pediatric HIV: Improving HIV treatment for children: an update (2018). Accessible at https://www.dndi.org/wp-content/uploads/2018/08/DNDi_Paediatric-HIV_2018.pdf

2 Alexandra C. Vrazo, David Sullivan, Benjamin Ryan Phelps. Eliminating Mother-to-Child Transmission of HIV by 2030: 5 Strategies to Ensure Continued Progress Global Health: Science and Practice 2018, Vol 6(2) at 249. (Accessed February 10, 2019)

This research focused on specific areas in paediatric HIV, including national regulatory environments, existing intellectual property barriers (i.e. patents), legal and policy frameworks and treatment guidelines in six countries, namely; Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe. The research comprised of four main parts: literature review, stakeholder engagements, investigative exercise and development of country profiles. This multifaceted design, allowed for the formulation of reasonable recommendations and actionable areas, to inform future advocacy efforts for paediatric HIV Point of Care (POC) diagnostics and treatments.

Research Methodology

Data collection was undertaken according to the following steps:

- **Step 1:** Research and information gathering phase (integrative literature/ desk review)
- **Step 2:** Broad survey to different public and private groups in the region (East, West and Southern Africa) with a mix of qualitative and quantitative questions
- **Step 3:** Key informant interviews – for more detailed feedback focusing on the specific issues
- **Step 4:** Review and analysis of country level patents landscapes for key health technologies
- **Step 5:** Requests for regulatory data related to key health technologies from country regulatory bodies

The different methods of engagement allowed for triangulation of data and validation of patterns that emerged through analysis. The survey and interviews constituted a series of inter-related questions that sought to clarify the situation with regards to access to paediatric HIV related issues from different perspectives, and examine the implementation process with regards to access, treatment and services.

Main Research Results:

- About 90% of the infants who are HIV positive, acquire it from their HIV-positive mothers either during pregnancy, delivery, or through breast-feeding (mother-to-child transmission - MTCT).
- Without treatment, one-third of infected children die in their first year of life and half by the age of two.[3]
- In 2018, there were 37.9 million people living with HIV. 1.7 million children (<15 years). Globally, around 160 000 children aged 0–14 years became newly infected with HIV in 2018.[4]
- Children living with HIV are not being diagnosed and treated early enough and are being left behind in HIV treatment scale-up. An estimated 940 000 children aged 0–14 years were accessing treatment in 2018, far short of the target of 1.6 million set for 2018.[5]
- Reviewing the latest national paediatric HIV treatment and guidelines in comparison to the World Health Organization (WHO) guidelines, showed existing gaps, which contributes towards diagnostics and paediatric HIV formulations barriers.
- There are existing gaps both in the structure of the various national HIV and Maternal and Child Health programmes.
- There is a lack of disaggregation of indicators being collected; especially in relation to HIV positive mothers and their infants; and there is a need to review and revise national reporting mechanisms in these public health systems.
- New diagnostic tools and medicines (including paediatric friendly formulations) are introduced into markets, which either have insufficient capacity to integrate them; such as the case in Zimbabwe, Mozambique and Uganda.
- Or these interventions seem to successfully be piloted, but not comprehensively integrated into existing systems (primarily due to many parallel public health programmes and systems). This was the case in South Africa, Nigeria and Kenya.

3 DNDi, Ending the Neglect of Pediatric HIV: Improving HIV treatment for children: an update (2018). Accessible at https://www.dndi.org/wp-content/uploads/2018/08/DNDi_Paediatric-HIV_2018.pdf

4 UNAIDS Global Report 2019, https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf

5 idem

- Key themes that have emerged in Maternal and Child Health (MNCH) intervention coverage and child survival in remote areas, impoverished and marginalised households and for mothers with limited education included persistent inequities.
- In most of the countries under view; this is attributed largely to socioeconomic status and location in urban "slum" communities as was noted in Kenya, Uganda and Nigeria or rural areas, as was also the case in South Africa, Mozambique and Zimbabwe:
  - Patients travelling long distances to access 'quality services' in the more urban health care settings.
  - Rural and community settings often have insufficient commodities (medicines), equipment (labs and diagnostic tools) and inadequately trained staff.
  - Inadequate political will and financial resources, to provide comprehensive services.
- During the informant interviews, some of the stakeholders noted the lack of access to routine viral load testing for the paediatric market, outside of donor funded programmes as a major challenge. This combined with incorrect dosing of ARVs by health care workers, has contributed to increased prevalence of HIVDR. The limited value of Non/ Nucleoside Reverse Transcriptase Inhibitor (NNRTI) based regimens in paediatrics is exacerbated by poor access to innovative paediatric formulations of new drugs.
- Developed country snapshots provided a quick backdrop of the country epidemics, paediatric HIV resistance and viral load scenarios; budget classifications according to national vs. donor support, civil society and other partners active in paediatric HIV advocacy and any existing legal barriers to access to treatment.

Photo: Erwin van den Berg

Focal Countries Status:

Country	Comment on progression
Kenya	- Implemented preferred first line regimens. - Sluggish pace of integration could be improved by integrated planning at state government level.
Mozambique	- No recommendations specific to neonates in country guidelines. - Persistent inequalities in delivery and implementation of paediatric HIV programming. This could be improved by strengthening community-led primary care and linkage programmes.
Nigeria	- No recommendations specific to neonates in country guidelines. - Sluggish pace of integration could be improved by integrated planning at state government level. - Improvement of community-led monitoring and primary care linkages programmes.
South Africa	- Progress in amending guidelines. - Implemented preferred first line regimens. - Recommended use of DTG (Dolutegravir). - Sluggish pace of integration could be improved by integrated planning at state government level.
Uganda	- Progress in amending guidelines. - Recommended use of DTG (Dolutegravir). - Persistent inequalities in delivery and implementation of paediatric HIV programming. This could be improved by strengthening community-led primary care and linkage programmes.
Zimbabwe	- Progress in amending guidelines. - Recommended use of DTG (Dolutegravir). - Persistent inequalities in delivery and implementation of paediatric HIV programming. This could be improved by strengthening community-led primary care and linkage programmes.

Key intervention areas which arose from the research included (but are not limited to):

- Supporting regulatory processes and harmonisation of existing national programmes.
- Greater civil society engagement which can lead to improving monitoring of the implementation of national guidelines, and ensure accountability.
- Price and information sharing mechanisms can facilitate access to lowest cost diagnostics and treatment options available.
- Redefining of political will and sustained support by national stakeholders and key influencers.
- Infrastructure considerations to support the maintenance and scale-up of POC Early Infant Diagnostics (EID) technologies.
- Accelerating domestic market approval processes for the uptake of the most needed Dolutegravir-based regimes and other fixed dose combination therapies.
- Improved access to routine viral load as part of a point-of-care package in order to prevent and/ or reduce HIVDR.

Table of Contents

Abbreviation List

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ARV	Anti-Retroviral
ATZ	Atazanavir
AZT/ ZDV	Zidovudine
BMS	Bristol-Myers Squibb
BZ	Beyond Zero campaign
cART	Combination Antiretroviral Therapy
CCM	Country Coordinating Mechanism
CE-IVD	European Conformity for In Vitro Diagnostic
CEPA	Campaign to End Paediatric HIV/AIDS
CHAI	Clinton Health Access Initiative
COP	Country Operational Plan
CSO	Civil Society Organisation
D4T	Stavudine
DR/T	Drug Resistance/ Test
DRV	Darunavir
DTG	Dolutegravir
e/MTCT	Elimination of/ Mother to Child Transmission
EFV	Efavirenz
EGPAF	Elizabeth Glaser Paediatric AIDS Foundation
EID	Early Infant Diagnostics
EML	Essential Medicines List
FDA	Food and Drug Administration
GAP-F	Global Accelerator for Paediatric Formulations
GF	Global Fund
GFF	Global Financing Facility
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
ICW	International Community of Women Living with HIV
KAMANEH	Kenya Association for Maternal & Neonatal Health
KII	Key Informant Interview/s
LPV/r	Lopinavir/ Ritonavir
MCHIP	Maternal and Child Health Integrated Program
MCSP	Maternal and Child Survival Program
MDG	Millennium Development Goals
MpM	Maes para Maes
MPP	Medicines Patent Pool
N/NRTI	Non/ Nucleoside Reverse Transcriptase Inhibitor
NEPHAK	Network of People Living with HIV and those affected by TB and HIV/AIDS
NVP	Nevirapine
OAFLA	Organisation of African First Ladies Against HIV / AIDS
P/MTCT	Prevention of/ Mother to Child Transmission
PATA	Paediatric AIDS Treatment for Africa
PATH	Programme for Appropriate Technology in Health
PDCS	Paediatric Care and Support
PDTX	Paediatric Treatment
PEPFAR	The United States President's Emergency Plan for AIDS Relief
POC	Point of Care

R/ MNC(A)H	Reproductive/ Maternal, Newborn and Child (and Adolescent) Health
RAL	Raltegravir
REC	Regional Economic Community
RTV	Ritonavir
SAPAM	Southern African Programme on Access to Medicines and Diagnostics
SDG	Sustainable Development Goals
TAC	Treatment Action Campaign
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TWG	Technical Working Group
UHC	Universal Health Coverage
UNAIDS	The Joint United Nations Programme on HIV and AIDS
UNICEF	United Nations International Children's Emergency Fund
UNITAID	United Nations International Organisation hosted partnership of the World Health Organization (WHO)
WHO	World Health Organisation
WHO PQ	World Health Organisation Pre-Qualification

Research Structure

Methodology

Data collection was undertaken according to the following steps:

- **Step 1:** Research and information gathering phase (integrative literature/ desk review).
- **Step 2:** Broad survey to different public and private groups in the region (East, West and Southern Africa) with a mix of qualitative and quantitative questions.
- **Step 3:** Key informant interviews – for more detailed feedback focusing on the specific issues.
- **Step 4:** Review and analysis of country level patents landscapes for key health technologies.
- **Step 5:** Requests for regulatory data related to key health technologies from country regulatory bodies.

The different methods of engagement allowed for triangulation of data and validation of patterns that emerged through analysis. The survey and interviews constituted a series of inter-related questions that sought to clarify the situation with regards to access to paediatric HIV related issues from different perspectives, and examine the implementation process with regards to access, treatment and services. This first phase of the research subsequently informed the country specific contexts below and allowed the team to develop environmental scans with recommended actions plans.

Photo: Chris de Bode

Data Frameworks

Below is a list of all the data frameworks, indicators identified, and sources analysed during this research.

1. Paediatric HIV Data Collection Matrix for Survey

Indicators:

- Paediatric HIV inclusion in the National HIV/TB Strategic Plans
- National paediatric HIV treatment guidelines
- Number of children on treatment per regimen
- Funding sources of the national paediatric HIV responses (national and international)
- Laws and policies affecting paediatric access to HIV
- National guidelines and/or standalone paediatric HIV guidelines specifically address diagnosis of HIV in paediatrics

2. Regulatory data request to relevant representatives of focus countries (Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe)

Indicators:

- Products (Medicines)
- Formulations
- Originator/ Generic registration status
- Early Infant Diagnostics (EID)
- EID Manufacturers
- EID Registration status

3. Key Informant Interviews

Indicators:

- Key informants: Ministry of Health representatives, key opinion leaders in the paediatric HIV field, technical partners working in paediatric HIV, and civil society organisations
- Transparency on access to paediatric HIV treatment and services, with focus on the following:
  - Key structural barriers
  - Challenges to incorporating new guidelines at country level
  - HIV diagnosis tools and implementation of these
  - Key donors supporting national paediatric HIV interventions

4. Table 1. WHO and focal country treatment guidelines comparisons

- 1st, 2nd and 3rd line treatment regimens comparison across WHO and all 6 focus countries

5. Table 2. Key drugs and formulations used for paediatric HIV treatment

- Key drugs and formulations included in our country level patent and regulatory analyses

6. Table 3. ARV medicine classes and year of introduction

- As approved by FDA

7. **Table 4.**
ARV Registration of key drugs and formulations used for paediatric HIV treatment
Indicators:
- Formulations that are recommended as per the WHO 2018 list for optimal and limited use formulary for paediatric HIV treatment
- Formulations that were recommended as per the WHO 2017 EML or the previous optimal use formulary, but not the 2018 formulary
- Registration status of these in the focal countries

8. **ARV's most used for treatment regimens in the focal countries**
- Depiction of the ARV's most frequently used in treatment line regimens

9. **Table 5.**
Companies with registered products in case countries
- Overview of pharmaceutical companies ARV registrations in the 6 countries

Limitations of the Research

Given the scope and duration of the research, only desktop research and grey literature were interrogated. Indicators from which inferences were drawn are also limited.

Key areas which were reviewed include:
- Existing approaches to testing and treating infants.
- Understanding how services were offered (decentralised or centralised) and
- Integrating HIV services into the broader maternal, child and reproductive health platforms.

Part 1: Overview of the Global and Regional (southern, east and west Africa) Landscape

1.1. Background - Paediatric HIV Drugs and Diagnostics

For the purposes of providing accurate context, two critical indicators were gleaned over. These include:

- Level of access to ART by infants & children under the ages of 5 years old; and
- Related inequalities posing as barriers to this target market's access to services.

The integrative literature review method was chosen to identify and synthesize various streams of literature related to this focus area.

This part of the report provides a summative overview of the systemic and systematic challenges related to paediatric HIV access in six countries in southern, east and west Africa; namely Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe. It primarily explores the policy as well as programmatic landscapes, which provides a reference point for the low numbers of HIV incidences reported among infants/ new-borns (terms are used interchangeably by country).

From the annual data presented to the World Health Organisation (WHO) and the Joint United Nations Programme on HIV and AIDS, the numbers seem to paint a fragmented picture that requires further interrogation. According to UNAIDS, "in most low-resource settings, health records for diseases, including HIV, are the primary source of data, but are often incomplete. Children are either not tested for HIV or, if they are, the result goes unrecorded in the clinic's, district's or national registers."[6] Contributing to this, is the fact that this scenario occurs in contexts with high HIV incidence rates among pregnant women and equally high birth rates. At the same time, this remains the case in countries which boast robust Prevention-of-Mother-to-Child-Transmission (PMTCT) HIV programmes. The under reporting to WHO and UNAIDS therefore indicates:

- Existing gaps both in the structure of the various national HIV and Maternal and Child Health programmes.
- A lack of disaggregation of indicators being collected; especially in relation to HIV positive mothers and their infants; and the need to review and revise national reporting mechanisms in these public health systems.

In most of these contexts, new diagnostic tools and medicines (including paediatric friendly formulations) are introduced into markets, which either have insufficient capacity to integrate them; such as the case in Zimbabwe, Mozambique and Uganda; or these interventions seem to successfully be piloted, but not comprehensively integrated into existing systems; this primarily due to too many parallel public health programmes and often weak public health systems. This was the case in South Africa, Nigeria and Kenya.

All the focus countries demonstrated the sluggish pace at which they reviewed and revised their national guidelines to allow for the integration of new and accessible point of care early infant diagnosis (EID) tools for HIV, except at those sites which received sustained funding and technical support from multilateral donors such as PEPFAR. Equally, in all six countries, national programmes are not found fully equipped to introduce the new paediatric formulations in their national programmes.

While these new formulations present as a game changer in getting more infants/ new-borns on HIV treatment; it will always be a challenge for these tools to be assimilated into national programmes, without addressing the systematic and regulatory barriers.

6 UNAIDS, Improving UNAIDS' Paediatric and adolescent estimates, at 2. Available at http://www.unaids.org/sites/default/files/media_asset/improving-unaids-paediatric-and-adolescent-estimates_en.pdf

1.2. Global Policy Trends

From Millennium Development Goals (MDGs) to Sustainable Development Goals (SDGs)

It is observed that the changing trends within global health governance continue to influence and frame how countries design their public health programmes. At the close of the MDG era in 2015, the annual death tolls were unacceptably high: 289,000 maternal deaths, 2.6 million stillbirths, 5.9 million deaths in children under the age of five— including 2.7 million new-born deaths[7]. It is observed that as of 2015, only 12 countries in the World Health Organization's AFRO region had met Millennium Development Goal #4 (MDG#4) to reduce under-five mortality by two-thirds by 2015. Kenya[8], South Africa[9], Zimbabwe[10] were countries selected for in-depth case studies due to their insufficient progress in reducing under-five mortality. Literature reviews undertaken on various country level MDG reports (including in the six focal countries) showed a great deal had been achieved, based on the overall set targets by the MDG indicators. In the focal countries, programmes were prioritised to address the high maternal and child mortality rates and HIV, STIs and TB, yet, similarities and differences existed on child and maternal mortality rates including HIV, STIs and TB management.[11]

In terms of the relevant global framework, for this particular target market; the 'Global Plan Towards Eliminating New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive' is of relevance.[12] Launched in 2011, this global level guidance, set a series of ambitious targets to be reached by the year 2015; with the goal of ultimately reducing the number of new HIV infections among children by 90% and AIDS related maternal mortality by 50% from 2009 through 2015.[13] It should be noted that the parameters of this mandate did not warrant a review of the prevention of mother-to child transmission (PMTCT) programmatic landscape in the focal countries. Yet, the advancements and successes achieved through this programmatic approach remain noteworthy. These highlight the level of coordination and stewardship between global allies and development partners and national programmes.

Prevention of mother-to child transmission (PMTCT) HIV programmes achieved such great strides in the last 30 years, that most countries have moved into the phase of elimination of mother-to-child-transmission (eMTCT), through the treatment as prevention model. In the focus countries of this assignment, PMTCT programmes have managed to curb the spread of HIV to unborn babies, thereby reducing HIV prevalence rates in new-borns. National PMTCT programmes scaled up interventions, to align with targets set by the Global Plan. This plan prioritised starting all pregnant and breastfeeding women on antiretroviral therapy (ART) regardless of CD4 T-cell count or clinical staging (known as Option B+)[14]. Evaluation of multinational PMTCT programmes within Africa, along the clinical trials that were

7 http://www.everywomaneverychild.org/wp-content/uploads/2016/12/EWEC_Global_Strategy_EN_inside_LogoOK_web.pdf

8 Brault MA, Ngure K, Haley CA, Kabaka S, Sergon K, Desta T, et al. (2017) The introduction of new policies and strategies to reduce inequities and improve child health in Kenya: A country case study on progress in child survival, 2000-2013. PLoS ONE 12(8). Available at https://doi.org/ 10.1371/journal.pone.0181777 (Accessed February, 14 2019)

9 Mulaudzi FM, Phiri SS, Peu DM, Mataboge MLS, Ngunyulu NR, Mogale RS. Challenges experienced by South Africa in attaining Millennium Development Goals 4, 5 and 6. Afr J Prm Health Care Fam Med. 2016;8(2), a947. http://dx. doi.org/10.4102/phcfm.v8i2.947

10 Connie A Haley, Sten H Vermund, Precious Moyo et al. Impact of a critical health workforce shortage on child health in Zimbabwe: a country case study on progress in child survival, 2000–2013. Available at https://academic.oup.com/heapol/article/32/5/613/2870065

11 Regional report. Getting to zero: HIV in eastern and southern Africa. New York: UNAIDS; 2013; . Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: A systematic analysis. Lancet. 2010;375:1969–1987 http://dx.doi.org/10.1016/S0140-6736(10)60549-1

12 Joint United Nations Programme on HIV/AIDS (UNAIDS). On the Fast-Track to an AIDS-Free Generation. Geneva: UNAIDS; 2016. http://www.unaids.org/en/resources/documents/2016/ GlobalPlan2016. (Accessed February 8, 2019)

13 UNAIDS, 2015 Progress Report on the Global Plan towards the elimination of new HIV infections among children and keeping their mothers alive (2015). Available at http://www.unaids.org/sites/default/files/media_asset/JC2774_2015ProgressReport_GlobalPlan_en.pdf

14 Fasawe O, Avila C, Shaffer N, et al. Cost-effectiveness analysis of Option B+ for HIV prevention and treatment of mothers and children in Malawi. PLoS One. 2013;8(3). (Accessed February, 10 2019)

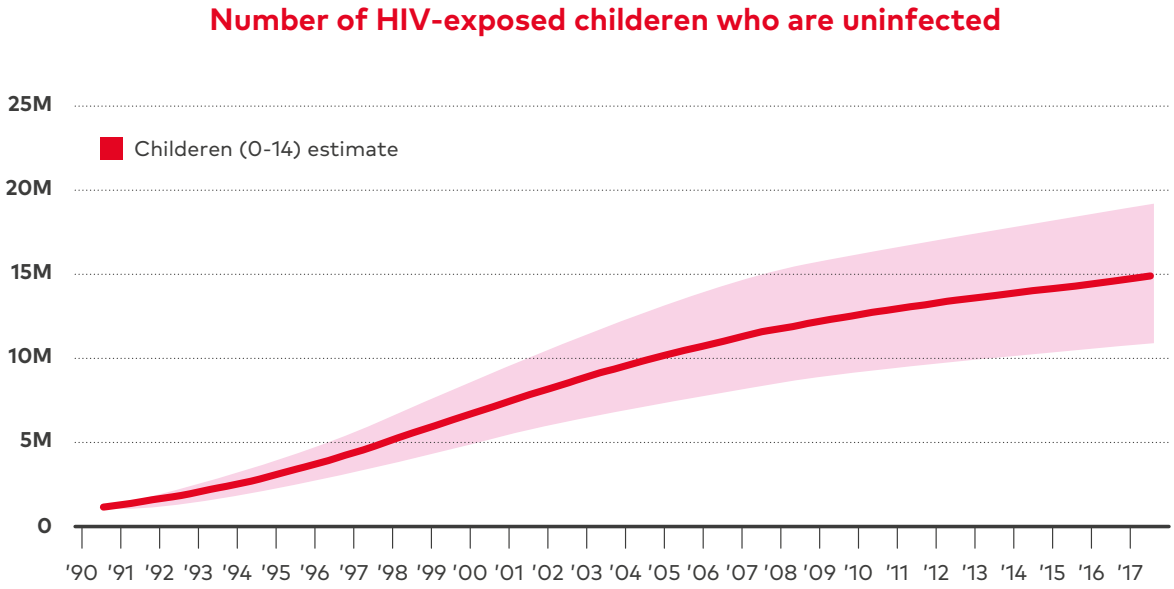


Figure 1: UNAIDS 2018 estimates of number of HIV-exposed children who are uninfected

conducted, demonstrated reduction in morbidity and mortality, increased linkages to care, faster immune system reconstitution, and decreased HIV transmission in those that started ART sooner. The rapid scale up of Option B+ to more than 21 countries has demonstrated that programs designed to test and then quickly start treatment in all pregnant and breastfeeding women with HIV lead to increased enrolment, infections averted, and lives saved.[15]

The key contributing factors to the success of these programmes at national level, included greater awareness about the benefits of early initiation of anti-retroviral therapy (ART), prompt linkages and access to services. There has been an appreciation that these interventions are only effective within an eco-system of strong public health infrastructures, committed political leadership, coordinated engagement of multiple partners, sufficient funding, and robust monitoring systems.[16]

82% of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their child in 2018, while ART coverage of all people living with HIV is lower, at approximately 62%.[17] When scanning how this strategic public health approach has contributed towards reduction to the global burden; evidence reveals that in 22 of the countries with the highest HIV burden (which together account for 90% of the global unmet PMTCT need) ART coverage has almost doubled for pregnant women, with 7 of these countries reaching 90% ART coverage rates among pregnant women living with HIV. In 2016 data from the World Health Organisation (WHO) revealed that mother-to-infant transmission rates are now below 5% in several countries, including Ethiopia, South Africa, and Tanzania, moving toward the criteria for elimination of MTCT, defined in part by lowering new HIV cases to fewer than 50 per 100,000 live births.[18] The success of these programmatic advanced is seen in Figure 1.

15 Alexandra C. Vrazo, David Sullivan, Benjamin Ryan Phelps. Eliminating Mother-to-Child Transmission of HIV by 2030: 5 Strategies to Ensure Continued Progress Global Health: Science and Practice 2018, Vol 6(2) at 249. (Accessed February 10, 2019)

16 Ibid

17 UNAIDS, Global HIV & AIDS statistics 2019 fact sheet, available at https://www.unaids.org/en/resources/fact-sheet

18 World Health Organization (WHO), Prevention of mother-to-child transmission (PMTCT): situation and trends. Global Health Observatory (GHO) data. Available at http://www.who.int/gho/hiv/epidemic_ response/PMTCT_text/en

The post-2015 Sustainable Development Goal agenda continues to prioritise reduced mortality in infants. In line with the targets set under Sustainable Development Goal 3 – ensure healthy lives and promote well-being for all at all ages – the new Global Strategy for Women's, Children's and Adolescents' Health (2016–2030) was launched.[19] Replacing the Global Plan, this renewed global agenda has expanded its focus to ensure that women and their babies not only survive labour complications if they occur, but also that they thrive and reach their full potential for health and life.

1.3. Global planning, local misalignment

The Reproductive, Maternal, New-born and Child health (RMNCH) indicator data gap

As of 2018, approximately 1.7 million are children living with HIV under 15 years of age. Since 2010, new HIV infections among children have declined by 41%, but only half (54%) of all children living with HIV are getting treatment and 100,000 children died of AIDS-related illnesses in 2018.[20]

Within the focus countries for this research proposal: Kenya, Mozambique, Zimbabwe, Nigeria, South Africa and Uganda; there are numerous structural, legal and policy barriers which impede access to HIV treatment. These barriers are not isolated for access to HIV treatment but carry through the treatment cascade and impact on the continuum of care.

It is observed that while these strides were noted leading to a reduction in AIDS-related deaths in infants, largely due to programmes such as PMTCT; there exist numerous systemic and systematic barriers facing women, infants and children – as sub-sets of the population – that have led to the current status quo. According to the World Health Organisation (WHO), inequalities are perpetuated when certain subgroups are routinely subject to discrimination, human rights violations and other structural barriers related to cultural, economic, environmental, political and social domains.[21] These contextual challenges, which are often prevalent in low-to-middle income countries; account for the less than optimal paediatric HIV programme outcomes and the existing gaps in data.

These inequalities in access to effective treatment for mothers and their infants are prevalent in low-to-middle income countries. A 2015 WHO Report, entitled; "State of inequality: Reproductive, Maternal, Newborn and Child Health" highlighted the levels of inequalities persisting in most reproductive, maternal, new born and child health (RMNCH) indicators. In the report, WHO laments on the overall state of inequality among certain subsets of population groups. The extent of inequality in some of these countries differed by dimension of inequality and by country, income group and geographical region. The report observed that the levels of inequalities were to the detriment of women, infants and children in disadvantaged population subgroups; that is, the poorest, the least educated and those residing in rural areas had lower health intervention coverage and worse health outcomes than the more advantaged.[22]

Reporting on various RMNCH indicators, gaps in coverage were noted between the richest and poorest, the most and least educated, and urban and rural areas. These indicators looked at reporting for births attended by skilled health personnel, followed by antenatal care coverage (at least four visits). Within these,

19 Global Strategy for Women's, Children's and Adolescents' Health (2016–2030), and the Every Woman Every Child movement. Available at http://www.everywomaneverychild.org/wp-content/uploads/2016/12/EWEC_Global_Strategy_EN_inside_LogoOK_web.pdf

20 UNAIDS, Global HIV & AIDS statistics 2019 fact sheet, available at https://www.unaids.org/en/resources/fact-sheet

21 World Health Organization (WHO), State of inequality: reproductive, maternal, newborn and child health.(2015) at 4. Available at https://apps.who.int/iris/bitstream/handle/10665/164590/9789241564908_eng.pdf?sequence=1 (Accessed February,14 2019).

22 World Health Organization (WHO), State of inequality: reproductive, maternal, newborn and child health.(2015) Available at https://apps.who.int/iris/bitstream/handle/10665/164590/9789241564908_eng.pdf?sequence=1 (Accessed February,14 2019)

inequalities were reported in antenatal care coverage (at least one visit). The proportion of births attended by skilled health personnel differed by up to 80 percent between the richest and poorest sub-groups; this difference was 37 percent or higher in half of the countries.

In half of the countries, antenatal care coverage (at least four visits) differed by at least 25 percent between both the most and least educated, and the richest and poorest. Antenatal care coverage (at least one visit) was at least 10 percent higher among women in the richest subgroup than those in the poorest subgroup in half of countries.

Indicators reported for health outcomes in children under the age of 5 years old revealed high levels of inequalities due to economic status, education, place of residence and, to a lesser extent, sex. A large majority of countries reported a higher under-five mortality rate in rural than in urban areas. In half of the countries, the difference between rural and urban areas exceeded 16 deaths per 1000 live births.[23]

1.4. Key Challenges in reproduction, maternal and child health (MNCH) Programmes

The countries of focus all have varying epidemiological contexts and disease burdens. While strides have been made in the way in which HIV programmes have been design and implemented to reduce the HIV burden among other sub-sets of the population group; these often do not reach populations not found in the central locale.

In all these contexts, key themes that have emerged from the desktop research, including persistent inequities in maternal and child health (MNCH) intervention coverage and child survival in remote areas, impoverished and marginalised households and for mothers with limited education. In most of the countries under view; this is attributed largely to socioeconomic status and location in urban "slum" communities as was noted in Kenya, Uganda and Nigeria or rural areas, as was also the case in South Africa, Mozambique and Zimbabwe – ultimately affecting access and utilisation of MNCH services resulting in:

- Patients requiring treatment often have to travel long distances to access 'quality services' in the more urban health care settings.
- Rural and community settings often have insufficient commodities (medicines), equipment (labs and diagnostic tools) and inadequately trained staff. This means that essential packages of services are not always available to those presenting for care.
- Paucity of human resources for health impedes on the delivery of child health service.
- Inadequate political will and financial resources, to provide comprehensive services.

Overall, the vertical design of most of these programmes, which are often concentrated in larger urban settings, slow integration of HIV and maternal and child health services; and the sluggish pace of decentralisation efforts of programmes are contributory factors for low access to paediatric HIV treatment in each country.

In settings where donors and development partners have mounted concentrated interventions (usually not country-wide); efforts have resulted in proof of concept; but these have not received adequate national or governmental attention for scale up.[24]

23 Ibid at xiii and xiv

24 Table of key interventions by INGOs, donors such as PEPFAR & Global Fund to Fight AIDS, TB and Malaria and others, developed as part of the deliverables

Part 2: Country Specific Contexts

2.1. Country and WHO treatment guidelines for paediatric HIV

Analysis of treatment guidelines for paediatric HIV, and barriers to key antiretroviral medicines

The World Health Organisation (WHO) adopted new recommendations for HIV treatment in 2018, which removed recommendations for non-nucleoside reverse transcriptase inhibitors (NNRTIs) – NVP and EFV – in preferred and alternative first-line regimens for infants and young children due to high levels of NNRTI resistance in this group. The updated guidelines also recommended the use of DTG over LPV/r (which is effective in patients with NNRTI resistance) in preferred first line regimens for infants and children – due to data that DTG outperforms LPV/r in terms of achieving viral suppression.[25] The 2018 guidelines further recommend the use of RAL for treatment of neonates (infants under 4 weeks) with HIV.[26]

To gain a better understanding of the state of affairs related to paediatric HIV treatment and care in Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe we undertook a comparative analysis of each countries' national treatment guidelines for HIV. Through our analysis we sought to identify similarities and differences in country-level recommendations for treating paediatric HIV. We also compared the country-level guidelines with the WHO guidelines to understand whether country-level guidelines aligned with or differed from the WHO's recommendations.

Our analysis revealed that all six case countries have consolidated national guidelines for the treatment of HIV, which include recommendations for treatment of paediatric HIV. South Africa and Zimbabwe also have relevant addendums updating paediatric treatment recommendations in the consolidated national guidelines. The national consolidated guidelines (and relevant addendums) were published between 2016 and 2019 and are available in English for all countries except Mozambique, whose guidelines are in Portuguese. The following national guidelines and addendums were included in our analysis:

- **Kenya:** Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya, 2018.[27]
- **Mozambique:** Tratamento Antiretroviral e Infecções Oportunistas do Adulto, Adolescente, Grávida e Criança, 2016 (Consolidated antiretroviral treatment guidelines for Mozambique).[28]
- **Nigeria:** National Guidelines for HIV Prevention, Treatment and Care, 2016.[29]
- **South Africa:** ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates, 2019.[30]
  National Consolidated Guidelines for the Prevention of Mother to Child Transmission of HIV (PMTCT), and the Management of HIV in Children, Adolescents and Adults, 2015.[31]
- **Uganda:** Consolidated Guidelines for Prevention and Treatment of HIV in Uganda, 2018.[32]
- **Zimbabwe:** Addendum to the 2016 Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe, 2019. Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe, 2016.[33]

25 https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1

26 https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1

27 http://cquin.icap.columbia.edu/wp-content/uploads/2017/04/ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018.pdf

28 http://www.misau.gov.mz/index.php/guioes?download=80:guiao-de-bolso-tratamento-antiretroviral-e-infeccoes-oportunistas-no-adulto-adolescente-gravida-e-crianca

29 http://apps.who.int/medicinedocs/documents/s23252en/s23252en.pdf

30 https://sahivsoc.org/Files/2019%20Abridged%20ART%20Guideline%20Final%2010%20May.pdf

31 https://sahivsoc.org/Files/ART%20Guidelines%2015052015.pdf

32 https://elearning.idi.co.ug/pluginfile.php/5675/mod_page/content/19/Uganda%20HIV%20%20Guidelines%20-%20September%202018.pdf

33 https://aidsfree.usaid.gov/sites/default/files/zw_arv_therapy_prevention.pdf

A comparison of recommendations for preferred first line, preferred second line and third line treatment regimens for infants and children recommended in country-level and WHO guidelines is provided in Table 1.

Our comparative analysis revealed that:

- There has been progress in Uganda, South Africa and Zimbabwe in amending country guidelines to expand the use of RAL and DTG in first line regimens for infants and children in line with WHO recommendations and phase out the use of NNRTIs.
- Zimbabwe now recommends the use of RAL in preferred first line regimes for neonates. Uganda recommends the use of the use of RAL in alternative first line regimens for neonates but continues to recommend LPV/r in preferred regimens. South Africa and Kenya continue to recommend NVP in preferred first line regimens for neonates, while Mozambique and Nigeria do not have recommendations specific to neonates in country guidelines.
- South Africa now recommends the use of DTG in preferred first line regimens for infants and children over 20 kgs – while LPV/r use should be continued in infants and children under 20kgs. Uganda now recommends the use of DTG in alternative first line regimens for children between 3 and 10 and Zimbabwe recommends the use of DTG in alternative first line regimens for children when dosing is available.
- LPV/r combined with ABC and 3TC remains the most commonly recommended preferred first line regimen for infants (excluding neonates) and children under 3 in country level guidelines – in line with the WHO's earlier 2016 guidelines.
- There is significant variation across countries in the age bands used to indicate patients' eligibility for different treatment regimens.

Photo: Chris de Bode

Table 1: WHO and case country treatment guidelines

Age Groups	WHO 2016	WHO 2018	South Africa	Kenya	MZM	Nigeria	Uganda	Zimbabwe
Preferred 1st line regimens for neonates								
0 < 4 weeks		AZT + 3TC + RAL	AZT + 3TC + NVP	AZT + 3TC + NVP				
0 < 6 weeks								AZT + 3TC + RAL
0 < 3 months							ABC + 3TC + LPV/r	

Age Groups	WHO 2016	WHO 2018	South Africa	Kenya	MZM	Nigeria	Uganda	Zimbabwe
Preferred 1st line regimens for infants and children								
0 – 3 years	ABC (or AZT) + 3TC + LPV/r					ABC (or AZT) + 3TC + LPV/r		
4 weeks – 3 years				ABC + 3TC + LPV/r				
3 months – 3 years							ABC + 3TC + LPV/r	
0 – 4 years					AZT + 3TC + NVP (or LPV/r)			
4 weeks – 9 years			ABC + 3TC + LPV/r (if under 20 kgs) ABC + 3TC + DTG (20kgs – 35kgs)					
6 weeks – adolescent								2 NRTIs + LPV/r (or EFV or DTG)
3 – 9 years	ABC + 3TC+ EFV						ABC + 3TC + LPV/r	
3 – 10 years						ABC + 3TC + EFV		
1 – 9 years		ABC + 3TC + DTG						
3 – 14 years				ABC + 3TC + EFV				
5 – 14 years					AZT + 3TC + NVP/EFV TDF + 3TC + EFV			

Age Groups	WHO 2016	WHO 2018	South Africa	Kenya	MZM	Nigeria	Uganda	Zimbabwe
Preferred 2nd line regimens for infants and children								
0 – 3 years	2 NRTIs + RAL (or LPV/r)					AZT (or ABC) + 3TC + RAL	AZT + 3TC + RAL	
4 weeks – 3 years				DRT-based 2nd line AZT + 3TC + LPV/r ABC + 3TC + LPV/r				
0 – 4 years					AZT (or ABC) + 3TC + LPV/r (or NVP or EFV)			
0 – 9 years			ABC/AZT + 3TC + LPV/r (if under 20 kgs) 2NRTIs + DTG (if over 20kgs)					2 NRTIs + DTG (or ATV/r or LPV/r if DTG dosing unavailable)
3 – 9 years							AZT + 3TC + RAL (or DTG)	
3 – 10 years						AZT (or ABC or TDF) + 3TC + LPV/r		
1 – 9 years	2 NRTIs + EFV (or LPV/r)	2 NRTIs + ATV/r or LPV/r or DTG Two NRTIs + DTG						
3 – 14 years				DRT-based 2nd line AZT + 3TC + LPV/r ABC + 3TC + LPV/r				
5 – 14 years					TDF + 3TC + EFV (or LPV/r)			

Age Groups	WHO 2016	WHO 2018	South Africa	Kenya	MZM	Nigeria	Uganda	Zimbabwe
3rd line regimens for infants and children								
	RAL (or DTG) + 2 NRTIs DRV/r + 2 NRTIs DRV/r + RAL (or DTG) ± 1–2 NRTIs	DRV/r ± DTG + 1-2 NRTIs (if possible, consider optimization using genotyping)	Refer to expert. Third-line dosing guidelines available online	Drug resistance testing-based regimen. Possible 3rd line regimens include: RAL (or DTG) + 3TC + DRV + RTV; AZT + RAL (or DTG) + 3TC + DRV + RTV; ABC/TDF + RAL (or DTG) + 3TC + DRV + RTV; or EFV + 3TC + DRV + RTV	No recommen-dations	Refer to specialist. If available, do drug sensitivity testing. For children 0 – 10 years 3rd line regimens contain RAL or DTG and/or DRV/r.	All PLHIV should receive resistance testing to inform the prescription of 3rd-line medicines. Since all 3rd-line PLHIV will have prior PI Exposure, DRV/r will be taken twice a day.	DRV/r + 1-2 NRTIs. When possible consider genotyping.

South Africa, Uganda and Zimbabwe have made progress in amending their national guidelines to expand the use of DTG and RAL in first line regimens for infants and children. Although LPV/r continues to be recommended in these countries in preferred first line regimens for infants and/or young children. The lack of appropriate formulations of DTG for infants and children under 25kgs is a barrier to the adoption of country level guidelines recommending their use. Access to appropriate paediatric formulations of LPV/r is also a challenge and, as a result, paediatric use of NNRTIs remains high in countries.[34] Barriers to appropriate paediatric formulations are explored and described in more detail below.

2.2. Patent and regulatory landscapes for key drugs and formulations

Methodology used to identify key drugs and formulations

As a first step to exploring barriers to key drugs and formulations used for paediatric HIV treatment at country levels, we sought to identify key drugs and formulations currently considered as essential drugs. Drugs were selected for inclusion in our analysis, given their inclusion in WHO or country level treatment guidelines for paediatric care. To identify formulations of key drugs for the analysis, we reviewed formulations and dosages of antiretroviral medicines recommended for the treatment of paediatric patients in the World Health Organisation's 2017 model list of essential medicines for children[35] and 2016[36] and 2018[37] optimal formulary and limited use list for paediatric ARVs.

According to the WHO, the 2018 optimal formulary and limited use list "is designed to include the minimum number of ARV formulations needed to deliver WHO recommended first- and second-line ARV treatment regimens for infants and children".[38] Key drugs and formulations included in our country level patent and regulatory analyses are listed in Table 2.

34 https://www.arvprocurementworkinggroup.org/public/componenti/1207/files/APWGAnticipatedDemandForecast_Dec122018.pdf

35 https://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf?ua=1

36 http://apps.who.int/medicinedocs/en/m/abstract/Js23120en/

37 https://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/

38 https://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/

Table 2: Key drugs and formulations used for paediatric HIV treatment

Antiretroviral medicine	Formulation
abacavir (ABC)	60mg tablet (dispersible scored)
abacavir/lamivudine (ABC/3TC)	120mg/60mg tablet (dispersible scored)
	60mg/30mg tablet (dispersible scored)
zidovudine (AZT)	50mg/5ml oral solution
	60mg tablet (dispersible scored)
zidovudine/lamivudine (AZT/3TC)	60mg/30mg tablet (dispersible scored)
zidovudine/lamivudine/nevirapine (AZT/3TC/NVP)	60mg/30mg/50mg tablet (dispersible scored)
atazanavir (ATV)	200mg capsule
	100mg solid oral dose
darunavir (DRV)	75mg tablet
dolutegravir (DTG)	50mg tablet (until better formulations and dosing data available)
efavirenz (EFV)	200mg tablet (scored dispersible)
lamivudine (3TC)	50mg/5ml oral liquid
	150mg tablet
lopinavir/ritonavir (LPV/r)	80mg/20mg oral solution
	40mg/10mg solid oral dosage form
	100mg/25mg tablet (heat stable)
	400mg/100mg oral liquid
nevirapine (NVP)	50mg/5ml oral solution
	50mg tablet (dispersible scored)
raltegravir (RAL)	25mg chewable scored tablet
	100mg granules for suspension
	400mg tablet
ritonavir (r/rtv)	25mg tablet
	100mg powder
	400/5ml oral liquid

Photo: Aidsfonds

2.3. Patent landscapes for key drugs and formulations used for paediatric HIV treatment in case countries

To inform our understanding of medicine access challenges, we undertook analyses of the patent and licensing landscapes for key drugs and formulations for paediatric HIV treatment in all six case countries. Our findings suggest that patents no longer pose significant barriers to paediatric HIV treatment in the case countries, as licenses[39] and non-assert declarations pave the way for generic use in countries where patents remain in force. (For MPP licensed drugs, patents may remain a barrier to entry for unlicensed companies that are willing and able to supply quality paediatric ARVs – however no products or companies fitting this description were identified in our analysis).

Analyses findings:

- Our analysis found that patents granted on key nucleoside reverse transcriptase inhibitors (NRTIs) used for paediatric HIV treatment [AZT, d4T, 3TC, ABC] have expired in all six case countries.
- Our analysis found that patents granted on key non-nucleoside reverse transcriptase inhibitors (NNRTIs) used for paediatric HIV treatment [NVP, EFV] have expired in all six case countries, except South Africa where evergreening patents on NVP and EFV remain in place. However, the evergreening patents do not block generic use in South Africa, as earlier Competition Commission complaints led to bilateral licensing agreements for manufacture, importation and sale of generic NVP and EFV in the country.
- Our analysis found that MPP licensing agreements and non-assert declarations allow for use of generic versions of key protease inhibitors [LPV/r, r, ATZ, DRV] and integrase inhibitors [RAL, DTG] recommended for paediatric HIV treatment in all six countries (even in countries where no blocking patents are in force).

39 Patents may remain a barrier to generic suppliers willing and able to develop paediatric formulations that are not included in licenses. Assessing whether this barrier exists was beyond the scope of our analysis.

Table 3: ARV medicine classes and year of introduction

Antiretroviral medicines reviewed		
ARV medicine	**Class**	**Year of approval by the FDA[40]**
Zidovudine (AZT)	Nucleoside Reverse Transcriptase Inhibitors	1987
Lamivudine (3TC)	Nucleoside Reverse Transcriptase Inhibitors	1995
Nevirapine (NVP)	Non-nucleoside Reverse Transcriptase Inhibitors	1996
Ritonavir	Protease Inhibitors	1996
Efavirenz (EFV)	Non-nucleoside Reverse Transcriptase Inhibitors	1998
Abacavir (ABC)	Nucleoside Reverse Transcriptase Inhibitors	1998
Lopinavir/ritonavir (LPV/r)	Protease Inhibitors	2000
Atazanavir (ATZ)	Protease Inhibitors	2003
Darunavir (DRV)	Protease Inhibitors	2006
Raltegravir (RAL)	Integrase Inhibitors	2007
Dolutegravir (DTG)	Integrase Inhibitors	2013

40 Aidsinfo.nih.gov

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Zidovudine (ATZ)

A review of patent data on MedsPaL revealed that there are no outstanding patents blocking access to generic AZT in case countries.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 50mg/5ml AZT oral solution, as well as dispersible scored AZT/3TC and AZT/3TC/NVP fixed dose combinations containing AZT 60mg for paediatric HIV treatment.

AZT	50mg/5ml oral solution
	60mg dispersible scored tablet
AZT/3TC	60mg/30mg dispersible scored tablet
AZT/3TC/ NVP	60mg/30 mg/50mg dispersible scored tablet

Patents on zidovudine's compound expired in Kenya, South Africa, Uganda and Zimbabwe in 2006. Several additional patents were granted related to zidovudine fixed dose combinations in these countries, with the latest combination patent (on AZT and 3TC combinations) expiring in October 2017. No patents on zidovudine were identified in Mozambique or Nigeria.

Lamivudine (3TC)

A review of patent data on MedsPaL revealed that there are no outstanding patents blocking access to generic lamivudine in the case countries.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 50mg/5mL oral solution, as well as dispersible scored FDC tablets of ABC/3TC, AZT/3TC and AZT/3TC/NVP – containing 3TC 30 and 60mgs for paediatric HIV treatment. In 2017, the WHO also recommended 150mg 3TC tablets as an essential medicine for children.

3TC	50mg/5ml oral liquid
	150mg tablet
ABC/3TC	120 mg/60mg
AZT/3TC	60mg/30mg
AZT/3TC/ NVP	60mg/30mg/50mg

The latest patent on lamivudine formulations granted on liquid compositions expired in March 2018 in Kenya, South Africa, Uganda and Zimbabwe. Several patents were also granted on 3TC combinations with AZT and/or ABC, with the latest combination patents expiring in 2018 in case countries – including a patent on ABC/3TC combinations that expired in Nigeria in May 2018. No patents on lamivudine were identified in Mozambique.

Abacavir (ABC)

A review of patent data on MedsPaL revealed that there are no outstanding patents blocking access to generic abacavir in case countries. Additionally, a 2013 memorandum of understanding between the MPP and ViiV Healthcare, as well as bilateral licenses signed directly with generic companies, have facilitated access to generic abacavir products in case countries for several years.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 60mg dispersible scored ABC tablets, as well as dispersible scored 120/60mg ABC/3TC combination tablets for paediatric HIV treatment. The 2016 WHO paediatric HIV formulary also recommended that countries stock 60/30mg ABC/3TC tablets.

ABC	60mg tablet (dispersible scored)
ABC/3TC	120mg/60mg tablet (dispersible scored)
	60mg/30mg tablet (dispersible scored)

A review of patent data on MedsPal patent database revealed that patents on abacavir compound expired in 2010 in Kenya, South Africa, Uganda and Zimbabwe. Additional evergreening patents were filed on abacavir formulations, combinations and manufacturing processes in Kenya, Nigeria, South Africa, Uganda and Zimbabwe. The last relevant patent granted on abacavir oral formulations in Kenya, South Africa, Uganda and Zimbabwe expired in February 2019 (no patents granted on ABC were identified in Mozambique).

However, prior to the expiry of evergreening patents, an MPP-ViiV memorandum of understanding was signed allowing for sale of generic abacavir products by licensed generic companies for paediatric HIV treatment in 121 countries – including all six case countries. Currently, the only listed sublicensee of the 2013 agreement is Aurobindo.[41] ViiV has also signed bilateral licenses directly with generic suppliers allowing for manufacture and use of generic abacavir products in sub-Saharan Africa, low income countries and LDCs.[42]

Non-Nucleoside Reverse Transcriptase Inhibitors

Nevirapine (NVP)

A review of patent data on MedsPaL revealed that only South Africa has an outstanding patent related to NVP. However, this patent does not inhibit generic access in the country, and the patent holder has committed to not assert NVP related patents in 135 countries, including Mozambique, Nigeria, South Africa, Uganda and Zimbabwe.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 50mg/5ml oral solution and 50mg dispersible scored tablets of NVP, as well as fixed dose combinations of AZT/3TC/NVP containing 50mgs of NVP, for treatment of paediatric HIV.

NVP	50mg/5ml oral solution
	50mg tablet (dispersible scored)
AZT/3TC/ NVP	60mg/30mg/50mg

Patents granted on nevirapine compound expired in Kenya, South Africa, Uganda and Zimbabwe in 2010. Additional evergreening patents were granted up to 2029 in South Africa, but not in Kenya, Uganda or Zimbabwe. However generic NVP has been available in South Africa since 2004, after a Competition Commission complaint led the patent holder to issue voluntary licenses allowing generic use in the country.[43] No patents on NVP were identified in Nigeria or Mozambique.

In 2007, Boehringer Ingelheim (BI) announced a non-assert declaration related to NVP that was expanded in 2016. Under the expanded declaration, BI has committed to not assert patents on NVP in 135 low- and middle-income countries – including Mozambique, Nigeria, South Africa, Uganda and Zimbabwe.

Efavirenz (EFV)

A review of patent data on MedsPaL revealed that patents on efavirenz compound and other formulations were granted in South Africa. No filed patents were identified in other case countries. While a patent on an improved formulation of EFV remains in place in South Africa until 2020, it does not inhibit access to generic EFV in the country. Generic EFV has been available in South Africa since 2008 after a Competition Commission case led the patent holder to issue voluntary licenses.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 200mg dispersible scored EFV tablets for treatment of paediatric HIV.

41 https://medicinespatentpool.org/licence-post/abacavir-paediatrics-abc/

42 https://www.medspal.org/?product_standardized_name%5B%5D=Abacavir+60+mg&product_standardized_name%5B%5D=Abacavir%2FLamivudine+120%2F60+mg&product_standardized_name%5B%5D=Abacavir%2FLamivudine+60%2F30+mg&country_name%5B%5D=Kenya&country_name%5B%5D=Mozambique&country_name%5B%5D=Nigeria&country_name%5B%5D=South+Africa&country_name%5B%5D=Uganda&country_name%5B%5D=Zimbabwe&page=1

43 https://khn.org/morning-breakout/dr00021291/

EFV	200mg tablet (scored dispersible)

Patents related to efavirenz were not filed in Kenya, Mozambique, Nigeria, Uganda or Zimbabwe. In South Africa, a patent on efavirenz compound expired in 2013, while an improved formulation patent (ZA200004313) lasts until 2020. However, patents have not inhibited access to generic EFV in South Africa since 2008 when MSD licensed four generic companies to market generic EFV in South Africa. The license was only granted after the Treatment Action Campaign filed a complaint with the Competition Commission for MSD's pricing and refusal to grant licenses to generic manufacturers on reasonable terms.[44]

Protease Inhibitors

Lopinavir/ritonavir (LPV/r) and Ritonavir (r)

A review of patent data on MedsPaL revealed multiple patents granted on LPV/r and ritonavir in South Africa- lasting until 2026. No filed patents were identified in other case countries. Additionally, two MPP licenses allow for the sale of generic LPV/r and ritonavir products – with or without other active ingredients – throughout Africa.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 80mg/20mg LPV/r oral solution, 40mg/10mg solid oral dose LPV/r and 100mg/25mg LPV/r tablets for paediatric HIV treatment. In 2017, the WHO also recommended 400mg/100mg LPV/r oral liquid as an essential medicine for children.

LPV/r	80mg/20mg oral solution
	40mg/10mg solid oral dosage form
	100mg/25mg tablet (heat stable)
	400mg/100mg oral liquid

The 2018 WHO optimal formulary and limited-use list recommends that countries stock 25mg tablets and 100mg powder of ritonavir for paediatric HIV treatment. The 2016 WHO formulary also recommended that countries stock 400mg/5ml ritonavir for paediatric HIV treatment.

r/rtv	25mg tablet
	100mg powder
	400/5ml oral liquid

The compound patents on LPV and r were not filed in Kenya, Mozambique, Nigeria, Uganda and Zimbabwe, and no additional filed secondary formulation patents were identified in the countries. A patent on lopinavir compound (ZA9610475) expired in South Africa in 2016, while the compound patent on ritonavir was not filed in the country. Multiple secondary formulation patents on LPV/r and r were granted in South Africa – lasting until 2026. However, secondary patents do not inhibit access to licensed generic LPV/r and ritonavir products.

In 2014, the Medicines Patent Pool and AbbVie signed a license allowing for generic manufacture and sale of paediatric tablets containing 40mg lopinavir and 10mg ritonavir and non-tablet paediatric formulations of LPV/r and r, with or without other active ingredients, in 102 countries – including all six case countries. A shortcoming of this license was that it did not allow for use of higher dose LPV/r products used for paediatric and adult use – including 100mg/25mg tablets which are included on the WHO paediatric formulary.

However, shortages and stockouts of LPV/r products in South Africa in 2015 due to the monopoly holder's (AbbVie) inability to provide adequate supply led to calls from South Africa civil society for compulsory licenses to allow generic access.[45] In response to pressure for compulsory licensing, AbbVie announced a new MPP licensing agreement in 2015 allowing for licensed generic companies to manufacture and sell products containing LPV/r and ritonavir to all African countries.

44 http://i-base.info/htb/560

45 https://www.spotlightnsp.co.za/2015/11/30/resisting-stock-outs/

Atazanavir (ATZ)

A review of patent data on MedsPaL revealed that secondary patent on atazanavir remain in place in South Africa until 2025. No atazanavir patents were identified in Kenya, Mozambique, Nigeria, Uganda or Zimbabwe. An MPP-BMS license allows for the sale of generic atazanavir products by licensed companies in 122 countries – including all six case countries.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock atazanavir 200mg capsules for use with 100mg ritonavir for paediatric HIV treatment. The 2016 formulary also recommended that countries stock 100mg atazanavir, which was recommended as an essential medicine for children in 2017.

ATZ	200mg capsule
	100mg solid oral dose

Patents on atazanavir's compound family and bisulfate salt have expired in South Africa (ZA9703387, ZA9900056). These patents were not filed in Kenya, Mozambique, Nigeria, Uganda or Zimbabwe. An atazanavir process patent remains in place in South Africa until 2025 (ZA200609084), matching patents were not filed in the other five case countries.

In 2013, the MPP announced a license with Bristol-Myers Squibb (BMS) allowing for generic manufacture of pharmaceutical products containing atazanavir by sub-licensees and for sale in 110 countries, including all six case countries. The license covers 150, 200 and 300mg ATZ – as well as other formulations, including paediatric formulations for which BMS receives FDA approval. The license was extended to 122 countries in 2017.

Darunavir (DRV)

A review of patent data on MedsPaL revealed that a patent on darunavir ethanolate solvate remains in place until 2023 in Kenya, Mozambique, South Africa, Uganda and Zimbabwe. However, patents on darunavir should not impede generic access given a 2012 declaration by Janssen to not assert its patents in sub-Saharan and least developed countries.

The WHO optimal and limited use formulary recommends that countries stock 75mg darunavir tablets for paediatric HIV treatment.

DRV	75mg tablet

Patents on darunavir compound were not filed in Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe. A patent on darunavir ethanolate solvate (AP200403191, ZA200410154) was granted in Kenya, Mozambique, South Africa, Uganda and Zimbabwe, which remains in place until 2023 in all countries except South Africa where it remains in place until 2024.

In 2012, Janssen announced it would not enforce its darunavir patents in sub-Saharan African countries and least developed countries – including all six case countries.[46]

Integrase Inhibitors

Raltegravir (RAL)

A review of patent data on MedsPaL revealed ongoing patents related to raltegravir in South Africa, but not in any other case countries. However ongoing patents do not block marketing of generic products by licensed companies in 92 countries (including all six case countries) included in a 2015 MPP-MSD licensing agreement.

The 2018 WHO optimal formulary and limited-use list recommends that countries stock raltegravir 100mg granules for suspension and 25mg chewable scored tablets for paediatric HIV treatment. In 2017, the WHO also recommended 400mg raltegravir tablets as an essential medicine for children.

46 https://www.jnj.com/media-center/press-releases/janssen-announces-intent-not-to-enforce-patents-for-darunavir-in-resource-limited-settings

RAL	25mg chewable scored tablet
	100mg granules for suspension
	400mg tablet

A review of MedsPal patent database revealed that patents on raltegravir compound (ZA200402796) and raltegravir potassium salt (ZA200704130) granted in South Africa last until 2022 and 2025 respectively. An additional patent on raltegravir tablets (ZA201203012) granted in South Africa lasts until 2030. No patents filed or granted on raltegravir were identified in Kenya, Mozambique, Nigeria, Uganda or Zimbabwe.

In 2015, the MPP and MSD announced a licensing agreement allowing for sale of generic raltegravir for paediatric HIV treatment by licensed companies in 92 countries – including all six case countries.

Dolutegravir (DTG)

A review of patent data on MedsPaL revealed ongoing patents related to dolutegravir in South Africa and Nigeria, but not Kenya, Mozambique, Uganda or Zimbabwe. However, ongoing patents do not block marketing of generic dolutegravir products by licensed companies in 121 countries (including all six case countries) included in a 2014 MPP-ViiV Healthcare licensing agreement.

The 2018 WHO optimal formulary and limited-use list recommends the use of 50mg adult dolutegravir tablets for children until better dosing information and paediatric formulations are available.

DTG	50mg tablet (until better formulations and dosing data available)

A review of MedsPal patent database revealed that patents granted on dolutegravir's compound in South Africa and Nigeria last until 2026 (ZA200708970, NG2007/12/473). Matching patents were not filed in Kenya, Mozambique, Uganda and Zimbabwe.

In 2014, the MPP and ViiV Healthcare announced two licensing agreements on paediatric and adult formulations of dolutegravir allowing licensed generic companies to produce dolutegravir for sale in 121 countries, including all six case countries.

2.4. Registration status of key ARVs used for paediatric HIV treatment in case countries

To explore additional access barriers, we conducted a review of the registration status of key drugs and formulations for treatment of paediatric HIV in case countries. Registration data was sourced from domestic regulatory authorities either directly or online where available.

- **Table 4** indicates whether key products and formulations are registered at country levels.
- **Figure 1** illustrates the ARV drugs most used in the 6 countries. The higher levels of use of older drugs are evident in countries slow to implement later WHO recommended treatment regimens.
- **Table 5** provides additional data on the companies with registered products at country level.

Below is a summary of key findings that emerged from our analysis of regulatory landscapes.

Key findings related to Mozambique

- Mozambique has far fewer domestically registered products than the other countries reviewed. Only 6 of the 14 ARVs listed in the WHO's optimal formulary and limited use list had a registered paediatric formulation in Mozambique. It is unclear why so few products are registered in the country, however the requirement for Portuguese package inserts and/or the ability of countries to use waivers[47 48] to import unregistered products bought through Global Fund or PEPFAR procurement mechanisms may be a hindrance to companies seeking local registration.[49]

Key findings related to dolutegravir

- All countries reported domestic registration of dolutegravir 50mg tablets – which the WHO recommends countries' stock until better dosages and formulations are available for paediatric patients. However, only GlaxoSmithKline (GSK) and ViiV's originator products are registered in Kenya, Nigeria and South Africa. (Multiple generic dolutegravir FDCs are also registered in South Africa for adult use.)

Key findings related to raltegravir

- Nigeria, South Africa, Uganda and Zimbabwe reported domestic registration of 25mg scored raltegravir tablets. Nigeria, South Africa and Uganda also reported domestic registration of 100mg granules for suspension. Only originator raltegravir products are registered in the countries, by MSD (Merck) and/or Merck manufacturers Pantheon[50] and Zhejiang Huahai Pharmaceutical Co.[51]

Key findings related to lopinavir/ritonavir

- All countries except Mozambique have registered generic versions of lopinavir/ritonavir 100mg/25mg tablet. The good generic accessibility of this product is likely due to its use in adults, in addition to children.
- All countries except Mozambique have registered originator versions of lopinavir/ritonavir 80mg/20mg solution used for infants and young children.
- Only Zimbabwe reported having registered 40mg/10mg solid oral doses (oral pellets). Zimbabwe's indicated that Cipla's 40mg/10mg solid oral doses are registered in the country – although one key informant noted that they have not seen this product in use in the country and that Zimbabwe continues to use LPV/r syrup.

47 https://www.who.int/bulletin/volumes/97/5/19-234468/en/

48 https://www.pepfar.gov/documents/organization/105842.pdf

49 Key informant interview

50 https://www.accessdata.fda.gov/drugsatfda_docs/

51 https://extranet.who.int/prequal/sites/default/files/WHOPIR_Huahai25-28July2017.pdf nda/2011/203045Orig1s000Lbl.pdf

Table 4: Registration of key drugs and formulations used for paediatric HIV treatment

		Kenya	Mozambique	Nigeria	South Africa	Uganda	Zimbabwe
Product	**Formulation**	**Registered**	**Registered**	**Registered**	**Registered**	**Registered**	**Registered**
		Y/N	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
abacavir (ABC)	60mg tablet (dispersible scored)	Y	N	Y	Y	Y	Y
abacavir/ lamivudine (ABC/3TC)	120mg/60mg tablet (dispersible scored)	N	N	N	N	Y	Y
	60mg/30mg tablet (dispersible scored)	Y	pending	Y	N	Y	Y
zidovudine (AZT)	50mg/5ml oral solution	Y	N	Y	Y	Y	Y
	60 mg tablet (dispersible scored)	N	N	Y	N	N	N
zidovudine/ lamivudine (AZT/3TC)	60mg/30 mg tablet (dispersible scored)	Y	Y	Y	N	Y	Y
zidovudine/ lamivudine/ nevirapine (AZT/3TC/ NVP)	60mg/30mg/50mg tablet (dispersible scored)	Y	Y	Y	N	Y	Y
atazanavir (ATV)	200mg capsule	N	N	Y	Y	N	N
	100mg solid oral dose	N	N	N	Y	N	N (150mg registered)
darunavir (DRV)	75mg tablet	Y	Y	N	Y	Y	Y
dolutegravir (DTG)	50mg tablets (until better dosing info available, sprinkles under development)	Y	Y	Y	Y	Y	Y
efavirenz (EFV)	200mg tablet (scored dispersible)	Y	N	Y	Y	Y	Y
lamivudine (3TC)	50mg/5ml oral liquid	Y	Y	Y	Y	Y	Y
	150mg tablet	Y	Y	Y	Y	Y	Y

		Kenya	Mozambique	Nigeria	South Africa	Uganda	Zimbabwe
Product	**Formulation**	**Registered**	**Registered**	**Registered**	**Registered**	**Registered**	**Registered**
		Y/N	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
lopinavir/ ritonavir (LPV/r)	80mg/20mg oral solution	Y	N	Y	Y	Y	Y
	40mg/10mg solid oral dosage form		N	N	N	N	Y
	100mg/25mg tablet (heat stable)	Y	N	Y	Y	Y	Y
	400mg/100mg oral liquid		N	N	N	N	N
nevirapine (NVP)	50mg/5ml oral solution	Y	Y	Y	Y	Y	Y
	50mg tablet (dispersible scored)		N	Y	N	Y	N
raltegravir (RTV)	25mg chewable scored tablet		N	Y	Y	Y	Y
	100mg granules for suspension		N	Y	Y	Y	N
	400mg tablet	Y	N	Y	Y	Y	Y
ritonavir (r/ rtv)	25mg tablet		N	N	N	N	N
	100mg powder		N	Y	Y	Y	Y
	400/5ml oral liquid		N	N	N	N	N

ARV's most frequently used in Treatment Regimens in the 6 Countries

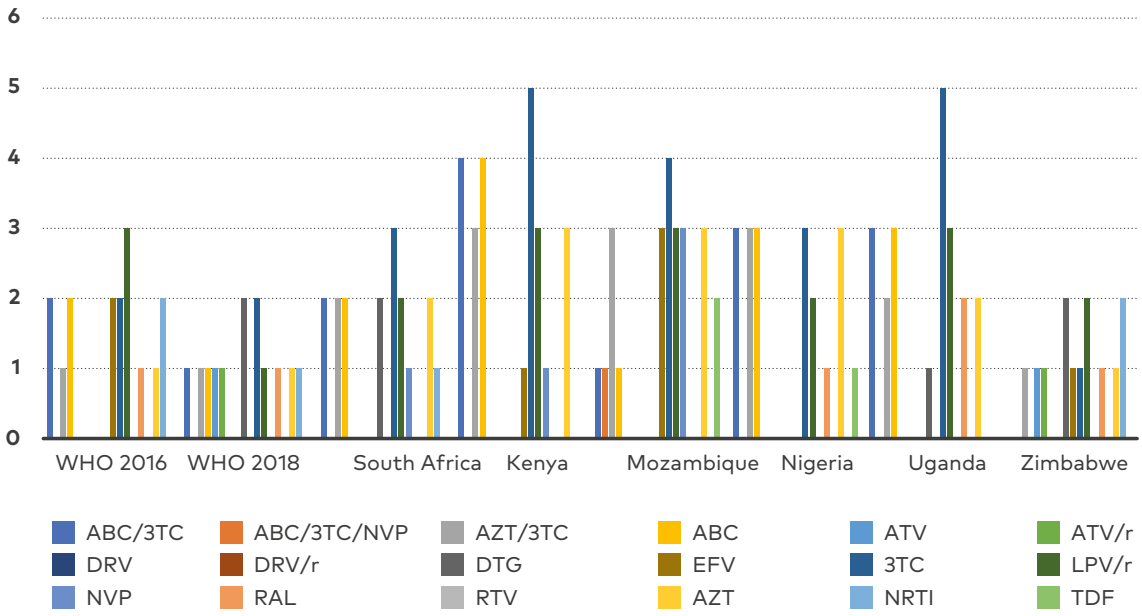


Figure 2: ARV Spread in the 6 Focus Countries

The above figure is a visual depiction based on the latest implemented treatment regimens (1st, 2nd and 3rd lines) in the 6 countries. It confirms the analysis of frequency of use of some of the older regimen drugs such EFV, and the lag in in implementing LPV/r and DTG in countries.

Table 5: Companies with registered products in case countries

		Kenya	Nigeria	South Africa	Uganda	Zimbabwe
Product	**Formulation**	**Products registered**	**Products registered**	**Products registered**	**Products registered**	**Products registered**
abacavir (ABC)	60 mg tablet (dispersible scored)	Mylan	Mylan	Mylan	Cipla	Mylan
abacavir/ lamivudine (ABC/3TC)	120mg/60mg tablet (dispersible scored)				Cipla	Mylan
	60mg/30mg tablet (dispersible scored)	Aurobindo	Cipla		Multi	Multi
zidovudine (AZT)	50mg/5ml oral solution	Hetero	Multi	Multi	Multi	Multi
	60 mg tablet (dispersible scored)		Multi			
zidovudine/ lamivudine (AZT/3TC)	60mg/30 mg tablet (dispersible scored)	Cipla	Multi		Multi	Mylan
zidovudine/ lamivudine/ nevirapine (AZT/3TC/ NVP)	60mg/30mg/50mg tablet (dispersible scored)	Strides	Multi		Multi	Strides
atazanavir (ATV)	200mg capsule	Mylan	Emcure	Multi		
	100mg solid oral dose			Indo Pharma (not marketed)		
darunavir (DRV)	75mg tablet	Janssen		Janssen (registered by Aspen)	Janssen	Janssen
dolutegravir (DTG)	50mg tablets (until better dosing info available, sprinkles under development)	GSK	GSK	ViiV	Multi	Multi
efavirenz (EFV)	200mg tablet (scored dispersible)	Strides	Multi	Multi	Aurobindo	Multi
lamivudine (3TC)	50mg/5ml oral liquid	Cipla	Multi	Cipla	Cipla	
	150mg tablet	Strides	Multi	Multi	Multi	Multi

		Kenya	Nigeria	South Africa	Uganda	Zimbabwe
Product	**Formulation**	**Products registered**	**Products registered**	**Products registered**	**Products registered**	**Products registered**
lopinavir/ ritonavir (LPV/r)	80mg/20mg oral solution	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie
	40mg/10mg solid oral dosage form					Cipla
	100mg/25mg tablet (heat stable)	AbbVie, Macleods	Multi	Multi	Multi	Aurobindo
	400mg/100mg oral liquid					
nevirapine (NVP)	50mg/5ml oral solution	Cipla	Multi	Cipla	Multi	Multi
	50mg tablet (dispersible scored)		Multi		Aurobindo	
raltegravir (RTV)	25 mg chewable scored tablet		Pantheon	MSD	Pantheon	N/A
	100mg granules for suspension		Pantheon	MSD	Pantheon	
	400mg tablet	MSD	Zhejiang Huanhai Pharm	MSD	Zhejiang Huanhai Pharm	MSD
ritonavir (r/ rtv)	25mg tablet					
	100mg powder		Multi	AbbVie	Multi	Mylan
	400/5ml oral liquid					

* *Multi indicates multiple product are registered in the country*

2.5. Global availability of paediatric formulations of key drugs

The lack and/or shortage of appropriate paediatric formulations of key drugs globally was reported as a significant barrier to treating paediatric HIV at a country-level.

The WHO's 2018 optimal formularly and limited-use list for paediatric ARVs recommends that countries use 50mg adult tablets of dolutegravir for children 25 kgs and above until dosing for lower weight bands is confirmed and paediatric formulations become available.

ViiV is currently undertaking clinical trials of 5mg dispersible dolutegravir tablets for treatment of infants and young children[52] and is aiming to file for FDA registration of 5mg and 10mg[53] dispersible dolutegravir tablets by the end of the year.[54] To allow for rapid registration of generic 5 and 10mg dispersible tablets following the filing by ViiV's to the Food and Drug Administration (FDA), ViiV is working with Mylan and Macleods to simultaneously develop bioequivalent generic 5mg and 10mg dispersible tablets for paediatric patients. This collaboration between ViiV, Mylan and Macleods is supported by Unitaid and CHAI.[55]

Another critical formulation for treatment of infants and young children with HIV is LPV/r 40mg/10mg pellets or granules. Two generic companies have FDA registered LPV/r granules and pellets – Cipla and Mylan – but the rollout of these products to countries has been extremely slow.

According to regulatory data collected in countries, only Zimbabwe has domestically registered 40mg/10mg pellets (Cipla), however other countries may by able to access this product through waivers for importation used by the Global Fund or Pepfar procurement processes. In South Africa, the lack of a registered originator 40mg/10mg product has reportedly been a barrier to regisration of generic pellets or granules domestically.

According to key informants, a key challenge to scaling up access to LPV/r pellets or granules is that demand for the product is significantly greater than Cipla and Mylan's combined supply. An additional challenge is that the pellets and granules cost around three times more than AbbVie's LPV/r syrup which they are meant to replace.[56] Substantially increased supply is required to improve access. Importantly, three companies are currently working on developing pellets or granules of LPV/r combined with ABC and 3TC[57], which should provide an important treatment option for paeds when available.

A further challenge to scaling up LPV/r is reported uncertainty among stakeholders regarding how much they should continue to push for appropriate formulations of LPV/r as paediatric formulations of DTG are expected to enter the market shortly and largely replace LPV/r in first line regimens for infants and young children.

Finally, while Merck has developed paediatric formulations of raltegravir, key informants did not predict generic availability of paediatric raltegravir any time soon – highlighting the small market (given that few infants are diagnosed as HIV positive as neonates) and short span of recommended use for paediatrics (up to 4 weeks) as disincentives to generic production. Further, according to one key informant the steps required to prepare and administer raltegravir paediatric granules are overly complex for caregivers, and easier to use drugs and formulations are needed. Cost was also identified as a barrier to expanded use of raltegravir.

52 http://i-base.info/htb/36027

53 Companies are developing 10 mg tabs in addition to 5mg tabs to lower the pill burden on the health system

54 Key informant interview

55 https://www.viivhealthcare.com/en-gb/media/press-releases/2018/july/innovative-public-private-partnership-initiative-to-accelerate-development-of-optimal-pediatric-formulations-of-dolutegravir-to-improve-the-lives-of-clhiv/

56 https://www.msf.org.za/stories-news/press-releases/pharmaceutical-corporations-failing-children-hiv

57 https://medicinespatentpool.org/uploads/2018/11/Update-on-progress-Paediatric-Sept-2018.pdf

2.6. Availability, use and barriers to use of point of care early infant diagnostics

To inform our understanding of the states of affairs related to paediatric HIV treatment in Kenya, Mozambique, Nigeria, South Africa, Uganda and Zimbabwe, we sought to gain insight into the availability and use of early infant diagnostics (EID) at country-levels, including point of care (POC) products.

The WHO recommends that "all HIV-exposed infants have HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter"[58] and that infants with initial positive tests are started on antiretroviral treatment without delay. This recommendation is based on evidence that early initiation of antiretroviral therapy significantly reduces the risk of infant HIV mortality. The Children with HIV Early Antiretroviral trial demonstrated that early infant diagnosis combined with early treatment reduces HIV mortality by around 76%.[59] Research shows that "without timely diagnosis and treatment, perinatally infected infants have a peak mortality between 8 and 10 weeks of age, with 20% of infants dying before 2 months of age, increasing to 35% by age 12 months and 50% by 2 years".[60]

A recent observational study comparing the outcomes of point-of-care early infant diagnosis (POC EID) and conventional early infant diagnosis (conventional EID), highlighted that POC EID can provide significant reductions in time to diagnosis and treatment when compared to conventional EID. Conventional EID refers to laboratory-based EID, which requires health care workers to send samples to laboratories for diagnosis. Slow turn-around of results and loss-to-follow up between the collection of sputum and return of results impedes timely treatment initiation for HIV positive infants.

The observational study compared outcomes of conventional EID with outcomes of POC EID in Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) supported countries and sites. EGPAF received funding from UNITAID in 2015 to implement and pilot POC EID in nine high prevalence countries: Cameroon, Côte d'Ivoire, Kenya, Lesotho, Mozambique, Rwanda, Swaziland, Zambia, and Zimbabwe. The observational study outlines outcomes from eight of these countries: Cameroon, Côte d'Ivoire, Kenya, Lesotho, Mozambique, Rwanda, Swaziland, and Zimbabwe. (Kenya, Mozambique and Zimbabwe are case countries of this analysis).

With UNITAID funding EGPAF began testing two POC EID technologies in supported countries in 2016: Alere's m-PIMA HIV ½ Detect (previously the Alere Q) and Cepheid's Xpert HIV-1 Qual.[61] An observational study showed that EGPAF supported POC EID significantly improved outcomes.

- The median time from sample collection to return of results to care givers was 0 days for POC EID versus 55 days for conventional EID.
- The median time from sample collection to ART initiation was 0 days for POC EID versus 49 days for conventional EID.
- The median age of ART initiation for infants tested between 6 and 8 weeks was 1,6 months for POC EID versus 3,3 months for conventional EID[62]

Piloting of Alere's m-PIMA and Cepheid's Xpert POC EIDs have also shown encouraging outcomes in South Africa and elsewhere.[63 64 65]

58 2016

59 Violari, Avy, et al. "Early antiretroviral therapy and mortality among HIV-infected infants." New England Journal of Medicine 359.21 (2008): 2233-2244

60 Bianchi et al. "Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: An observational study in eight African countries." 2019. http://dx.doi.org/10.1016/S2352-3018(19)30033-5

61 Bianchi et al. "Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: An observational study in eight African countries." 2019. http://dx.doi.org/10.1016/S2352-3018(19)30033-5

62 Bianchi et al. "Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: An observational study in eight African countries." 2019. http://dx.doi.org/10.1016/S2352-3018(19)30033-5

63 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0189226

64 https://www.sciencedirect.com/science/article/pii/S1386653219300654?via%3Dihub

65 https://eidconsortium.org/Files/EID%20Poster%20v5%20Low%20res.pdf

UNITAID has also provided Diagnostics for the World (DRW) support to prepare the market (including seek registration) in six African countries (Cameroon, Kenya, Malawi, Nigeria, Uganda, and Zimbabwe) to implement SAMBA point of care diagnostics.[66] The implementation and use of these diagnostics at a country level has also been supported by Médecins Sans Frontieres and Wellcome Trust.[67 68 69 70] SAMBA I is semi-automated allowing for semi point of care implementation at clinics, whereas SAMBA II is fully automated and can be used in resource poor settings.[71]

Table 6 indicates key point-of-care early infant diagnostics.[72 73 74]

In addition to conducting POC EID, m-PIMA, Xpert and SAMBA diagnostics can also be used to measure viral load.[76 77 78]

We explored barriers to the use of POC EIDs at country levels through key informant interviews and surveys and data requests sent to regulatory authorities and national health laboratories. Unfortunately, response rates to data requests sent to regulatory authorities and laboratories were poor, with some individuals citing a lack of ethical approval as a reason for not responding. Surprisingly, EGPAF staff indicated that domestic regulatory approvals were not a barrier to the use of POC EIDs in their projects, as registration proceeded relatively quickly or, in cases where regulatory approval was not in place, waivers were provided.

An urgent concern of key informants related to access and use of POC EIDs was the rapidly approaching conclusion of the UNITAID grant to support EGPAF implementation of POC EIDs in nine countries. According to key informants the conclusion of the grant in July 2019 threatened to interrupt access to POC diagnostics in EGPAF supported countries and sites, as additional funding to support their continued provision has not yet been sourced from Ministries of Health, PEPFAR, the Global Fund or other funders. The need for ramped up advocacy to secure ongoing funds was highlighted by key informants, however challenges to ramping up advocacy and securing funds were also reported.

66 https://unitaid.org/project/drw-samba-machines-early-infant-diagnosis/#en

67 https://wellcome.ac.uk/press-release/samba-ii-offers-spot-hiv-testing-millions-africa\

68 https://www.youtube.com/watch?v=tEfTLaHzEcU

69 https://journals.lww.com/jaids/Fulltext/2017/10010/Multicountry_Validation_of_SAMBA___A_Novel.18.aspx

70 https://unitaid.org/project/drw-samba-machines-early-infant-diagnosis/#en

71 https://www.ncbi.nlm.nih.gov/pubmed/27568275

72 https://apps.who.int/iris/bitstream/handle/10665/255857/WHO-HIV-2017.16-eng.pdf;jsessionid=97B012D0F43ADBDFCCF36DA6BAA6BC51?sequence=1

73 https://www.childrenandaids.org/node/583

74 https://www.who.int/diagnostics_laboratory/evaluations/pq-list/hiv-vrl/public_report/en/

75 Sourced from EGPAF

76 https://www.theglobalfund.org/media/5765/psm_viralloadearlyinfantdiagnosis_content_en.pdf

77 https://www.who.int/diagnostics_laboratory/evaluations/pq-list/190408_pqdx_0359_032_00_pqpr_mpima.pdf?ua=1

78 https://www.who.int/medicines/news/2019/1st-in-vitro-diagnostic-prequalified-through-alt-perf-mech/en/

Table 6: Key point-of-care early infant

Diagnostic	Manufacturer	WHO PQ	CE-IVD	Per test costs[75]
m-PIMA HIV 1/2 Detect (previously Alere Q)	Alere/Abbott	Yes	Yes	$25.00 - $29.51
Xpert HIV-1 Qual	Cepheid	Yes	Yes	$14.90 - $19.07
Samba II	Diagnostics for the Real World	No	Yes	N/A

The lack of civil society champions advocating for funding and scale up of POC EIDs was identified as a challenge to ensuring their ongoing provision. In speaking with civil society, we identified perceptions that likely discourage CSO advocacy.

- There was a perception that international manufacturers and groups are always introducing new 'things' and technologies, and that these technologies are not properly maintained or sustained. CSOs felt that, as a result of poor maintenance and sustainability plans, health facilities have broken with unusable technologies lying around.
- There was also a perception that because of health care worker turn-over, including rotation of nurses to ensure the integration of services, health care workers were often untrained to use available technologies, which impeded their use.
- There was a perception that inadequate investment in transport and community health care workers would reduce the benefits of POC technologies, even when technologies were available.
- There was a perception that the need for civil society and government to respond to other more pressing concerns – such as immediate subsistence concerns arising from natural disasters – made it difficult to put sustained effort into campaigns for procurement of diagnostic technologies.

Cost concerns also impacted CSO, health departments and funders willingness to champion the need for funding and scale-up of POC EIDs – particularly given that significant investments were already made at country levels to implement conventional EID and strengthening laboratory systems, and that cartridges for POCs are generally more costly that cartridges for conventional EIDs.

In addition to highlighting challenges, key informants highlighted potential strategies to better demonstrate the need for, and benefits of, POC EIDs to local CSOs, health ministries and global funders, and engage these stakeholders in championing and ensuring their accessibility and use. In part 3, we have provided recommendations for improving access to POC EIDs informed by key informant interviews, surveys and other data reviewed for this analysis.

Part 3: Country Situational Snapshots

To provide an overview of the key indicator areas for each of the selected contexts, country snapshots have been developed. These provide a minor situational analysis of the paediatric HIV health data, including viral load suppression rates; as well as aspects of paediatric HIV drug resistance (HIVDR). These snapshots also delve into these countries' national budgets and donor contributions towards the health budget. It offers an overview of civil society organisations working on paediatric HIV and any key country-level campaigns. Laws and policies were also investigated, but minimal data was found.

These snapshots provide a reference point for key recommendations and actions to be undertaken at national levels.

3.1. Kenya Snapshot

Of a population of 51.3 million, 1.6 million people are living with HIV in Kenya, of this 120.000 are children of which 61% are receiving ART.[79] According to the Kenya PEPFAR 2019 Country Operational Plan (COP), 82.9% of the paediatric HIV clients achieved HIV viral Suppression[80]. While viral load suppression rate of children under the age of 15 years is 65%. Due to PEPFAR's increased support in some districts of the focal counties in the country, Kenya's paediatric viral load has started to improve.

Paediatric HIV drug resistance: The drug resistance concerns in Kenya are noted as incidents occurring pre-treatment and during the course of treatment – due to under and/or over-dosing of treatment. There is a paucity of literature around paediatric HIV drug resistance. Of the limited studies found, at least 100 children were identified as having been diagnosed with HIV paediatric drug resistance in 2017. Of these, 34% experienced virological failure and 68% had detected resistance mutations. 7% out of 14 of these children had persistent viremia during second-line treatment. This is an area of work in which further research and investment is required.

Budget: Although government spending has more than doubled between 2006 and 2012 (from $US 57.49 million to $US153 million), dwindling funds from international donors pose a challenge for the sustainability of Kenya's HIV response. The country is working towards increasing its domestic financing for HIV by 2020 (National AIDS Control Council, Kenya AIDS Response Progress Report, 2018)[81]. No information could be found on a separate funding allocation for the paediatric HIV response. The country does not have a designated budget for the treatment of HIV resistance.

79 https://www.unaids.org/en/regionscountries/countries/kenya

80 https://www.pepfar.gov/countries/cop/fy2018/c80143.htm

81 https://nacc.or.ke/wp-content/uploads/2018/11/KARPR-Report_2018.pdf

Funding Sources UNAIDS Data 2018				
Domestic Private	**Domestic Public**	**International PEPFAR**	**International Global Fund**	**Total**
US$ 91 422 168	US$ 342 351 186	US$ 615 277 224	US$ 121 902 916	US$ 1 174 884 586

Global Fund site grants[82]			
Component	**Signed**	**Committed**	**Disbursed**
HIV/AIDS	US$847,308,559	US$686,954,090	US$618,884,675

News information on procurement of ARVs

"Kenya has received a Sh400 million HIV grant to buy antiretroviral drugs for children. The money was donated by the Children's Investment Fund Foundation. It will be channelled through the Global Fund, which supports HIV, TB and malaria control programmes in Kenya. - The Star, April 2018[83]

Civil society working on paediatric HIV: There are a limited number of civil society organisations focused solely on paediatric HIV. During our informant interviews, we learnt that the national HIV movement play a minor role in the paediatric HIV advocacy. Organisations such as the Network of People Living with HIV and those affected by TB and HIV/AIDS (NEPHAK) and others are involved in the national level Technical Working Group (TWG) on elements of the paediatric HIV access cascade. Civil society organisations have expressed an increased willingness to engage in national paediatric HIV access issues.

Key Country Level Campaigns on Paediatric HIV:

- **Beyond Zero Campaign:** (BZ) secretariat is responsible for assisting H.E the First Lady to operationalize her framework to support programs that address HIV, maternal and child health. EGPAF is also part of this campaign which advocates for programs to reduce maternal and infant mortality rates in Kenya.
- **Free to Shine Campaign:** Part of the Organisation of African First Ladies Against HIV / AIDS (OAFLA) which Kenya is a member.

Laws and Policies: There are HIV laws, but there is no specific mention of paediatric HIV.

82 https://www.theglobalfund.org/en/portfolio/country/?k=013e944b-94da-41e1-90d1-b22b4f87f1cc&loc=KEN

83 https://www.the-star.co.ke/news/2018/04/27/kenya-gets-sh400m-to-buy-arvs-for-children_c1749955

Maternal & Child Survival Programming in Kenya	
(USAID) Maternal and Child Survival Program (MCSP)	Project timeframe: September 2014 - December 2017 Objective 1: (i) To strengthen the core capacities of county governments and health teams. (ii) To increase coverage and utilisation of evidence-based, sustainable, high-impact interventions in reproductive, maternal, new-born, and child health (RMNCH) Objective 2: To foster an enabling environment, and promote program learning, documentation, and dissemination for improved RMNCH
The Partnership for Maternal, Newborn & Child Health (The Partnership, (PMNCH)[84]	An alliance of more than 1000 organizations in 192 countries from the sexual, reproductive, maternal, newborn, child and adolescent health communities, as well as health influencing sectors.
Kenya Association for Maternal & Neonatal Health (KAMANEH)[85]	KAMANEH's vision is of an equitable community where all women, children and adolescents have access to safe childbirth, affordable and quality health care and health education services.
PATH Kenya[86]	Kenya County Governor Signs Landmark Maternal Child Health and Family Planning Act. The law is the first in the country to allocate county-level resources to support access to critical health services for the most vulnerable mothers, newborns, and children.

84 https://www.who.int/pmnch/about/members/database/kenya_community_health_network/en/

85 https://kamaneh.or.ke/

86 https://www.path.org/media-center/kenya-county-governor-signs-landmark-maternal-child-health-and-family-planning-act/

3.2. Mozambique Snapshot

The country of roughly 30 million has the 8th highest prevalence and third in the world after Nigeria and South Africa for new paediatric infections. (UNICEF, Mozambique)[87] There are approximately 18000 new paediatric HIV infections in 2018 with ART treatment coverage of 51%. 41% of these were virally suppressed.

Paediatric Drug Resistance HIV (HIVDR): Like the other countries sampled, there has been insufficient research undertaken in Mozambique on the subject matter. Few studies have focused on delays in detecting treatment failure and switching to second line combination ART in HIV infected children. Historically, the paediatric age group has been a sensitive cohort for research due to ethical concerns. The most recent study undertaken was in children aged 1 to 14 years on ART for ≥12 months at 6 public facilities in Maputo, Mozambique. This study found that prior to ART initiation, 5.4% of children had HIVDR that was associated with nevirapine perinatal exposure. Twelve months after ART initiation, 77% had viral load suppression (<1000 copies/mL), exceeding the WHO target of ≥70%; 10.3% had HIVDR at 12 months."[88]

Budget: Donor contributions to the government's budget for the health sector have been varying and declining. (PEPFAR COP, 2018)[89] Foreign donors cover only 3% of the overall sector budget managed by MISAU. In 2017, Mozambique spent 7.8% of the country's budget on health. Overall, PEPFAR and the Global Fund are responsible for the largest share of the resources provided. One hundred percent of ARVs over the next GFATM implementation period 2018-2020 are procured by donors, principally by the GFATM (74 percent) and PEPFAR (26 percent). These are sourced through international pooled procurement mechanisms (GHSC-PSM, GFATM Wambo). The country also relies substantially on donors, particularly the USG, for other HIV commodities such as reagents (viral load (VL) and, early infant diagnosis (EID)." There was no disaggregated data for HIV or health funding for paediatrics.

Civil society working on paediatric HIV: The informant interviews revealed little interest in paediatric HIV by civil society organisations. Generally, women's organisations as well as those working on PMTCT have been the most vocal advocates around access to EID for the paediatric market. This is primarily due to pressure from groups such as EGPAF.

87 http://www.unicef.org.mz/en/our-work/what-we-do/hivaids/

88 Vaz, P et al. "Surveillance of HIV drug resistance in children receiving antiretroviral therapy: a pilot study of the World Health Organization's generic protocol in Maputo, Mozambique." 2018

89 https://www.pepfar.gov/countries/cop/fy2018/c80143.htm

90 https://www.theglobalfund.org/en/portfolio/country/?k=013e944b-94da-41e1-90d1-b22b4f87f1cc&loc=KEN

Funding Sources UNAIDS Data 2018					
Domestic Private	**Domestic Public**	**International PEPFAR**	**International Global Fund**	**International all donors**	**Total**
	US$ 8 501 812	US$ 206 158 981	US$ 84 130 028	US$ 18 854 333	US$ 329 521 478

Global Fund Site Grants[90]			
Component	**Signed**	**Committed**	**Disbursed**
HIV/AIDS	US$847,308,559	US$686,954,090	US$618,884,675

Maternal & Child Survival Program	
(USAID) Maternal and Child Survival Program (MCSP)[93]	Project timeline: October 2015 - June 2019 "Over the past five years, MCSP has developed tools and strategies to address gender-based constraints and opportunities related to reproductive, maternal, newborn, child and adolescent health (RMNCAH) outcomes and integrated these into national strategies, training packages and quality improvement tools.
The Partnership for Maternal, Newborn & Child Health (The Partnership, (PMNCH)[94]	"The GFF was launched at the Third International Conference on Financing for Development in July 2015. A total of 62 lower-middle income countries are eligible to receive grant resources from the GFF Trust Fund. It is phasing in its operations, beginning with an initial set of four frontrunner" countries—the Democratic Republic of Congo, Ethiopia, Kenya and Tanzania. In July 2015, Bangladesh, Cameroon, India, Liberia, Mozambique, Nigeria, Senegal and Uganda were announced as the second wave of GFF countries."

Key Country Level Campaigns on Paediatric HIV:

- **Mother 2 Mother[91]:** As part of the national strategy to combat HIV, Mozambique has operated Maes para Maes (MpM), a community support programme for HIV-positive mothers which contains elements of m2m's Mentor Mother Model, since 2010. M2m supported the Ministry of Health (MISAU) to establish this model with support from UNICEF. Starting in 2016, to support further efforts in Mozambique to eliminate paediatric AIDS and meet global treatment goals, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and MISAU collaborated to revitalise the MpM strategy.
- **Free to Shine Campaign[92]:** Part of the Organisation of African First Ladies Against HIV / AIDS (OAFLA) which Mozambique is a member.

Laws and Policies: There are no specific laws affecting paediatric access to health, but there are laws criminalizing the transmission of, non-disclosure of or exposure to HIV transmission. Parental consent for HIV testing for adolescents younger than 12 years.

91 https://www.m2m.org/where-we-work/mozambique/)

92 http://www.oafla.org/

93 https://www.mcsprogram.org/resource/gender-technical-brief/

94 https://www.who.int/pmnch/gff/en/

3.3. Nigeria Snapshot

Nigeria has the highest HIV-infection rate among babies in the world, three times that of South Africa. The limited access to ARVs, gaps in HIV testing is among the causes for the high child infection rate. The HIV prevalence rate among children between the ages of 0-14 years of age is 0.2%, with 26% of those on ARV treatment. There is no recent viral load suppression rates data for children below the age of 15 years.

Paediatric HIV Drug Resistance (HIVDR): Like the other countries sampled, there has been insufficient research undertaken in Nigeria. Few studies have focused on delays in detecting treatment failure and switching to second line combination ART in HIV infected children. A study by Boerma et al published in 2017 found that out of the total 82 PMTCT-naïve children, 3 (15.9%) had Pre-treatment HIV drug resistance (PDR).

Budget: The monthly national allocated Federal budget for health is 05-1% in Nigeria, while 95% of the overall health and HIV budget is financed by international donors. There was no information found on any allocations in any of the states in Nigeria for the paediatric HIV response.

95 https://www.theglobalfund.org/en/portfolio/country/grant/?k=a03b38ca-6c2f-4a24-a0e5-b16fd601b56d&grant=NGA-H-FHI360

96 http://docs.theglobalfund.org/program-documents/GF_PD_002_6d9277fa-0a6c-4755-9427-12c0eef269af.pdf

International funding sources of paediatric HIV responses:

PEPFAR Budget				
	Budget Code Description	**New Funding**	**Applied Pipeline**	**Total Amount Allocated**
Paediatric Care & Support (PDCS)	Paediatric Care and Support	$5,368,380		$5,368,380
Paediatric Treatment (PDTX)	Paediatric Treatment	$3,230,311		$3,230,311
Global Fund Site Nigeria/Grants[95]				
Component	**Signed**	**Committed**	**Disbursed**	
HIV/AIDS	US$189,844,261	US$122,476,461	US$109,393,037	
Information from Global Fund Agreement[96]				
Strategies and Planned Activities: - Early infant diagnosis - Anti-retroviral treatment and monitoring - Prophylaxis and treatment of opportunistic infections - TB/HIV collaborative activities Target Group/Beneficiaries: - HIV positive women and their infants/ children				

Civil society working on paediatric HIV: There is weak civil society support for paediatric HIV. The national Network of People Living with HIV, including organisations such as International Community of Women Living with HIV (ICW) have indicated interest in undertaking advocacy in this area, but so far, their work has been limited to articulating these issues during PEPFAR COP planning processes and during Global Fund CCM meetings.

Key Country Level Campaigns on Paediatric HIV:

- **Free to Shine Campaign[97]:** The campaign was initially launched at the 20th ordinary session of the general assembly of the Organisation of African First Ladies against HIV/AIDS (OAFLA).

Laws and Policies: There is no information on any specific laws or policies affecting access to paediatric HIV. The Revised National HIV and AIDS Strategic Framework 2019-2021 "recognizes that the enactment of appropriate and supportive laws and development or revision of guidelines that will facilitate improved access of key, vulnerable and general populations to comprehensive and high- quality HIV prevention intervention, testing services, treatment, care, and support is required." Nigeria's HIV and AIDS Anti-discrimination Act, 2014, makes it illegal to discriminate against people based on their HIV status.

97 Ibid

Photo: Chris de Bode

3.4. South Africa Snapshot

With a population of roughly 58 million, South Africa has the largest national treatment coverage in the world. There were 13 000 new HIV paediatric infections in 2018. Of the 280'000 paediatrics diagnosed with HIV, 58% received ARV treatment; while 45% were virally supressed.

Paediatric Drug Resistance HIV (HIVDR): In South Africa, the drivers of HIVDR in paediatrics is mainly found in Pre-treatment HIV Drug resistance (HIVDR) as well as acquired HIVDR from the First- and second-line treatment responses. A few studies have been done in the country on various infant cohorts and these indicate that where infants fail HIV-prophylaxis, they must be placed on NNRTI-resistant HIV regimens. This suggests that resistance will likely persist through 36 months of age, when children qualify for NNRTI-based ART (Persistence of HIV drug resistance among South African children given nevirapine to prevent mother-to-child-transmission, 2018)[98]. In May 2019, South Africa released new guidelines recommending DTG in first line regimens for infants over 20kg.

Budget: Around 13% of the South African budget is externally funded by donors, while the government of South Africa significantly contributes to the health budget. The country does not have a disaggregated paediatric HIV budget, although the national health budget covers this area.

98 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5884446/

99 https://www.theglobalfund.org/en/portfolio/country/?k=f1b33974-aeec-4ab8-9519-bd3600122512&loc=ZAF

100 https://sanac.org.za/download-the-full-version-of-the-national-strategic-plan-for-hiv-tb-and-stis-2017-2022/

Funding Sources UNAIDS Data 2018					
Domestic Private	**Domestic Public**	**International PEPFAR**	**International Global Fund**	**Total**	**Total**
	US$ 1 545 826 721	US$ 472 582 374	US$ 44 793 341	US$ 2 073 272 539	US$ 2 073 272 539

Global Fund Site Grants[99]			
Component	**Signed**	**Committed**	**Disbursed**
HIV/AIDS	US$553,493,737	US$553,493,737	US$553,493,737

Information from the SA National Strategic Plan for 2017-2022[100]

"The Global Fund to Fight AIDS, Tuberculosis and Malaria (GF) allocated US$ 312 million for HIV and TB programming in South Africa for the period 2016/17 to 2018/19, and recently gave an indicative allocation of another US$ 353 million for the 3-year funding cycle thereafter."

Maternal & Child Survival Program	
USAID Maternal and Child Survival Program (MCSP)[101]	Project timelines: June 2015 - June 2019 MCSP is working closely with the Nelson Mandela Children's Hospital (NMCH) to develop its nursing capacity in tertiary pediatric care, and to establish the hospital as a regional center for learning in the Southern African region. We are also supporting the mentorship of clinical pediatric nurses and nurse managers at NMCH by partnering with a US-based children's hospital.
The Partnership for Maternal, Newborn & Child Health (The Partnership, (PMNCH)[102]	Success Factors country case studies: South Africa. Collaborating across sectors improves women, children and adolescents' health.

Civil society working on paediatric HIV: South African civil society organisations including the Treatment Action Campaign (TAC), the Paediatric AIDS Treatment for Africa (PATA) have indicated a willingness to increased advocacy in this area. There was increased advocacy for additional funding towards the paediatric HIV response by civil society during the 2019 PEPFAR COP regional meetings in Johannesburg, South Africa.

Laws & Policies: No laws on paediatric access, but there are laws based on general criminal laws. Parental consent for HIV testing for adolescents younger than 12 years.

101 Ibid

102 Ibid

3.5. Uganda Snapshot

In 2018, Uganda reported around 95 000 children who are living with HIV, with 7600 recorded new infections. The ARV treatment coverage is at 68%, while the paediatric viral suppressions rates are at 44%. (UNAIDS, 2018)[103]

Paediatric HIV Drug Resistance (HIVDR): There have been increasing studies and reports of HIV Drug Resistance Among Children initiated on first-line ARV treatment in Uganda. A recent observational study, which enrolled 279 HIV-infected children found that HIVDR was present in 10% of the children. The contributing cause higher rate of pre-treatment HIVDR, especially in children with PMTCT exposure. The fact that the availability of protease inhibitor (PI)–based regimens as advocated by the World Health Organization, limited means that increased HIV resistance. Due to increasing paediatric HIVDR, Uganda is transitioning to DTG-base regimens. (PEPFAR, Uganda 2018 COP)[104]

Budget: The country's Health budget is declining and dependency for external health funding remains high. 90% of the allocated health budget is externally funded. Most of these funds allocated to the procurement of HIV commodities. There is no national disaggregation of the budget towards the paediatric HIV response.

103 http://www.unaids.org/en/resources/documents/2018/unaids-data-2018

104 https://www.pepfar.gov/countries/cop/fy2018/c80142.htm

105 https://www.theglobalfund.org/en/portfolio/country/?loc=UGA&k=9e8b8568-adaa-4b26-af09-da5b112c51e7

Funding Sources UNAIDS Data 2018					
Domestic Private	**Domestic Public**	**International PEPFAR**	**International Global Fund**	**International all donors**	**Total**
	US$ 38 693 159		US$ 2 295 076	US$ 8 691 470	US$ 296 649 946
PEPFAR COP2018 Summary of Planned Funding					
Paediatric Care and Support (PDCS)	USD$ 11,828,221				
Paediatric Treatment (PDTX)	USD$ 3,875,291				
Global Fund Site Grants[105]					
Component	**Signed**	**Committed**	**Disbursed**		
HIV/AIDS	US$746,919,707	US$622,113,785	US$580,438,870		

Maternal & Child Survival Program	
(USAID) Maternal and Child Survival Program (MCSP)	MCSP is supporting the Ministry of Health and the Uganda National Expanded Program on Immunisation (UNEPI) in reaching every community and child with high-quality immunization services. They are continuing work begun under USAID's predecessor flagship Maternal and Child Health Integrated Program (MCHIP), with an added emphasis on new themes in the global health landscape—on gender, equity and quality.
The Partnership for Maternal, Newborn & Child Health (The Partnership, (PMNCH)	The GFF was launched at the Third International Conference on Financing for Development in July 2015. In July 2015, Uganda was announced as one of the focal countries under the second wave of GFF countries."

Civil society working on paediatric HIV: Ugandan civil society organisations have seemed to have paid little attention to this area of advocacy. During the informant interviews, many organisations spoke about technical partners being the ones prioritising this agenda. CEPA was the campaign that most organisations referred to and are supporting as part of the national CSO coalition.

Key national level campaign:

- **Free to Shine Campaign:** The project is being implemented by the Organisation of African First Ladies against HIV/Aids. According to the [2016-2021] ruling NRM party manifesto, government aims at having a health centre III in each of the 1,403 sub-counties in the country.
- **Campaign to End Paediatric HIV/AIDS (CEPA)[106]:** With support from Global AIDS Alliance, civil society organisations (CSOs) in Uganda have launched a three-year Campaign to End Paediatric HIV/AIDS (CEPA) that focuses on overcoming policy and implementation bottlenecks to scaling up prevention of Mother -to-Child Transmission (PMTCT+) and paediatric diagnosis, treatment and care.

Laws & Policies: Uganda has got an HIV legislation, which criminalises HIV non-disclosure, exposure and transmission. Anecdotal reports from civil society organisations such as UGANET suggestions that this law has an indirect impact on how care-givers and mothers access health care services.

106 https://www.heps.or.ug/news/campaign-end-pediatric-hivaids-cepa

3.6. Zimbabwe Snapshot

Zimbabwe has 77 000 children living with HIV[107], with 4300 new infections recorded in 2018. Of these children, 89% are receiving ART. The viral load suppression data is disaggregated as follows: 58% of boys and 34% in girls.

Paediatric HIV Drug Resistance (HIVDR): There is paucity of information on the number of HIVDR in the paediatric cohort in Zimbabwe. The studies that have been limited, observation and often cross-sectional evaluation.

Budget: 86% of the Zimbabwe budget is externally funded. Of the externally funded donor contributions, PEPFAR and Global Fund are contributing 78%. The Zimbabwe AIDS Levy[108] has generated substantial resources, but the country still relies heavily on external funding. It is noted that there has been no disaggregated funding for the Paediatric HIV response.

Civil society working on paediatric HIV: Civil society in Zimbabwe have noted with concern the weak coordination efforts in prioritising paediatric HIV. Civil society have not traditionally investigated this area of advocacy and women's groups have focused heavily on PMTCT and eMTCT advocacy. The is appetite by CSOs in Zimbabwe to take this agenda forward, beyond supporting technical partners such as EGPAF.

107 http://www.unaids.org/en/resources/documents/2018/unaids-data-2018

108 https://www.ncbi.nlm.nih.gov/pubmed/26781215

109 https://www.theglobalfund.org/en/portfolio/country/?loc=UGA&k=9e8b8568-adaa-4b26-af09-da5b112c51e7

Funding Sources UNAIDS Data 2018				
Domestic Public	**International PEPFAR**	**International Global Fund**	**International all donors**	**Total**
US$ 38 693 159		US$ 2 295 076	US$ 8 691 470	US$ 296 649 946
PEPFAR FY2018 Country Operational Plan				
Budget Code		**Budget amount**		
Paediatric Care and Support (PDCS)		2,684,915		
Paediatric Treatment (PDTX)		412,490.00		
Global Fund Site Grants[109]				
Component	**Signed**	**Committed**	**Disbursed**	
HIV/AIDS	US$1,275,248,003	US$1,067,530,088	US$1,065,080,187	

Maternal & Child Survival Program	
Maternal and Child Health Integrated Program (MCHIP)	Project timelines: January 2014 to December 2016 MCHIP Partners Involved JSI, Jhpiego and Save the Children. Oct 1, 2010 – May 31, 2014 The USAID-funded Maternal and Child Health Integrated Program (MCHIP) / Zimbabwe was launched in 2010 as a strategic response to the alarming increase in levels of maternal, newborn, and child deaths in the country.[111]
The Partnership for Maternal, Newborn & Child Health (The Partnership, (PMNCH)	Not much recent information.

National level campaigns: The Free to Shine Campaign has also been launched in Zimbabwe. Start Free, Stay Free, AIDS Free Framework[110]: November 2016, a super fast-track framework for ending AIDS among children, adolescents and young women by 2020.

Laws and policies: There are no specific laws hindering access to paediatric HIV services. Zimbabwe does have a criminal codification of HIV non-disclosure and exposure. This is under Article 79 of the Criminal Code.

110 http://procurement-notices.undp.org/view_file.cfm?doc_id=114051

111 Ibid

Part 4: Research Based Recommendations and Actionable Items

4.1. For addressing acquired Paediatric HIV Drug Resistance (HIVDR)

Since the majority of HIV infected children reside in the African region, HIV drug resistance is also a growing problem in paediatric HIV. The main driver of HIVDR seems to be pre-treatment HIVDR – this is because as part of the PMTCT programmes, the majority of mothers are on combination antiretroviral therapy (cART). The second driver – acquired HIVDR – is caused by first- and second-line treatment, used in Infant prophylaxis (either NVP or NVP/AZT).

During the informant interviews, some of the stakeholders noted the lack of access to routine viral load testing for the paediatric market, outside of donor funded programmes as a major challenge. This combined with incorrect dosing of ARVs by health care workers, has contributed to increased prevalence of HIVDR. The limited value of NNRTI based regimens in paediatrics is exacerbated by poor access to innovative paediatric formulations of new drugs.

For each of the focal countries under review, the country situation snapshots highlighted under Part 3, provided greater details as to the country scenarios.

Recommendations from the research for addressing acquired HIVDR:

- The focal countries have started taking proactive steps in updating their national guidelines to align with the latest WHO recommendations for paediatric treatments, and require country specific support going forwards.
- Donors' such as PEPFAR have increased contributions towards Paediatric HIV Care and support, including Treatment. The transition towards DTG-based regimens will replace NNRTI paediatric formulations, which will continue to present a dosage challenge.
- Improved access to routine viral load as part of a point-of-care package is critical to prevent HIVDR.
- Accelerating the development and uptake of the most needed drug formulations for children. The introduction of pooled mechanisms such as the Global Accelerator for Paediatric Formulations (GAP-F)[112], a drug development consortium that will accelerate timelines, reduce development costs, and improve global health outcomes through a coordinated and purposeful clinical, product development for paediatric formulations. This mechanism operates through formalized collaboration across sectors to ensure accelerated development and uptake of the most needed drugs and formulations for children and focused on HIV, with the intention to address similar challenges in other disease areas soon.

4.2. For improving access to new and better ARVs and formulations for infants and children with HIV in case countries

- Three years after the adoption of WHO guidelines recommending the use of LPV/r in first line regimens for infants and children under 3, the lack of adequate supply of appropriate paediatric formulations of LPV/r remains a barrier to their use. While LPV/r pellets and granules are available, they continue to have bitter tastes making them difficult to administer, and companies with registered products have been unable to meet supply. Therefore nevirapine and efavirenz remain in high use among infants and young children despite high rates of resistance.[113]

112 http://www.gap-f.org/

113 https://www.arvprocurementworkinggroup.org/public/componenti/1207/files/APWGAnticipatedDemandForecast_Dec122018.pdf

Countries should learn from ongoing delays experienced in the introduction of LPV/r pellets and granules and undertake monitoring and advocacy efforts to ensure timeous access to new LPV/r FDCs and paediatric formulations of DTG. Importantly, at an international level, there are several ongoing efforts to speed up the delivery of paediatric formulations of DTG – including a collaboration between Unitaid, CHAI, ViiV, Mylan and MacLeods to allow for rapid registration of generic DTG formulations following ViiV's submission for FDA registration of paediatric DTG products (5 and 10mg dispersible tablets).[114] Additionally, the recently adopted Vatican Action Plan set out multi-stakeholder commitments to accelerate the introduction of optimal ARV drugs for infants and children.[115]

- At a country level, civil society must monitor developments related to the development of new paediatric formulations and their registration (including FDA registration, WHO prequalification and country-level registration). However, a barrier to effective monitoring and timeous and strategic advocacy related to the country level introduction of drugs, is the lack of transparency around filed and pending regulatory applications at country levels. To facilitate monitoring and transparency, a global database should be developed that provides data on the filing and status of applications for approval by the FDA, WHO and regional and country regulatory authorities. Local civil society should use this information to call for rapid regulatory review and approval at country levels.

- Civil society can play an important role in educating care givers, health care workers and policy makers about new paediatric drugs and formulations, as well as the need for and benefits of new drugs and formulations, to generate demand for timeous local availability of new products.

- Country level civil society can play an important role in advocating for reform of country-level treatment guidelines to expand the use of new drugs and phase out NNRTIs in first line regimens for infants and children.

- Finally, civil society can play an important role in monitoring the implementation of new drugs and formulations to identify and highlight barriers and challenges. Some potential challenges highlighted by key informants, include lack of confidence among nurses in initiating infants on care, challenges faced by care givers in administering drugs, and challenges in identifying missing children with HIV. Civil society is also well-placed to draw attention to challenges among stakeholders and advocate for appropriate reforms to address them.

4.3. For improving access to POC EIDs in case countries

- Civil society groups working on issues of paediatric HIV should be convened by international champions of POC EIDs for a meeting or call to discuss the benefits of POC EIDs, to give CSOs the opportunities to discuss their concerns related to POC EIDs and to identify where further advocacy may be needed to facilitate the successful implementation of POC EIDs. For example, to address civil society's concerns related to the service manufacturing agreements, international stakeholders can stress where achievements have been made (for example, diagnostic manufacturers committed to improving service agreements in the Vatican Action Plan[116]) and where further advocacy can be done to improve maintenance and

114 https://www.viivhealthcare.com/en-gb/media/press-releases/2018/july/innovative-public-private-partnership-initiative-to-accelerate-development-of-optimal-pediatric-formulations-of-dolutegravir-to-improve-the-lives-of-clhiv/

115 dditoonhttps://www.paediatrichivactionplan.org

116 https://www.paediatrichivactionplan.org/2018-diagnostics

service agreements. Further to address civil society concerns about the need for transport and staff to reach patients in remote areas, international stakeholders can shed light on how this has been done to date and what resources are needed at a local level to maintain this.

- Further costings should be undertaken to provide greater clarity on the costs of maintaining and using POC EIDs, which look at the full continuum of care, and outline cost differences when using POC EIDs in remote versus urban areas. An observational study of EGPAFs implementation of POC EIDs in 8 African countries reported that the cost per test was lower for POC EID than conventional EID.[117] EGPAF and CHAI have highlighted that the high rates of results not returned when using conventional testing drives up the cost per test.[118] Better costing data will allow governments to optimize the combined use of conventional EIDs (in which they have already invested) and new POC technologies. At the same time, civil society can advocate for diagnostic manufactures to further reduce the costs of POC devices and consumables.

- Civil society can play an important role in highlighting the ability of POC technologies to save lives, situating their availability as a human rights issue, and generating demand for POC technologies among care givers, health care workers and policy makers. Civil society can also play a role in highlighting the potential benefits of including multi-use POC platforms in UHC packages of care.[119]

- Finally, engagement of civil society and other local stakeholders is critical to overcoming challenges to finding the 'missing children' with HIV and linking them to both POC and conventional EID and treatment. Many children with HIV are never identified for testing. More active case finding, better resources for follow up and other creative strategies are needed to locate the missing children. Civil society can play a vital role in informing caregivers about the need for testing and overcoming stigma that discourages testing. Local stakeholders can also play a role in identifying creative opportunities for locating the missing children – such as through vaccination programs and drives – and linking them to diagnostic and treatment services.

Conclusion

The research has uncovered different layers of shortfalls in paediatric HIV treatment in the focal countries, with areas of commonality and country specific issues that have been presented above.

Treatment and Access should be approached holistically as there are usually a multitude of factors that challenge adequate Paediatric HIV treatment and access. It is therefore recommended that any solution targeting improving EID and access to treatment, includes:

- Supporting regulatory processes and harmonisation of existing national programmes to ensure that access to diagnostics and treatment are not only designated in maternal and child health programmes but integrated into primary health care service delivery.
- Greater civil society engagement through treatment literacy on HIV paediatric diagnostics and newer formulations, to encourage demand creation from communities. This will also improve monitoring of the implementation of national guidelines, and ensure accountability in national budget prioritisation efforts, to support paediatric HIV interventions. The role of civil society is also critical in market preparedness for newer drug formulations, which are being spearheaded through partnerships, such as GAP-f.

117 https://www.sciencedirect.com/science/article/pii/S235230181830328X

118 https://clintonhealthaccess.org/innovative-diagnostic-technology-can-save-hiv-positive-infants/

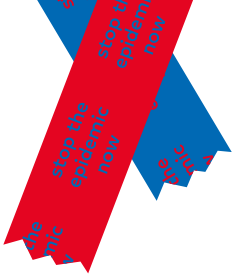
119 https://clintonhealthaccess.org/improving-diagnosis-through-integrated-testing/

- Price and information sharing mechanisms can facilitate access to lowest cost diagnostics and treatment options available.
- Redefining of political will and sustained support by national stakeholders and key influencers.
- Infrastructure considerations (including cost analysis and maintenance buy-downs) to support the maintenance and scale-up of POC EID technologies.
- Accelerating domestic market approval processes for the uptake of the most needed Dolutegravir-based regimes and other fixed dose combination therapies.

Integrated Approach

Transition to later paediatric HIV treatment regimens and the implementation thereof may address country-level gaps in parallel with regional influences such as regional demand and local manufacturing, which has the potential to reduce costs of drugs and improve access. Careful and coordinated forecasting is necessary at the international level to ensure paediatric ART remains available.

Photo: Chris de Bode



Aidsfonds
Condensatorweg 54
1014 AX Amsterdam
The Netherlands
aidsfonds.org/community/children

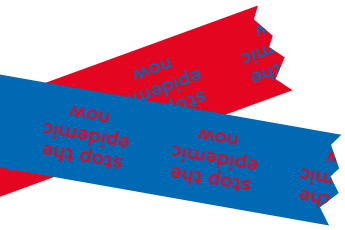
For more information, please contact:
Sabrina Erné
Senior Advisor Children Affected by HIV
serne@aidsfonds.nl

Anna Nijsters
Press Officer
anijsters@aidsfonds.nl

Acknowledgements
SAPAM
Southern African Programme on Access to Medicines and Diagnostics
www.sapam.net

Graphic Design
De Handlangers, Utrecht

Publication Date
November 2019



For more information, visit aidsfonds.org/community/children

aidsfonds