

CHILDREN AND THE 'BIG THREE' EPIDEMICS

Ending the burden of HIV, malaria and TB in children

JUNE 2020

Children in low- and middle-income countries still remain on the frontline of the 'big three' infectious diseases. Despite great advances over the years, AIDS, malaria and TB continue to account for over half a million child deaths each year, mostly in children under the age of five. This series of articles assesses the current situation for each of the three epidemics. It stresses the urgent need for a diverse range of new treatments that are suitable for children, especially with the growing threat of drug resistance, with recommendations for governments, regulators, the pharmaceutical industry and others.

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The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine.

For over 10 years, the Foundation has been building consensus on the role for the pharmaceutical industry in improving access to medicine and vaccines. It publishes the Access to Medicine Index every two years. The Foundation published the first Access to Vaccines Index in 2017, and published the second Antimicrobial Resistance Benchmark in early 2020.

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A blueprint for ending the 'big three' burden on children

ABOUT THIS SERIES

HIV, malaria and TB have long been recognised as the 'big three' epidemics, with children living in low- and middle-income countries (LMICs) being the most vulnerable to all three diseases. Through international cooperation and funding, remarkable progress has been made against the diseases. Such focused efforts have helped spur action towards ending the epidemics by 2030, as set out in the Sustainable Development Goals (SDGs). Yet, a number of factors make it difficult to mark the endgame for these three diseases:

- **Few child-friendly treatments are available for these diseases.** This puts children at risk of severe illness or death for two main reasons: 1) their medicine most often comes in hard pills made for adults or bitter syrups that are difficult to swallow — contributing to poor adherence; and 2) increasing rates of drug resistance means that new medicines are needed to replace those no longer effective. Despite these clear product gaps, children are often last in line in the drug development process.
- **The increasing reliance on a few pharmaceutical companies and financial subsidies** to sustain the fight against these diseases increases the vulnerability of children as a group. This dependence can create downstream supply issues, delays and rising prices that can be particularly challenging for low- and middle-income countries with limited resources and diverse public health priorities.
- **Disruptions to healthcare systems**, especially as other epidemics and pandemics interrupt global priorities, also threaten to slow progress. Pandemics like COVID-19 disrupt even basic services and supply of treatments for many diseases including HIV, malaria and TB, with a consequent impact on mortality and infection rates.

This series of articles identify key areas where action is needed in response to these challenges, linking to the pharmaceutical industry, regulators and governments. It includes three articles that dive into the current situation per disease, highlighting the factors that threaten progress made so far and setting out the specific requirements needed for the development of new child-friendly treatments. To show where action is possible, each article comprises case studies of how some pharmaceutical companies and organisations are already working towards the development and delivery of much-needed paediatric treatments.

For over ten years, the Access to Medicine Foundation has been researching how the world's largest pharmaceutical companies are working to improve access to medicine and more recently, how they are responding to the rise of drug resistance. By identifying key areas for reform, these articles seek to stimulate pharmaceutical companies and others to take specific actions to safeguard the path to progress in children's health.

What is needed to end the 'big three' disease burden on children?



Market size is shrinking, leaving few incentives

HIV

New child-friendly treatments are needed for children living with HIV

The number of new paediatric HIV infections has decreased significantly in recent years. While this is very positive, it also means that the market for child-friendly antiretrovirals (ARVs) is shrinking, making it less financially attractive for pharmaceutical companies to invest in developing new ones. This could stall progress – especially when combating resistance. With one in two newly diagnosed children showing resistance to commonly used ARVs, new treatments that are child-friendly are needed to replace those that are no longer effective.



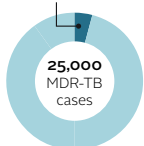
Substandard meds prove a major challenge

MALARIA

High-quality child-friendly antimalarials are needed to combat malaria

Children under five are the most vulnerable to malaria. There is increased attention on the need for child-friendly antimalarials, yet the availability of these treatments is limited. In the meantime, millions of children are at risk of being exposed to suboptimal treatments or even substandard and falsified medicines, which increases the threat of drug resistance in children. The development and delivery of high-quality, optimal formulations for children must be ensured.

4% get diagnosed and treated



Multidrug-resistant TB is hugely undertreated

TUBERCULOSIS

New incentives and priorities are needed to direct focus on multidrug-resistant TB

In the last 50 years, only three new medicines for the treatment of multidrug-resistant TB (MDR-TB) have reached the market. Today, harmonised guidelines on how to effectively treat patients with MDR-TB are limited, including for children. Adherence is a particular challenge for children with MDR-TB as treatment regimens can be long and gruelling, yet poor adherence also drives drug resistance. New child-friendly medicines against MDR-TB are urgently needed, along with improved diagnostics. New incentives will be needed to spur this development, particularly as the market for MDR-TB is considered small, with uncertainty over patient numbers due to the lack of diagnostics. Sustained collaborative action between public and private actors will be essential to ensure access to these much-needed medicines for children.

How can the end of the 'big three' burden be achieved?

While each of the three epidemics pose unique challenges, five areas of action have been identified as a basis for shaping policy and informing action plans in scaling up progress.

1

Close the gap between the approval of adult and children formulations

The development process for paediatric medicines is lengthy, with nearly a decade lag between the approvals of treatments for adults and the child-friendly versions. This is partly because children are extremely vulnerable and recruiting them into clinical trials requires specific ethical considerations. It is generally considered to be safer to first start a trial in adults to assess the risk–benefit profile of the treatment before assessing that for children.

To help accelerate the development of medicines for children, new paediatric legislation in the EU and the United States has been developed. Specific plans for paediatric drug development are required by both the US FDA (Paediatric Study Plan) and the European Medicines Agency (Paediatric Investigation Plan). The aim of these plans is to integrate children's needs into the overall development process of new treatments.

While this has shown some success in terms of new approvals (e.g., in Europe) regulation challenges remain worldwide as variations and inconsistencies between regulatory systems have resulted in significant delays across jurisdictions. The regulatory costs and burdensome steps required often result in waiver or deferral requests by pharmaceutical companies. What's more, the small and fragmented markets for HIV, malaria and TB offer few incentives for pharmaceutical companies to invest, deterring paediatric innovation overall, including for smaller R&D-focused companies.

Harmonised regulatory approaches that safeguard health outcomes along with reduced inefficiencies in processes and costs are needed. This is particularly important for LMICs who look to the FDA as the 'gold standard' for determining if a new medicine is safe and ready for market. Such approaches can help strengthen paediatric development and accelerate the pathway to new treatments.

2

Prioritise unmet formulation needs

Paediatric HIV, malaria and TB predominantly affect children in LMICs. With few optimal treatments available for children, healthcare providers and parents often resort to using or manipulating adult medicine, increasing the risk of inadequate dosing and resistance. With drug resistance increasing for all three diseases, new optimal treatments are needed to replace those that are no longer effective.

To help mobilise the pharmaceutical industry towards the development of optimal treatments that are tailored to the needs of children, continued efforts are crucial to identify the most urgently needed formulations. Groups like the Paediatric Antiretroviral Drug Optimization and the Paediatric Antituberculosis Drug Optimization (PADO) led by the World Health Organization (WHO) have been developed to lay out clear priorities to accelerate access to optimal formulations for HIV and TB, respectively. Such priority setting needs constant updating that requires ongoing funding and investment, and R&D engagement. Clear priorities must then be translated into new products through the combined efforts of pharmaceutical companies, product development partnerships and other organisations to spur innovation and advance much-needed formulations to market.

3

Harmonise treatment guidelines

Globally, clinical guidelines for diagnosing and treating HIV, malaria and TB vary widely in terms of content and recommendations, including for children. For example, how children are diagnosed, use of ages and/or weight and dosages differ across treatment centers and even between doctors. Such variations can hinder the effective management of these infections.

The harmonisation of treatment guidelines has been a focus for WHO for the past number of years. To ensure the implementation of improved treatment guidelines and the effective management of these infections, coordination and collaboration is needed. Such harmonisation will help ensure safe, effective, and high-quality treatments are developed and registered in the most resource-efficient manner.

4

Advance vaccine development

The search for vaccines for all three diseases has been ongoing for decades, all the while facing complex technical and clinical challenges. Vaccines are currently in development for all three infectious diseases and although progress has been made, the scientific innovation needed to end the epidemic through a vaccine is yet to come. Further, a limited number of companies are engaged in vaccines R&D for these diseases.

Prioritisation and financial incentives along with new innovative, clinical and regulatory approaches are needed to expedite the pathway to these much-needed vaccines. If these three infectious diseases received a similar level of funding and prioritisation as the COVID-19 pandemic, successful vaccine development could have been likely years ago. Until vaccines for these diseases are proven effective and widely available for all at-risk groups, even in hard to reach areas, the need for new child-friendly formulations remains.

5

Ensure broader and more secure access to optimal treatments

The role that pharmaceutical companies play to ensure access to treatments depends on their R&D expertise, manufacturing capacities and their global reach. The role extends from the R&D of treatments and vaccines, to making products available at the local level, reliably and in sufficient quantities. Ultimately the aim is to ensure the right medicine reaches the right patient at the right time and at the right affordable price.

Yet, the heavy reliance on only a few pharmaceutical companies in this paediatric space raises the risk of access issues and delays in supply. To ensure sustainable access, companies should ensure the rapid uptake of their paediatric medicines through early registration, put in place affordable pricing strategies, and secure the uninterrupted supply of medicines.

2020 has already seen major disruptions in the local availability of medicines, brought on by the COVID-19 pandemic that resulted in shortages of active pharmaceutical ingredients (APIs), final products and rising medicine costs. Disruptions in the supply chain must be prevented through increased transparency and coordinated efforts to secure regional supplies. This is particularly important for new medicines that have the best chance for combating resistance.

Practices to address over-reliance at both the API and manufacturing level, such as pooled procurement mechanisms and local production, can help sustain the supply of medicines at the local level. Improving the resilience of the supply chain can also help ensure medicines reach caregivers and children living in remote areas and communities.

LEADING GRAPHIC

Ending the 'big three' burden: What do children need?

Collectively, AIDS, malaria and TB cause more than a half a million child deaths per year, mostly in children under the age of five.* These deaths can be prevented through the use of vaccines or through appropriate access to treatments. Although significant progress has been made over the years, further action to improve treatment for children with these diseases is needed across three main areas.

1 NEW VACCINES FOR HIV, MALARIA AND TB

Vaccines are a cornerstone of modern health systems — a few shots can protect a child for life against disease and resistance. However, there are still no vaccines on the market for HIV and malaria, and only one for TB — though it is only effective in infants, not in older children. While progress has been made over the past few years in the development of novel vaccines against the three most challenging infectious diseases, complex technical and access challenges exist. Prioritisation and financial incentives along with new innovative, clinical and regulatory approaches are needed to accelerate the pathway to these much-needed vaccines.

What is needed once reliable vaccines and formulations are developed?

- Effective immunisation strategies
- Effective procurement systems
- Robust supply chains
- Affordable access for all populations

2 PAEDIATRIC FORMULATIONS THAT BEST SUIT CHILDREN'S NEEDS

One of the major obstacles in treating paediatric infectious diseases is the limited availability of paediatric formulations. Developing paediatric formulations are challenging — ensuring maximal efficacy and no toxicity, all the while being easy to administer. Healthcare providers and parents often resort to manipulating medicines that are intended for adults (e.g., by crushing or breaking the pills) and giving them to children. The results are bitter tasting medicines that are hard to keep down along with many adherence challenges. What's more, the complex changes in growth and development during childhood often means children respond to treatments much differently than adults. Children need a diverse range of formulations that are easily administered and palatable so adherence to treatments can be facilitated.

3 EASY TO ADMINISTER AND AFFORDABLE TREATMENTS FOR PARENTS AND CAREGIVERS

It is primarily the parents and caregivers who are responsible for administering medicine to children properly. To ensure children have the best chance of receiving the treatment they need, parents and caregivers require formulations that are:

- High-quality
- Affordable
- Easily adjustable to the size, weight and age of the child
- Easy to administer
- Palatable (taste masked and easy to swallow)

FIGURE 1 Defining the age range of the paediatric population

The paediatric age range is defined as ages 0-18 (birth to 18 years of age).

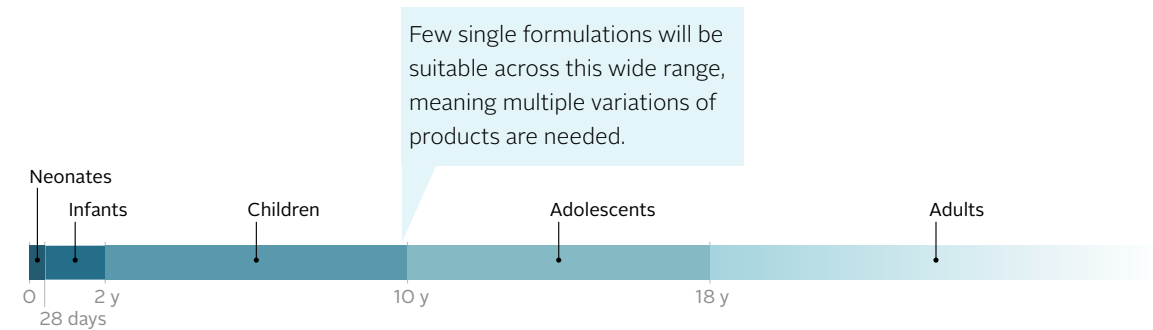


TABLE 1 Children are faced with varying adherence challenges with currently available formulations, showing many opportunities for improvement.

Properties	Rectal tablets	Oral Solutions	Dispersible tablet	Powder, granules, pellets	Chewable tablet	Tablet
Solid/liquid	Solid	Liquid	Solid	Solid	Solid	Solid
Easy to swallow	○	●	●	●	●	●
Palatable	○	●	●	●	●	●
Dissolves in water	○	●	●	●	●	●
Heat stable	●	●	●	●	●	●
Suitable for neonates	●	●	●	●	○	○

Legend (exceptions may occur)
 ● Available
 ● Available in some cases
 ● Not yet available
 ○ Not applicable



What formulations are needed to tackle resistance?

The big three infectious diseases encounter the common problem of drug resistance. The pace of drug development has been slow for these diseases, especially for children. New treatments that can be used for paediatric formulations are needed to replace the ones that are no longer effective due to resistance.

What happens when these actions are not addressed?

- Formulations that are not suitable for children can often lead to the unlicensed use of adult medicines;
- Parents and caregivers may have to break or crush pills to approximate the required dose leading to poor adherence, and an increased risk of drug-resistance;
- If treatments are expensive or hard to reach, parents and caregivers of children living with diseases such as HIV, malaria and TB often have to resort to suboptimal treatments that are of low-quality and/or difficult to administer.

* HIV: Unicef, HIV Global & Regional Trends (July 2019). Available at: <https://data.unicef.org/topic/hiv/aids/global-regional-trends/>. (Accessed: 08 June 2020).
 TB: Dodd, P., et al. The global burden of tuberculosis mortality in children: a mathematical modelling study. The Lancet Global Health, Volume 5, Issue 9, e898 - e906
 Malaria: WHO. World malaria report 2019. WHO (2019). Available at: <https://www.who.int/publications/i/item/world-malaria-report-2019>. (Accessed: 08 June 2020).

HIV, MALARIA AND TB:

Article series on the 'big three' diseases

The next three articles dive into the current situation for each disease, highlighting the specific burden on children, setting out what needs to happen next in terms of product development and the remaining product gaps. It underscores the need for a diverse range of new treatments that are suitable for children, especially with the growing threat of drug resistance.

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ARTICLE: TUBERCULOSIS

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HIV - CONTEXT

Despite significant advances in HIV, many children remain at risk

AT A GLANCE



Progress has been made

In East and Southern Africa, mother-to-child transmission of HIV has decreased by almost half.



Yet challenges remain

Of 160,000 infected children, 50% die before the age of 5 due to lack of access to treatments.



Emerging resistance

1 in 2 children with HIV show resistance to ARVs.



Market challenges put children at risk

- 1) While there is still a large unmet need for ARVs, the market size for infants and young children is shrinking;
- 2) Clinical trials that include children pose challenges;
- 3) Pharma companies have few incentives to take action.

Forty years after its outbreak, HIV is one of the greatest pandemics of modern times. Great progress has been made in the prevention and treatment of the disease, including paediatric HIV and AIDS. This is thanks in large part to coordinated and sustained commitment from governments, NGOs, civil society and industry.

In East and Southern Africa, mother-to-child transmission of HIV has decreased by almost half since 2010.¹ At the same time, the global percentage of children living with HIV on antiretroviral (ARV) treatment has increased by 33%.²

Despite these advances, almost 160,000 children under the age of 14 are infected each year, with 91% living in low- and middle-income countries (LMICs).³ Without intervention, half of these children would die before the age of two.¹ Most often, their medicine comes in hard pills or bitter syrups that are very difficult to swallow.⁴ These suboptimal treatment options have long contributed to low treatment coverage, poor adherence and HIV drug resistance.

One in two newly diagnosed children show resistance to the most commonly used ARVs (efavirenz and nevirapine) due to pre-exposure before and after birth.⁵ There is a visible link between the treatment previously used for prevention of mother-to-child transmission, a single dose of nevirapine, and subsequent resistance in children.

How can suboptimal treatments drive resistance?

Suboptimal treatments often result in poor adherence and poor absorption, ultimately promoting resistance, yet the relationship is multifaceted. Firstly, a significant proportion of children living with HIV have unreliable access to optimal ARVs, as the development of new ARVs that are child-friendly lags considerably behind drug development in adults. Several treatments that do exist in such form are currently facing high levels of resistance, including efavirenz and nevirapine. Secondly, in the absence of new and optimal paediatric HIV

ARVs, healthcare providers and caregivers often resort to manipulating adult formulations such as breaking or crushing pills to approximate the required dose, causing issues related to absorption and increasing the risk of inaccurate dosing.

Ensuring uninterrupted supply

Weaknesses or distributions in ARV supply chains are also considered driving factors behind the development of HIV drug resistance, especially in LMICs. When shortages or stockouts occur, healthcare professionals either dispense a smaller amount than what was prescribed or temporarily substitute components of ARV regimens, hampering the ability of patients to routinely adhere to ARV therapy. In order to maximise adherence and prevent shortages and stockouts, the uninterrupted supply of ARVs must be ensured. For infants and children too young to swallow, bitter tasting syrups with a high-alcohol content that require refrigeration are generally prescribed, creating a range of adherence and supply chain challenges. New formulations, such as lopinavir/ritonavir pellets and granules have helped to overcome this issue but product gaps in the market still exist.

A small, fragmented market with few incentives

While there are still significant unmet needs in terms of ARV coverage, the size of the overall need is decreasing. With effective prevention of mother-to-child transmission, the number of new child infections has been steadily declining over the past decades.¹ While this is a positive trend, it has meant that the market size for infants and young children is shrinking, making it commercially less attractive for pharmaceutical companies. Further, once an ARV medicine is approved for adult use, it can take years for it to be approved for use in children, in part due to the risks and limitations associated with clinical trials that include children. Such challenges combined with a small and fragmented market concentrated mainly in LMICs, has left few incentives in place for pharmaceutical

companies to develop and market paediatric HIV medicines. Yet, over the last number of years, progress has been made in the face of these challenges.

The role for pharmaceutical companies

While market challenges exist, increased attention and activities have emerged in the field of access to paediatric HIV treatment. Pharmaceutical companies have an important role to play in this space by developing formulations that can

be used across different age and weight bands and that are easy to use for parents and caregivers. In doing so, they can increase ARV uptake amongst the paediatric population, prevent further fragmentation of the market and help limit the spread of resistance.

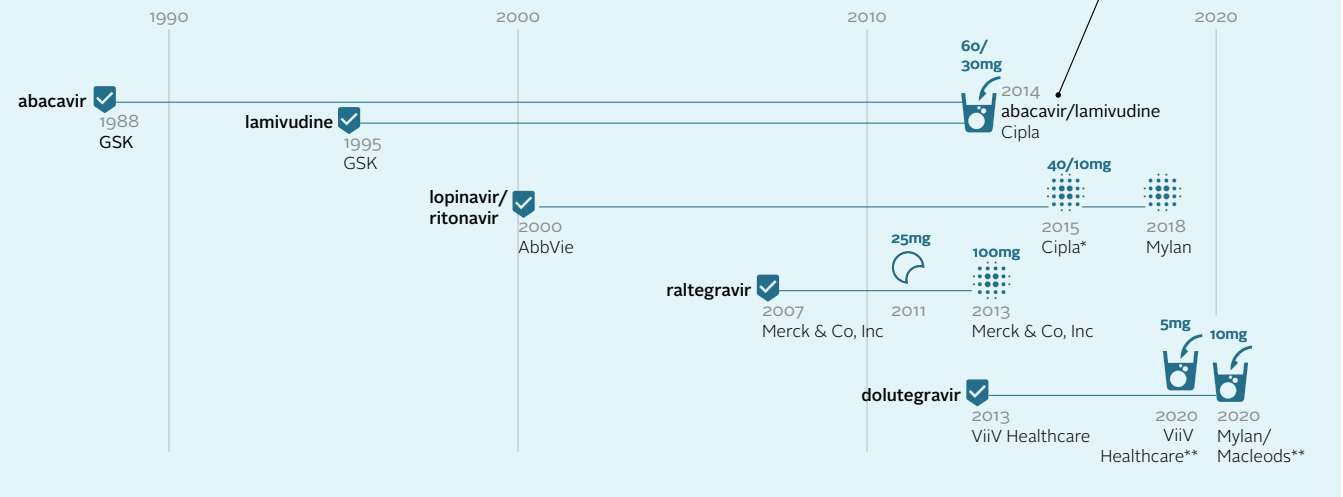
COLLABORATIVE ACTION IN RESPONSE TO MARKET CHALLENGES

In response to paediatric market challenges, multiple initiatives have arisen in the past number of years. Mechanisms such as the WHO-led Paediatric Antiretroviral Drug Optimization (PADO) group, WHO Optimal Formulary List and the ARV Procurement Working Group aim to overcome consensus challenges and market fragmentation by setting priorities and shaping a healthy market, respectively. Efforts to harmonise paediatric drug development and availability with the adult market can promote a faster, more efficient approach to paediatric formulation development and help secure the long-term future of the paediatric market.

The Global Accelerator for Paediatric Formulations (GAP-f), a collaborative network convened by WHO, aims to accelerate the availability of optimal HIV treatments for children in LMICs by coordinating support across sectors.⁶ It supports various stakeholders including pharmaceutical companies, to study and develop optimal paediatric formulations, while harmonising efforts with regulators, and coordinating communication with suppliers. Building on lessons learned and best practices from the HIV community, such a unified and active response to development and access issues has already helped shorten the time lag of paediatric product development compared to adults and bring more paediatric formulations to market.

FIGURE 2 Timelines for paediatric ARV approvals are shortening but unnecessary delays remain

This figure shows the time from initial approval of adult ARVs to the approval of paediatric formulations.



* 4-in-1 LPV/r/ABC/3TC (bringing together ABC + 3TC above and LPV/r on this line) has been submitted for FDA approval by Cipla in November 2019

** Expecting approval in 2020

HIV - MARKET INSIGHT

While many companies are making paediatric ARVs, gaps still remain

The optimisation of ARVs for infants and children has been a key pillar in the HIV and AIDS global health agenda over the past number of years. Since 2002, WHO recommends treatment regimens for all populations that are most effective, well tolerated and have the highest barrier to resistance. In 2011, the Optimal Formulary List for Paediatric ARVs and the Limited Use List were developed to address the challenge of market fragmentation with over 60 formulations and dosages on the market — of which many were suboptimal and far less were actually necessary to implement WHO guidelines. Further, the lists help guide country programmes, procurement entities and funding agencies to deliver the WHO recommended treatment regimens to the paediatric HIV and AIDS population.⁶ The Optimal Formulary List currently consists of eight medicines across all lines of treatment and children's weight bands and is routinely updated to provide the right set of formulations to cover WHO treatment recommendations. The Limited Use List aims to ensure that children in special circumstances, such as children with tuberculosis, neonates and children on third-line treatments, also have access to the ARVs they need in adapted formulations.

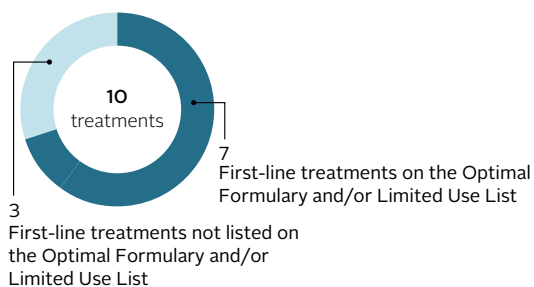
Ten companies with listed products in their portfolios

In total, ten companies are producing formulations for the recommended first-line treatment of HIV in children or neonates that are listed on the Optimal Formulary and/or Limited Use List. Eight companies are producing at least one of the eight products in the Optimal Formulary List, of which the majority are generic medicine manufacturers. Companies manufacturing the most products on the Optimal Formulary List are the generic medicine manufacturers Cipla, Mylan and Aurobindo with six, four and four products, respectively.

Gaps in the market

In 2018, WHO recommended dolutegravir (DTG)-based regimens as the preferred first-line regimen for adults, adolescents and children, to promote the phase out of efavirenz (EFV) and lopinavir/ritonavir (LPV/r), respectively. In general, DTG has a high rate of efficiency and higher barrier to resistance compared to other ARVs.⁷ However, the lack of paediatric indication and corresponding adapted paediatric formulation of DTG for children weighing below 15kg explains its absence from the Optimal Formulary despite its important position in WHO treatment guidance. In addition to DTG, tenofovir alafenamide (TAF), which is recommended as an alternative first-line treatment for children above 25kg, is currently not available in paediatric form. These formulations, as well as fixed-dose combinations (FDC) that are in line with the WHO treatment guidelines, have been identified by the PADO group as R&D priorities that are critically needed to tackle treatment and adherence barriers in the paediatric population.

FIGURE 3 Three of the 10 recommended first-line treatments for children do not have a formulation listed on the Optimal or Limited Use list



GUIDANCE FOR PAEDIATRIC HIV TREATMENT

WHO treatment guideline (2019)

Provides guidance on the preferred and alternative regimens for the treatment of HIV.

Optimal/Limited Use Formulary List (2018)

Provides guidance on the set of paediatric ARV dosage forms needed to deliver WHO-recommended ARV regimens to neonates, infants and children for all lines of treatment.

Five treatments are not available in a formulation that is considered optimal or listed for limited use for the specific age group

TABLE 2 Which companies are making child-friendly ARVs available on the market?

This table* looks at which companies are marketing first-line paediatric ARVs that are recommended by WHO and listed on the Optimal Formulary and Limited Use List.**

Line of treatment	WHO treatment guideline (2019)	Formulation	Optimal/Limited Use Formulary List (2018)	Companies										Total no. of companies		
				AbbVie	Aurobindo	Boehringer Ingelheim	Cipla	Hetero	Macleods	Merck & Co, Inc	Micro Labs	Mylan	Viv Healthcare		Strides	
Neonates	Preferred first-line treatment	zidovudine (AZT) + lamivudine (3TC) + raltegravir (RAL)	AZT oral sol. 50/5 mg/mL	Optimal	●		●	●	●				●		5	
		3TC oral sol. 50mg/5mL	Limited	●		●	●					●		4		
		RAL granules for susp. 100mg	Limited						●					1		
	Alternative first-line treatment	zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP)	AZT oral sol. 50/5mg/mL	Optimal	●		●	●	●				●		5	
		3TC oral sol. 50mg/5mL	Limited	●		●	●					●		4		
		NVP oral sol. 50mg/5mL	Optimal	●	●	●								3		
	Special circumstances	zidovudine (AZT) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r)	AZT oral sol. 50/5 mg/mL	Optimal	●		●	●	●				●		5	
		3TC oral sol. 50mg/5mL	Limited	●		●	●					●		4		
		LPV/r oral sol. 80/20mg/mL	Limited	●		●								2		
Children	Preferred first-line treatment	abacavir (ABC) + lamivudine (3TC) + dolutegravir (DTG)	ABC disp. tablet 60mg	Limited			●				●				2	
		ABC/3TC FDC disp. scored tablet 120/60mg	Optimal			●					●			2		
			Not Listed												0	
	Alternative first-line treatment	abacavir (ABC) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r)	ABC disp. tablet 60mg	Limited			●					●				2
		ABC/3TC FDC disp. scored tablet 120/60mg	Optimal			●						●			2	
		LPV/r heat stable tablet 100/25mg	Optimal	●	●			●	●			●			5	
		DTG is the preferred first line treatment, yet the current formulation is only approved in children weighing above 20kg.†	LPV/r solid oral form. 40/10mg‡	Optimal			●					●			2	
		LPV/r oral sol. 80/20mg/mL	Limited			●					●				2	
		Ritonavir (RTV) tablet 25mg	Limited	●		●									2	
		Ritonavir (RTV) powder 100mg	Limited	●											1	
	Alternative first-line treatment	abacavir (ABC) + lamivudine (3TC) + raltegravir (RAL)	ABC disp. tablet 60mg	Limited			●					●				2
		ABC/3TC FDC disp. scored tablet 120/60mg	Optimal			●						●			2	
		RAL chew. scored tablet 25mg	Optimal							●					1	
	Alternative first-line treatment	tenofovir alafenamide (TAF) + lamivudine (3TC) or emtricitabine (FTC) + dolutegravir (DTG)		Not Listed												0
			There are no formulations of TAF and FTC listed on the Optimal Formulary or Limited Use List.	Not Listed												0
				Not Listed												0
				Not Listed												0
	Special circumstances	abacavir (ABC) + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP)	ABC disp. tablet 60mg	Limited			●					●				2
		ABC/3TC FDC disp. scored tablet 120/60mg	Optimal			●						●			2	
		EFV scored tablet 200mg	Limited										●		1	
	Special circumstances	zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP)	AZT/3TC/ NVP FDC disp. scored tablet 60/30/50mg	Limited			●					●	●		3	
AZT/3TC FDC disp. scored tablet 60/30mg		Optimal			●						●			2		
EFV scored tablet 200mg		Limited										●		1		
AZT/3TC/NVP FDC disp. scored tablet 60/30/50mg		Limited			●						●	●		3		
AZT/3TC FDC disp. scored tablet 60/30mg		Optimal			●						●			2		
Special circumstances	zidovudine (AZT) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r)	AZT/3TC FDC disp. scored tablet 60/30mg	Optimal			●					●			2		
	LPV/r heat stable tablet 100/25mg	Optimal	●	●			●	●			●			5		
	LPV/r solid oral form. 40/10mg	Optimal			●						●			2		
	LPV/r oral sol. 80/20mg/mL	Limited			●						●			2		
	Ritonavir (RTV) tablet 25mg	Limited	●		●									2		
	Ritonavir (RTV) powder 100mg	Limited	●											1		
	or raltegravir (RAL)	RAL chew. scored tablet 25mg***	Optimal							●				1		
															0	
Postnatal prophylaxis (PNP)	nevirapine (NVP)	NVP disp. scored tablet 50mg	Optimal		●		●								2	
	NVP oral sol. 50mg/5mL	Optimal		●	●	●									3	

None of the preferred first-line treatments come in the form of a child-friendly fixed-dose combination that covers the complete treatment regimen.

* This is not an exhaustive list. Data was collected and verified using data provided by companies and publicly available data.
 ** Darunavir (DRV) 75mg tablet is also listed on the Limited Use List but not included in this table as it is only recommended as a third-line treatment.
 *** 25mg RAL chewable produced by Merck & Co, Inc is not scored.
 † Both DTG 5mg dispersible and 10mg scored dispersible versions are soon expected.
 ‡ LPV/r solid oral formulation is available in both pellets form and granules form.

HIV - R&D INSIGHT

Opportunities remain for innovators to develop child-friendly ARVs

There are significant gaps in the availability of paediatric ARVs compared to adults. To direct R&D efforts towards the most needed paediatric formulations the WHO-led Paediatric Antiretroviral Drug Optimization (PADO) has identified priority R&D targets. The PADO group aims to identify short- and long-term priorities for paediatric drug development, in order to treat children living with HIV in LMICs. The current priorities are laid out in the PADO 4 priority list, which is routinely updated in line with emerging evidence and the evolving ARV landscape.⁸ Without action from the pharmaceutical industry and other organisations, there is little chance that these products will be developed and commercialised. By publishing an evidence-based informed consensus, the PADO 4 priority incentivises companies to invest and spurs cross-sectoral collaboration.

In addition to the priorities identified on the PADO 4 priority list, companies are developing additional HIV treatments specifically for children. This section looks at paediatric products that are currently in development, if the industry is actively addressing the identified priorities and how they are ensuring future accessibility. It is important to note that this is not an exhaustive representation of the paediatric HIV R&D pipeline.

Six priority projects in pipeline

Currently, three projects in the pipeline are listed on the PADO 4 short-term priority list (table 3), namely dolutegravir

(DTG) 10mg dispersible scored tablet, emtricitabine (FTC)/tenofovir alafenamide (TAF) dispersible tablet, and DTG/lamivudine (3TC)/abacavir (ABC) 5/30/60mg dispersible tablet, developed by Mylan/Macleods, Gilead and ViiV Healthcare, respectively. An additional three projects are on the PADO 4 watch-list. In addition to the projects listed in table 3, there are four projects currently in development that cover long-term PADO 4 priorities, such as doravirine (MK-1439) and projects with broadly neutralising antibodies, novel delivery technologies, and long-acting parenteral formulations. However, they do not yet target the paediatric population.

Fourteen projects in the paediatric ARV pipeline

There are six companies with a total of 14 projects in the paediatric pipeline. Many of these (5/14) are developed by ViiV Healthcare (a joint venture between GSK, Pfizer and Shionogi). Of the 14 projects, five are being developed exclusively for children over the age of 12.

In general, children over the age of 12 are eligible for adult dosing and do not need specific formulations such as dispersible tablets, granules or pellets. In addition, five (out of 14) medicines are developed in an appropriate paediatric formulation, such as a dispersible tablet suitable for young children who are unable to swallow tablets.

While it is encouraging to see that companies are active in paediatric R&D for HIV, greater attention should be placed on the development of dispersible formulations and adjustable doses for young children, infants and neonates. Further, all listed projects that target the PADO 4 priorities should consider neonates, infants, children and adolescents as well as pregnant and lactating women as early as possible in the development process.

PRIORITISING UNMET NEEDS - PADO 4 PRIORITIES

The WHO-led PADO group identifies the ARV formulations that are most needed for treating children living with HIV in LMICs in a public health context.⁸

Medium-term

- dolutegravir (DTG) 10mg dispersible scored tablet
- darunavir/ritonavir (DRV/r) 120/20mg
- DTG/lamivudine (3TC)/abacavir (ABC) 5/30/60mg dispersible tablet
- emtricitabine or lamivudine (XTC)/tenofovir alafenamide (TAF) dispersible tablet
- DTG/XTC/TAF

Long-term

- Doravirine
- MK-8591 (islatravir)
- Broadly neutralising antibodies
- Long acting parenteral formulations
- Novel delivery technologies

FIGURE 4 Six projects in the pipeline are listed on the PADO 4 priority list

The figure shows the number of projects targeting at least one priority identified by on the Paediatric Antiretroviral Drug Optimization (PADO) 4 priority list, of these, three are short-term priorities.

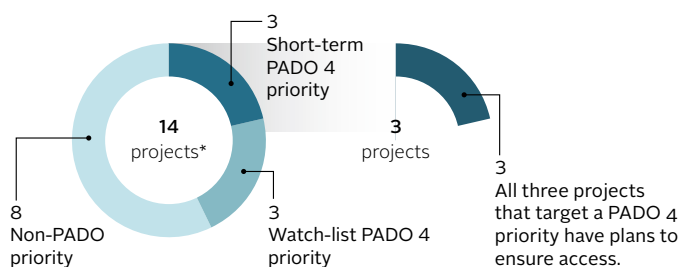


TABLE 3 What is in the paediatric HIV pipeline?

This table* provides a snapshot of companies' R&D pipelines for specific HIV medicines that are tailored for infants, children and adolescents and identifies those that are listed on the PADO 4 priority list**

Company	Phase I	Phase II	Phase III	Approval	Other †
Cipla				Lopinavir/ritonavir (LPV/R)/abacavir (ABC)/lamivudine (3TC) - Weight: 3-25kg - FDC oral granules - Partner: DNDi***	
Gilead		GS-6207 (Capsid inhibitor) (P) - Age: >12 years - Injectable Emtricitabine (FTC) / tenofovir alafenamide (TAF) (P) - Age: 1 month-17 years - Dispersible tablet			
Johnson & Johnson	Emtricitabine (FTC) / tenofovir alafenamide (TAF) / darunavir (DRV)/cobicistat (CO) - Age: >6 years - FDC scored tablet - Partner: Gilead	Darunavir / cobicistat (DRV/co) - Age: 3 - 17 years - FDC, specific formulation unknown - Partner: Gilead			
Merck & Co, Inc			MK-8591 (islatravir) + doravirine (DOR) - Weight: >35kg - Formulation unknown	MK1439 (doravirine (DOR) - (P) - Age: 12-17 years - Tablet MK-1439A (doravirine (DOR)/lamivudine (3TC) /tenofovir disoproxil fumarate (TDF) - Age: 12-17 years - FDC, specific formulation unknown	
Mylan/Macleods					Dolutegravir (DTG) 10mg (P) - Age: paediatric, specific age unknown- Dispersible scored tablet - Partners: CHAI, Unitaid, ViiV Healthcare
ViiV Healthcare	Cabotegravir (CAB) / rilpivirine (RPV) (P) - Age: 12-17 years - Injectable - Partner: Johnson & Johnson	Dolutegravir (DTG)/rilpivirine (RPV)- Age: 6-17 years - FDC, specific formulation unknown - Partners: IMPAACT, Johnson & Johnson	Dolutegravir (DTG)/ abacavir (ABC)/ Lamivudine (3TC) (P) - Age: 6 months -12 years - FDC dispersible tablet Dolutegravir (DTG)/ lamivudine(3TC) - Age: 12-17 years - FDC tablet - Partner: IMPAACT	Dolutegravir (DTG) 5mg - Age: 0-25 years - Dispersible tablet - Partners: IMPAACT, PENTA	

WHAT VACCINES ARE IN THE PIPELINE?

There are several vaccine candidates for the prevention of HIV currently being tested in large-scale efficacy trials, yet none are currently tested for efficacy in children. One example of a promising candidate is the HPX2008/HVTN 705 vaccine in development by Johnson & Johnson, the HIV Vaccine Trials Network (HVTN), the International Aids Vaccine Initiative (IAVI) and the Bill & Melinda Gates Foundation. This Phase IIb study enrolled 2,600 women in five countries across sub-Saharan Africa. In this region, more women than men are becoming newly infected with HIV. The results of the study are expected in late 2022.

(P) Listed on the PADO 4 short-term priority list
(P) Listed on the PADO 4 watch list

* This is not an exhaustive list. Data was collected and verified using data provided by companies and publicly available data.
** This list only includes treatments that are recommended by WHO, either as first-, second- or third-line treatment.
*** LPV/r/ABC/3TC is under review by the US FDA, and a Phase I/II trial is ongoing in Uganda. It was previously listed as a priority by PADO and has been removed in recognition of the progress made.
† This category includes projects that cannot be grouped into the other categories as they follow different clinical trial pathways. This includes generic versions of treatments that are awaiting approval while the originator is still under review for approval.

HIV - ENSURING ACCESS

How are companies ensuring access to their current and future paediatric ARVs?

It is important that companies continue to manufacture products listed on the Optimal Formulary List for Paediatric ARVs and ensure their widespread accessibility and affordability in all paediatric HIV-endemic countries. To this extent, large R&D-based companies and generic medicine manufacturers each have unique and shared responsibilities.

To help achieve wide accessibility and availability, companies can put access strategies in place that include the following: broad registration at country level; equitable pricing strategies; non-exclusive voluntary licences with a broad geographic scope; ensure manufacturing capacity; and ensure sufficient, uninterrupted supply. While the product is still in development, companies can plan ahead to ensure that the product is widely available for children that need it. Table 4 provides some examples of access strategies that companies apply to their paediatric ARV products on the market and/or projects in the pipeline.

Other than pharmaceutical companies, national governments, funding agencies and procurement bodies also have a responsibility to ensure that these products reach the people who need them as well as to develop guidance for transitioning to new treatments, improving capacity building and creation of demand at the local level. This can be achieved through fast-tracking in-country registration, support for procurement and supply-chain planning, and facilitating commercialisation.⁹ Organisations working to improve ARV access such as the Antiretroviral Procurement Working Group (APWG), chaired by the Global Fund, support HIV-endemic countries with transitioning to optimal regimens by ensuring greater availability of products on the Optimal Formulary List. They aim to achieve this through coordinated procurement mechanisms and active engagement streams with manufacturers and suppliers.⁹

TABLE 4 Companies and partners are taking steps to ensure the availability and accessibility of their paediatric HIV products on the market and/or projects in the pipeline

This table provides examples of access strategies that companies and partners apply to their paediatric ARV products on the market or projects in the pipeline to ensure new and existing products are accessible and affordable for patients.

Access strategies	Example of company practice
Registration	ViiV Healthcare has registered dolutegravir (DTG) (Tivicay®) approved for use in children and adults weighing above 30kg (FDA) or 15kg (EMA) in 60 LMICs.
Equitable Pricing Strategy	ViiV Healthcare has equitable pricing strategies in place for its paediatric ARV R&D projects, enhancing accessibility upon approval.
Ensuring adequate supply	Mylan has expanded its capacity for lopinavir/ritonavir (LPV/r) oral granules to over 200,000 packs per month, which matches the need as identified by the global health community.
Non-exclusive voluntary licence	Tenofovir alafenamide (TAF), dolutegravir (DTG) and raltegravir (RAL) are examples of HIV treatments that have been granted a non-exclusive voluntary licence by the originator company, Gilead, ViiV Healthcare and Merck & Co, Inc, respectively, through the Medicines Patent Pool. Such licences allow generic medicine manufacturers (non-exclusive) permission to develop and manufacture versions of on-patent products in low- and middle-income countries under transparent and access-friendly terms, which can support affordability and availability, and can support the development of adapted single and fixed-dose combinations of priority products, such as DTG 10mg dispersible scored and LPV/r/ABC/3TC 4-in-1.
Access through partnerships	Following the approval of Cipla's lopinavir/ritonavir (LPV/r) oral pellets, the Drugs for Neglected Diseases initiative (DNDi) partnered with Cipla to ensure the new pellets are registered and adopted through a large 'implementation study' that will be carried out in several sub-Saharan African countries.

HIV - CASE STUDIES

How companies and organisations are working to improve access to paediatric ARVs

Accelerating access to ABC/3TC through voluntary licensing

AUROBINDO, CIPLA, HETERO, MPP, MYLAN, SUN PHARMA, VIIV HEALTHCARE

Abacavir/lamivudine (ABC/3TC) is a single-pill combination treatment for HIV and is the backbone of the preferred and alternative first-line treatment for paediatric use when taken in combination with dolutegravir (DTG), lopinavir/ritonavir (LPV/R) or raltegravir (RAL), respectively.

What is ABC/3TC?

Abacavir/lamivudine (ABC/3TC) is a single-pill combination treatment for HIV. It is the preferred first-line treatment for children when taken in combination with dolutegravir (DTG) (for approved weight bands for which dosing of DTG is available) – as it is well tolerated and its single dose administration increases adherence. It is further recommended as the alternative first-line treatment when taken in combination with lopinavir/ritonavir (LPV/r) or raltegravir (RAL), for example when appropriate dosing of DTG is not available. WHO has listed ABC/3TC 120/60mg dispersible scored tablet on its 2018 Optimal Formulary List for paediatric ARVs.

Enabling generic manufacturing of ABC/3TC

It took almost 15 years after ABC and 3TC were first approved for child use before an adequate supply of generic versions of the fixed-dose combination of the treatment became available.¹⁰ ViiV Healthcare (a joint venture between GSK, Pfizer and Shionogi) is the originator company of ABC (Ziagen®) and 3TC (Epivir®) which are both off-patent. In 2013, ViiV Healthcare signed a non-exclusive voluntary licence agreement with the MPP. This was followed by a technology transfer for ABC/3TC with the generic medicine manufacturer Mylan in 2014. The licence enables other manufacturers to re-formulate and manufacture paediatric versions of abacavir and abacavir-containing formulations for paediatric HIV treatment, specifically for distribution in LMICs. The paediatric licence covers at least 121 countries, including countries that are together home to 99% of children living with HIV in LMICs. Five companies, Aurobindo, Cipla, Hetero, Mylan, and Sun Pharma now manufacture ABC/3TC in a paediatric fixed-dose combination (60/30mg and/or 120/60mg). Additionally, Cipla and Mylan manufacture paediatric-friendly dispersible tablets and tablets for oral suspension, which are listed on the Optimal Formulary List.

Collaborative efforts help bring paediatric DTG to the market

CHAI, GSK, MACLEODS, MPP, MYLAN, UNITAID, VIIV HEALTHVARE

A dolutegravir (DTG-based treatment regimen) is considered to be among the best treatments for HIV but its availability for paediatrics has been limited.

What is DTG?

Dolutegravir (DTG) is a first-line HIV medicine. It has a high resistance barrier, meaning it has demonstrated no emergent resistance when used as part of an initial treatment regimen. This is a highly desirable trait, particularly for patients who may not be fully adherent. In the last number of years, progress for the development of paediatric DTG has been accelerated in comparison to other ARVs. This is partly due to the various actors and collaborative initiatives in place that support the entire product life-cycle, from identifying R&D priorities, providing financial support, and supply and demand forecasting. Such initiatives help mitigate some of the barriers and risks generally associated with paediatric product development.

An accelerated timeline for paediatric drug development

DTG (Tivicay®) was first approved by the US FDA in 2013. In 2014, the patent holder ViiV Healthcare entered into a non-exclusive voluntary licence negotiated via the MPP. In 2016, the FDA approved a reduction in weight limit for patients eligible to take DTG, from 40 to 30kg, meaning children aged six to 12 years were eligible for the treatment. The European Medicines Agency has approved DTG for children weighing more than 15kg.

Generic versions of DTG then became available in 2017 in LMICs covered by the MPP licence. In that same year, Unitaid, an organisation that invests in innovations to treat HIV, malaria and tuberculosis, and the Clinton Health Access Initiative (CHAI) released a Request for Proposal (RfP) for the development of a paediatric formulation of DTG. The RfP was awarded to Macleods and Mylan in 2018, who received a financial incentive from Unitaid and technical assistance from ViiV Healthcare to catalyse the development, manufacturing and supply of a generic DTG 10mg dispersible scored formulation. Initial regulatory approvals are expected in late 2020. GAP-f — a collaborative network that aims to accelerate the availability of optimal HIV treatments for children — has committed to provide reliable demand forecasting to ensure the right quantities of the treatment are produced and delivered when people

need it.

ViiV Healthcare is also developing a paediatric formulation for DTG, in the form of a 5mg dispersible tablet, which has been submitted for approval to the FDA and the EMA in December 2019 with approval expected in 2020. This is the first time generic medicine manufacturers will be able to file with the FDA while the originator is still under review. The 5mg dispersible by ViiV is the reference product for the generic 10mg dispersible tablets. This could mean an approval time of less than six months between originator and generic, which has been unprecedented in the paediatric infectious disease space.

Partnerships help drive action

A DTG-based ARV regimen is considered to be among the best current treatments for HIV in children and adolescents.⁷ These collaborative efforts along the product life cycle are helping to bring a paediatric formulation of the first-line recommended treatment DTG to the market, by providing financial incentives, technical knowledge, manufacturing capacity and ensuring adequate supply. The partnership works to expedite the development, registration and market entry of generic formulations of paediatric DTG in resource-limited settings. The aim of this project is to reduce the gap - between ViiV Healthcare's 5mg dispersible tablet formulation being available and the Mylan/Macleods 10mg dispersible scored tablet formulations being available to children in LMICs.

Ensuring access to ARV treatment for neonates

MERCK & CO, INC, MPP, EGPAF, PEPFAR

Raltegravir (RAL), in combination with zidovudine (AZT)/lamivudine (3TC), is the recommended first-line treatment for neonates with HIV.

HIV and neonates

Globally, almost 500 children under the age of 14 become infected with HIV each day — the majority of them neonates.³ Neonates who are born with HIV should undergo an ARV regimen immediately, as babies' developing immune systems are especially vulnerable to HIV.¹¹

What is raltegravir?

Merck & Co, Inc is the patent owner of raltegravir (Isentress®). The treatment is available in various paediatric dosages and formulations: 100mg scored chewable; 25mg chewable tablets; 100mg granules. Raltegravir (RAL), in combination with zidovudine (AZT) and lamivudine (3TC), is the recommended first-line treatment for neonates infected with HIV. Currently, RAL is the first and only integrase inhibitor available for newborns.

A small market

While thousands of neonates are infected with HIV each year, the market for RAL is considered commercially unviable.

Currently, RAL is recommended as a preferred first-line treatment in neonates only — babies up to four weeks old — representing a small market with slim margins. Above four weeks, these babies are likely to transfer to a new treatment regimen as there are various alternative treatment options that are superior options for children in different age groups. Further, with the number of newly infected neonates decreasing every year due to effective prevention, the market will continue to shrink, leaving neonates with HIV extremely vulnerable.

Making raltegravir accessible

To help ensure access, Merck & Co, Inc partnered with the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) and the President's Emergency Plan For AIDS Relief (PEPFAR) through the Rome Paediatric HIV Action Plan, to facilitate the treatment of neonates with raltegravir (Isentress®) oral granules at a not-for-profit price.

While Merck & Co, Inc has signed a voluntary licence through the MPP to make raltegravir (Isentress®) widely available, no generic paediatric products have yet been developed, partly due to the small market size. With no generic versions available, it is important that Merck & Co, Inc ensures broad registration, especially in countries where mother-to-child transmission is prevalent. As of June 2019, Merck & Co, Inc has registered raltegravir (Isentress®) granules for oral suspension in 36 countries, mainly high-income countries, in addition to China, Colombia and Peru. Merck & Co, Inc has processes in place to ensure that countries, public hospitals, procurement organisations of the Global Fund or PEPFAR, or healthcare practitioners who request raltegravir (Isentress®) oral granules, can be supplied even if the formulation is not registered.

Advancing a 4-in-1 ARV for infants and children

CIPLA, DNDI, MPP

Current ARVs are often unpalatable, difficult-to-use, and require refrigeration. The new '4-in-1' aims to act as a better alternative to improve adherence.

Why '4-in-1'?

In 2013, during the International AIDS Society conference, WHO released new HIV treatment guidelines, including new ARV therapy recommendations for HIV-infected children. To fulfil the need for better paediatric formulations, the Drugs for Neglected Diseases Initiative (DNDi) partnered with Cipla to develop a 4-in-1 lopinavir/ritonavir (LPV/r)/abacavir (ABC)/lamivudine (3TC) fixed-dose combination specifically for children under three years of age, or until they are able to swallow tablets. The new formulation will provide a more pleasant-tasting, heat stable and easy-to-use alternative compared to previous ARV formulations.

What are the benefits?

The 4-in-1 combination contains LPV/r/ABC/3TC in a paediatric dose (40/10/30/15mg) and is currently under review

by the FDA for use in children between 3kg and 25kg body-weight. The taste-masked 4-in-1 ARV tackles the issues surrounding high alcohol contents, heat instability and the unpalatable taste of syrups, specifically of LPV/r. Furthermore, it makes adherence easier as it requires one act of administration instead of up to four. Easier administration and a relatively high barrier to resistance makes this product crucial in the fight against resistance, as HIV is a chronic disease that requires constant suppression over the lifetime of the child and going into adulthood. The medicine is expected to be approved in 2020.

Ensuring broad roll-out

All single agents in the 4-in-1 formulation, LPV/r/ABC/3TC, were first approved for adults before and in the 1990s - taking almost 30 years to move from single adult formulations to a child-friendly fixed-dose combination. The establishment of new collaborations in the past 15 years, such as the DNDi, MPP, PADO and GAP-f have enabled the development of this product. However, with new treatment guidelines, these actors must collectively continue to ensure effective and broad roll-out of the 4-in-1 medicine for paediatrics. This formulation will remain of great importance for young children until the new low-dose formulations of dolutegravir (DTG) are approved, as well as for children who cannot tolerate DTG and need an alternative treatment.

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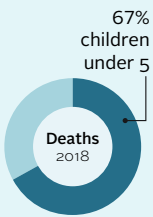
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MALARIA - CONTEXT

With signs of progress, challenges still remain for children with malaria

AT A GLANCE



Children under 5 are most at risk

Up to 50% of deaths in children under 5 are caused by substandard and falsified medicines.



Substandard meds prove a major challenge

1 in 5 antimalarials circulating in LMICs are substandard or falsified.



Especially in the fight against resistance

While still mostly effective, the rise of artemisinin-based combination therapy (ACT) resistance has been detected in high-burden regions such as the Greater Mekong Subregion.

Malaria continues to infect millions of people every year. In 2018, approximately 228 million malaria cases were reported worldwide. Yet progress has been made over the last number of years. Between 2010 and 2018, malaria deaths dropped from 585,000 to approximately 405,000 deaths.¹ But although this shows signs of improvement in mortality rates, there has been a steadily increase in the number of malaria infections since 2014, particularly among pregnant women and children.¹

A 2019 report found that pregnant women and young children are the most vulnerable to this disease.¹ In 2018, children under the age of five accounted for 67% (272,000) of all malaria related deaths, deaths which could have been prevented with access to appropriate treatments.¹ Approximately half of these deaths were caused by substandard and falsified antimalarial medicines, accounting for 122,000 deaths among children under the age of five in sub-Saharan Africa alone.²

Pregnancy reduces a woman's immunity to malaria, making her more susceptible to infection, while maternal malaria also interferes with the growth of the foetus, increasing the risk of premature delivery and low birth weight. In 2018, nearly 900,000 children were born with a low birth-weight as an estimated 11 million pregnant women were infected with malaria, mostly in sub-Saharan Africa.¹ Today, the disease remains one of the leading causes of high morbidity and mortality in

children under the age of five.

The need for better access to treatments

While children are disproportionately affected by malaria, they often struggle to access appropriate treatments. A study conducted in sub-Saharan Africa found that the median percentage of children under the age of five with malaria and a history of fever who received any antimalarial treatment was less than 30%.³ This number was less for children under the age of five receiving artemisinin-based combination therapies (ACT), at around 14%.³ Combination therapies, as opposed to monotherapies, offer a higher success rate and a lower risk of developing resistance.⁴ With such access-related challenges and the prevalence of substandard and falsified medicine on the market, ensuring access to high-quality combination therapies is an unmet high-priority need.

Challenge fuelled by drug resistance

The pathogen most commonly responsible for causing malaria, *P. falciparum*, has developed resistance to almost all classes of antimalarial medicine.⁵ Resistance to commonly used medicine such as chloroquine started emerging in the 1950s and 1960s.⁶ By 1990, chloroquine resistance reached fixation levels across malaria endemic countries. It is estimated that the loss of chloroquine to resistance was responsible for more than doubling malaria-associated mortality

SEASONAL MALARIA CHEMOPREVENTION

Seasonal malaria chemoprevention (SMC) is a highly effective intervention to prevent malaria in children living in areas of exclusive seasonal malaria transmission, mainly in the Sahel region. SMC requires a monthly dose of long-acting antimalarial treatments and has proven to be effective in reducing morbidity and mortality. As of 2012, WHO recommends that all children living in seasonal transmission areas receive SMC.⁸

Global initiatives such as the President's Malaria Initiative (PMI) and the Malaria Consortium have been actively supporting SMC activities across the Sahel region.

Approximately 39 million children under the age of five live in areas where SMC is deemed appropriate.⁹ Yet, only one company, Guilin, is producing quality assured SMC treatment, sulfadoxine/pyrimethamine + amodiaquine (SPAQ™). Such reliance on a single manufacture may have an impact on ensuring a reliable continuous supply.

in sub-Saharan Africa, which bears over 90% of the global malaria burden.⁷ Since then, ACTs were introduced and have acted as the preferred malaria treatment.

ACTs are generally associated with a high rate of efficiency and higher barrier to resistance, contributing substantially to reductions in global morbidity and mortality from malaria. Further, as the fast-acting artemisinin derivative is combined with a second, longer-acting antimalarial partner medicine, the parasite is attacked by two different modes of action allowing for a greater success-rate and lower risk of resistance.¹⁰ Yet, recent studies have reported some ACT resistance in malaria endemic countries such as the Greater Mekong Subregion - at least in part due to the continued use of less effective monotherapies - which drives an urgent need for new and novel treatment options.¹¹ WHO has urged all regulatory authorities to withdraw any oral artemisinin-based monotherapies in order to preserve the efficiency of ACTs.¹²

At present, resistance to artemisinin or key partner drugs included in combination therapies does not appear to be a substantial problem in sub-Saharan Africa, where most malaria cases occur. However, the emergence of resistance to ACTs in sub-Saharan Africa would likely have devastating consequences, and continued surveillance of the emergence of resistance in this region is a high priority.¹³

Poor-quality treatments drive resistance

The existence of substandard and falsified (S&F) medicines in regions where malaria is most prevalent (Southeast Asia and sub-Saharan Africa) are also a major factor in the high mortality rates and rising resistance.

Substandard medicine are authorised medical products that fail to meet either their quality standards or specifications, or both. Falsified medicines deliberately/fraudulently misrepresent their identity, composition or source. Alarming, nearly one in five antimalarials circulating in low- and middle-income countries (LMICs) are substandard or falsified.¹⁴ High prevalence of S&F medicine is often caused by a combination of factors on the local level, including weak technical capacity, poor governance and issues with access.¹⁵

What children need and the role for pharmaceutical companies

Malaria treatments have been generally developed for the use in adults first. However, as malaria predominantly affects children, efforts are being made to develop malaria treatments for both adults and children in parallel. Yet, suitable formulations are still needed for children, particular those under the age of five. In cases where children are affected by complications due to severe malaria, such as coma or kidney failure, alternative treatments must be available, such as intravenous artesunate. This is of particular importance as the majority of severe cases with rapid progression to death occur in young children without acquired immunity.

Pharmaceutical companies have an important role to play in enabling the availability and accessibility of child-friendly formulations of ACTs that include single-dose, easy to administer, palatable regimes. Such formulations can help ensure correct dosing and adherence which can ultimately help limit the emergence of resistance. Companies also have a critical role in the development of new and novel treatments that are needed to replace the ones that are no longer effective due to resistance.

MALARIA - MARKET INSIGHT

Which companies are producing antimalarials that are suitable for children?

According to WHO guidelines, children and adults with *P. falciparum* malaria should be treated with an ACT, as artemisinin derivatives are effective and generally well tolerated in children. The choice of ACT, however, is based on the safety and tolerability of the partner drug that is used in combination with the artemisinin-based drug, as combination therapies work best in combating resistance.¹⁶ Additional considerations include palatability, ease of preparation/administration, and tolerability.

Specifically, WHO recommends six ACT treatments for both children and adults, of which three come in the form of an optimal paediatric formulation and three are in the form a

low-dose tablet that is suitable for children, but not for those who cannot swallow tablets. Furthermore, two (pre-referral) treatments for severe malaria and one preventative treatment are also recommended for use in children.¹⁶

Most recommended treatments are available in fixed-dose combinations

In total, six paediatric formulations for the treatment of malaria are already available by at least eight pharmaceutical companies. All eight companies have been granted WHO prequalification for the products, which ensures that these medicines meet unified standards of high-quality, safety and

TABLE 5 Which child-friendly treatments for malaria are available?

This table looks at which companies are providing specific treatments for *P. falciparum* malaria tailored for paediatric use.* It looks specifically at companies whose products have been WHO-prequalified, ensuring quality and allowing them to be procured broadly.

There are no treatments available for infants that weigh below 5kg. This means that low-weight or malnourished babies are the most vulnerable without optimal treatments.

Company with WHO Prequalification**	Treatment	Brand name	Paediatric formulation
Recommended first-line ACTs***			
Originator: Novartis Generic: Ajanta; Cipla; Ipca; Macleods; Strides	Artemether/lumefantrine	Coartem® Dispersible	FDC dispersible tablet 20/120mg †
Originator: Sanofi Generic: Ajanta; Cipla; Guilin; Ipca; Macleods; Micro Labs	Artesunate/amodiaquine	ASAQ® Winthrop	FDC tablet 25/67.5mg †
DNDi/Cipla	Artesunate/mefloquine		FDC tablet 25/50mg †
Alfa Sigma	Dihydroartemisinin/piperazine	Euratesim®	FDC tablet 20/160mg FDC tablet 40/320mg †
Guilin		D-ARTEPP® Dispersible	FDC dispersible tablet 20/160mg FDC dispersible tablet 40/320mg †
Guilin	Artesunate + sulfadoxine/pyrimethamine	ARTECOSPE®	Tablet 50mg + FDC tablet 25/500mg †
Shin Poong	Pyronaridine/Artesunate	Pyramax®	Oral granules 60/20mg †
Pre-referral treatment severe malaria			
Guilin/Ipca	Injectable Artesunate	Artesun® Larinate®	(Vial + Ampoule); 60mg/vial
Cipla/ Strides	Rectal Artesunate		Rectal capsule 100mg
Seasonal malaria chemoprevention (SMC)			
Guilin	Sulfadoxine/pyrimethamine + amodiaquine	SPAQ-CO™ Dispersible	FDC dispersible tablet 25/500mg + dispersible tablet 153mg FDC dispersible tablet 12.5/250mg + dispersible tablet 76.5mg †

* This is not an exhaustive list. Data was collected and verified using data provided by companies and publicly available data.

**The focus on WHO Prequalified medicine means that local companies that are producing anti-malarial medicines and selling them in the local market are not included, as well as other manufacturers of these medicines.

***While not identified as a recommended treatment in the 2015 WHO Malaria Treatment Guideline, the WHO issued a statement in 2019 that "artesunate- pyronaridine can be considered a safe and efficacious artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas."

† Also available in higher dose tablet form.

efficacy, and allows for international procurement and accelerates registration in countries. The majority of the ACTs listed in table 5 are available in a paediatric dose, either as a fixed-dose combination (FDC) low-dose tablet, a dispersible tablet or as oral granules. Additionally, there are child-friendly formulations available of pre-referral treatments for severe malaria and seasonal malaria chemoprevention. Importantly, there are no treatments currently available for infants that weigh below 5kg — meaning low-weight or malnourished babies are the most vulnerable without optimal treatments. It is important that companies fill this crucial gap in the market. Further, due to the high prevalence of S&F medicines,

companies should work with procurers and international organisations to combat the issue, including the reporting of identified cases to national authorities and WHO Rapid Alert.

FIGURE 5 The majority of products are registered in less than 30 LMICs

This figure demonstrates how many recommended malaria products are registered in low- and middle-income countries (LMICs).

Novartis	artemether/lumefantrine (Coartem® Dispersible)
Sanofi	artesunate/amodiaquine (ASAQ® Winthrop)
Guilin	Injectible artesunate (Artesun®)
Alfa Sigma	dihydroartemisinin/piperaquine (Euratesim®)
Guilin	dihydroartemisinin/piperaquine (D-ARTEPP® Dispersible)
Guilin	artesunate/amodiaquine (ASUAQ®)
Shin Poong	pyronaridine/artesunate (Pyramax®)
Cipla and Strides	artesunate rectal capsules (ARC)
Guilin	sulfadoxine-pyrimethamine/amodiaquine (SPAQ-CO™ Dispersible)
Cipla	artesunate/mefloquine

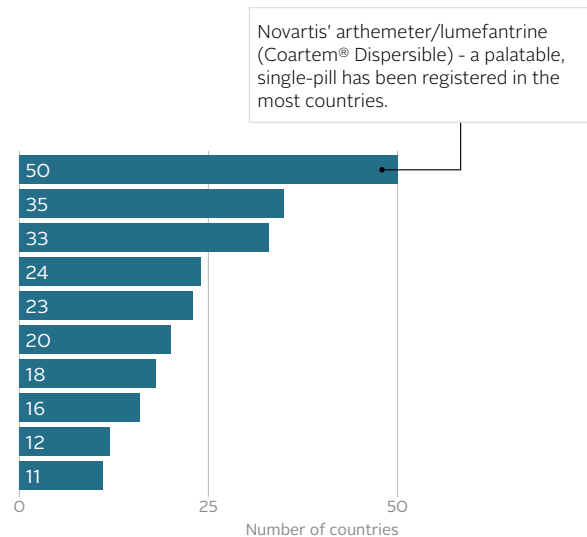
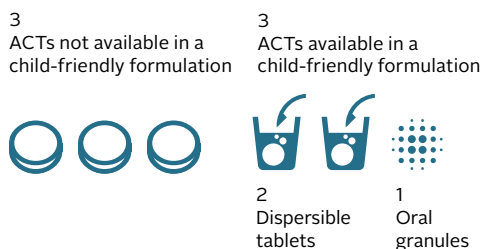


FIGURE 6 Half of the recommended antimalarials are available in a child-friendly formulation

This figure shows which WHO recommended ACTs for the treatment of *P. falciparum* are available in a child-friendly formulation, taking into account the needs of children and infants who cannot swallow tablets or hold down bitter syrups. Three out of the six recommended ACTs are available in a dispersible or granular form.



MALARIA - R&D INSIGHT

What new antimalarials are in development for children?

There are approximately 52 projects in the global malaria pipeline, including 14 approved. Of the projects in the pipeline, 10 projects, including five approved, are specifically targeting the paediatric population through the development of a paediatric indication and/or formulation. The growing attention to malaria over the past decades, through funding and development partnerships, has resulted in the increased development of child-friendly formulations of antimalarials.

One novel treatment in the paediatric pipeline

While just a snapshot of the global malaria pipeline, table 6 reflects the projects that take the specific needs of children into consideration. Notably, there is one novel treatment in the paediatric pipeline, KAF156/lumefantrine, being developed by Novartis and MMV. In addition to treatments for *P. falciparum*, there are two paediatric projects to treat malaria caused by *P. vivax*, tafenoquine by GSK and MMV and primaquine by Sanofi. Given the fact that children are disproportionately affected by this disease, companies must ensure that their projects, especially those with novel mechanisms of action, take the specific needs of children into account and ensure rapid access to child-friendly formulations, once safety and efficiency are established.

WHAT VACCINES ARE IN THE PIPELINE?

There are several groups around the world who are developing targets and vaccines for preventing malaria. The Malaria Vaccine Initiative, for example, reports working on a total of six vaccines in clinical development, targeting different age groups. GSK is involved in all six vaccine projects. Five of the six projects involve the RTS,S/ASo1 vaccine against *P. falciparum*. Of these, one project is for paediatric indication and was introduced in a pilot programme in selected areas of Ghana, Kenya and Malawi. The Malaria Vaccine Implementation Programme (MVIP) is funded by Gavi, the Vaccine Alliance, the Global Fund and Unitaid and is a country-led, WHO-coordinated initiative to assess the feasibility, impact and safety of RTS,S/ASo1 in routine implementation. GSK has stated a commitment to donate up to 10 million doses and are undertaking additional post-approval pharmacovigilance, effectiveness and impact studies. GSK is also working with WHO and PATH, Gavi, the Vaccine Alliance, and other potential funders to address the supply of the vaccine for a potential broader implementation beyond the pilot.

TABLE 6 **What is in the paediatric malaria pipeline?**

This table* provides a snapshot of companies' R&D pipelines for specific malaria treatments tailored for infants, children and adolescents.**

MEDICINES

Company	Phase I	Phase II	Phase III	Approval	Other
GSK			Tafenoquine - <i>P. vivax</i> Age: 6 months - 15 years - Dispersible tablet - Partner: MMV		
Novartis		KAF156/lumefantrine • Novel - <i>P. falciparum</i> malaria - Age: >2 years - FDC dispersible tablet - Partner: MMV	Artemether/lumefantrine - <i>P. falciparum</i> malaria- Weight:<5kg - FDC dis- persible tablet - Partner: MMV		
Alfasigma			Dihydroartemisinin- piperaquine (DHA-PQP) - <i>P. falciparum</i> malaria - FDC dispersible tablet - Partner: MMV		
Sanofi					Primaquine - <i>P. vivax</i> malaria - Age: unknown - Dispersible tablet

One novel project in development for children by Novartis and MMV.

* This table excludes five paediatric projects that have been approved

** This is not an exhaustive list. Data was collected and verified using data provided by companies and publicly available data

MALARIA - ENSURING ACCESS

Ensuring broad access to paediatric antimalarials

While developing child-friendly antimalarial treatments, companies can consider access early in the development process. Nearly all projects in the paediatric pipeline are co-developed with the Medicines for Malaria Venture (MMV). Such partnerships help bolster access and appropriate use, as they tend to set standards for product characteristics, including dosing, palatability and efficiency targets, as well as for access clauses. Furthermore, MMV promotes responsible use and

engages in education and training activities for healthcare professionals and caregivers. In addition to partnerships, companies can take a number of steps to ensure wide availability and accessibility of their products such as equitable pricing, non-exclusivity, broad registration and sustainable supply. Table 7 demonstrates some examples of the access strategies companies have applied to their paediatric antimalarial products on the market and/or projects in the pipeline.

TABLE 7 Steps are taken by companies and their partners to ensure access

This table provides examples of access strategies that companies and partners apply to paediatric malaria products on the market or projects in the pipeline.

Access strategies	Example
Registration	Novartis has registered artemether/lumefantrine (Coartem® Dispersible) in over 50 countries.
Equitable pricing strategy	Sanofi has an equitable pricing strategy in place for artesunate/amodiaquine (ASAQ Winthrop®) that takes into account a payer's ability to pay by considering socioeconomic factors. Further, Sanofi's artesunate/amodiaquine (ASAQ Winthrop®) for children is available at 50 cents, for partners such as the Global Fund, WHO and MSF. This is in general the lowest-priced fixed-dose ACT combination.
Ensuring adequate supply	Novartis engages with primary and local healthcare facilities to align supply and demand forecasting for artemether/lumefantrine (Coartem® Dispersible).
Non-exclusivity	A non-exclusivity agreement between DNDi and Sanofi for artesunate/amodiaquine (ASAQ Winthrop®) allowed for increased access and subsequent technology transfer to the pharmaceutical company Zenufa in Tanzania, which can lead to improved supply.
Access through partnerships	Generic medicine manufacturer Cipla partnered with product development organisation DNDi to develop artesunate/mefloquine fixed-dose combination tablets.

MALARIA - CASE STUDIES

How companies and organisations are working to improve access to antimalarials for children

Expanding the availability of a truly child-friendly antimalarial

MMV, NOVARTIS

Since 2009, steps have been made to improve access to dispersible artemether/lumefantrine (Coartem® Dispersible) - a palatable, single pill for the treatment of malaria in children.

ACTs for Children

In 2000, the first fixed-dose artemisinin-based combination therapy (ACT) for adults was brought to the market by Novartis —artemether/lumefantrine (Coartem®). Yet until 2009, no quality-approved child-friendly ACT existed, even though infants and children under the age of five are predominantly affected by malaria.

Answering calls for 'child-size' medicines

In 2007, seven years after the adult formulation was marketed, WHO and UNICEF announced the initiative 'Make Medicines Child Size' to improve access to better medicines for children. Responding to this call, Novartis and the Medicines for Malaria Venture (MMV) teamed up to develop a child-friendly version of artemether/lumefantrine, in the form of a dispersible and flavour-masked formulation.

Approved in 2009, Coartem® Dispersible was found to be highly effective for children, achieving a 98% clinical cure rate in a large study involving several African countries.¹⁷ Its palatable taste and cost for public-sector buyers have helped facilitate the uptake of this ACT for the treatment of malaria in children.¹⁸ To date, 390 million treatments of Coartem® Dispersible have been distributed in more than 50 countries.¹⁸

Making Coartem® Dispersible widely available

In the 2018 Access to Medicine Index, Novartis reported to have an inter- and intra-country pricing strategy, making Coartem® available at USD 0.38 for its youngest patients.¹⁹ In addition to Novartis, five manufacturers have received a WHO prequalification and a further three are currently under review. In early 2020, the Global Fund pooled procurement price for the lowest dose artemether/lumefantrine dispersible for children was reported at USD 0.28. In part, Novartis' challenge to compete with this low price due to generic competitors has led to the steady decline in Global Fund's allocation of Novartis' artemether/lumefantrine dispersible (Coartem® Dispersible).

Since the approval of Coartem® for both adults and children, Novartis is currently developing a version of artemether/

lumefantrine for children under 5kg. If successful, this will be the first antimalarial product approved for neonates and children under 5kg.

Securing the supply of ARC for severe malaria

CIPLA, MMV AND STRIDE PHARMA

A collaborative effort aims to improve the availability of high-quality artesunate rectal capsules, used for the treatment of severe malaria.

What is ARC?

Injectable artesunate (Inj AS) is administered intravenously for the treatment of severe malaria. Yet when patients do not have immediate access to injectable artesunate, WHO recommends the use of artesunate rectal capsules (ARC) for the pre-referral management of severe illness prior to patient transport to higher level care centers that can administer injectable artesunate. However, the lack of quality-assured ARC products on the market has hindered widespread availability, forcing malaria-endemic countries to allow poor-quality treatments that do not meet international standards onto the market.

Making ARC available

To ensure the continuous supply of ARC, MMV collaborated with Cipla and Strides to develop high-quality ARC and guarantee their access, by submitting products through WHO's prequalification process. This process allows for UN procurement and accelerated registration in countries with weak national regulatory authorities. The collaboration was formed as part of the Unitaid-funded project 'Improving Severe Malaria Outcomes' aimed at increasing the availability of injectable artesunate.

With funding from MMV, Transaid, Health Partners Zambia (HPZ), Development Data and Disacare started an access to severe malaria care-and-intervention in Zambia using ARCs at the community level through the MaMaZ Against Malaria (MAM) project. The project aims to address the lack of access to quality severe malaria treatments and case management in the Serenje District, Zambia, which has high malaria prevalence rates.²⁰

The impact of WHO prequalification on ARC

In 2018, ARC products developed by both Cipla and Strides secured WHO prequalification. It is estimated that over 80% of procured ARC are now WHO prequalified.²¹

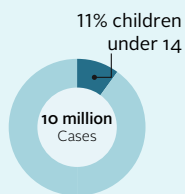
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Tuberculosis in children: underdiagnosed and undertreated

AT A GLANCE



1.1 million children are infected each year

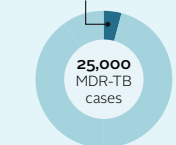
11% of all TB cases are children under the age of 14.



Children under 5 are most at risk

Up to 80% of child-TB deaths are children under the age of five.

4% get diagnosed and treated



Multidrug-resistant TB is hugely undertreated

Only 3-4% of MDR-TB cases in children are diagnosed and treated, resulting in thousands of deaths annually.

Tuberculosis (TB) is currently the leading cause of death from a single infectious agent and is one of the top ten causes of death globally.¹ In 2018, an estimated 10 million cases were reported and a total of 1.5 million deaths occurred. Children represent an estimated 11% of all TB cases, as at least 11 million children under the age of 14 have TB each year.¹ Almost 80% of these cases occur in the 30 ‘High Burden Countries (HBCs)’ – countries that have been acknowledged as shouldering the greatest share of the global TB burden.¹

Studies have estimated that 80% of children who died from TB were under the age of five – making TB one of the top 10 causes of paediatric deaths.²

The threat of drug-resistance

Compounding these alarming numbers is the challenge of drug resistance – specifically, multi-drug resistant tuberculosis (MDR-TB). MDR-TB is a form of TB which does not respond to the recommended first-line treatments, isoniazid and rifampicin – the two most potent TB treatments. Further, extensive drug resistant TB (XDR-TB) is a type of MDR-TB that is also resistant to three or more second-line treatments. Drug-susceptible TB, however, means that TB can be effectively treated with the first-line treatment regimen when used appropriately. Each year, approximately 25,000 children fall ill with MDR-TB. Of these, only 3-4% are diagnosed and treated and consequently approximately 21% of children with MDR-TB likely die.³

Few incentives, few options

Despite the significant burden of MDR-TB among children, the market size is small with little commercial incentive, exacerbated by the uncertainties over patient numbers and the inability to correctly diagnose children in resource limited settings. This low-volume/low-profit market has proven to be a disincentive for pharmaceutical companies to invest in developing TB treatments, let alone

treatments for MDR-TB. What's more, additional clinical studies and even further investments are needed to establish safety in children and develop appropriate child formulations.⁴ In turn, few paediatric treatments for MDR-TB exist, leaving many children continually at risk as they turn to adult formulations for treatment. Yet even for the treatment of adults, the success rate with the existing treatment regimens is low.¹

When parents and healthcare providers have to resort to manipulating or administering adult formulations, this increases the risk of inadequate dosing, and the subsequent probability of developing resistance. Splitting TB pills also removes coatings which mask bitterness, making palatability and therefore administration very difficult. Further, MDR-TB regimens require approximately seven different types of pills and/or liquids combined, sometimes with different modes of administration, as well as lengthy treatment regimens that can last as long as 18 months, creating additional adherence challenges.⁵

A MAJOR CHALLENGE IN CHILDHOOD TB MANAGEMENT IS DIAGNOSIS

With existing diagnostic tools, it is difficult to determine whether a child has drug-resistant TB. Children usually cannot spontaneously produce sputum – the specimen needed for analysis – to confirm TB infection through a bacteriological test, also referred to as the diagnostic ‘gold standard’.

Only 30% of diagnosed children are confirmed through this approach.⁶ Consequently, the diagnosis of TB in children relies mostly on non-specific clinical symptoms, supported by evidence from TB contacts and radiographs of the chest. Existing diagnostic tests for TB in children have shortcomings and are often unavailable in high-burden countries where children often access general (child) health services where capacity to recognise and diagnose TB is limited. The development of affordable, reliable diagnostic tests for children in low-resource settings will be a crucial step in combating TB.

A unified approach

Under such market conditions, it is unlikely that this issue will change. High-levels of intervention are needed to establish clear priorities and incentives that can help foster the development of treatments and their availability. With such measures, companies are more likely to take action. Coordination with governments, multilateral organisations like the World Health Organization (WHO), donors, regulators and the pharmaceutical industry is required for this to happen.

The role for pharma companies

Pharmaceutical companies have a role to play in enabling the availability and accessibility of child-friendly formulations for the prevention and treatment of MDR-TB. Existing MDR-TB treatment regimens are limited in their effectiveness, showing a need to develop new, more effective MDR-TB treatments for both the adult and paediatric populations. The availability of new and existing treatments for younger children who are not yet eligible for the adult dosage and formulation must be ensured.

Effective MDR-TB treatments that are easy to administer and palatable are specifically needed so adherence in children can be facilitated. Solid oral formulations such as granules, pellets, dispersible, heat stable, chewable, taste-masked, and scored tablets can help overcome the current challenges associated with adherence issues. Notably, MDR-TB treatment require a combination of various medicines, some of which are under patent by different companies. In order to develop safe and effective treatments, R&D collaboration among companies and investment is needed, alongside clear recommendations on dosing.

TUBERCULOSIS - MARKET INSIGHT

What TB treatments are on the market that are suitable for children?

According to WHO guidelines, children with drug-susceptible TB (DS-TB) should be treated with a regimen of a combination of TB treatments including isoniazid, rifampicin, pyrazinamide. In settings with high prevalence of HIV, treatments should also include ethambutol.⁷ The dosing of these treatments depends on the body weight of the child. In 2010, WHO updated its dosing guideline for paediatric DS-TB treatments, but until recently there were no existing formulations that matched the new dose recommendations.⁸ Currently, few companies are marketing paediatric treatment options for DS-TB, in both a single and FDC formulation, that correspond to these updated guidelines. Yet, paediatric treatments for DS-TB do exist, serving a large proportion of the market and are outlined in table 8.

For multidrug resistant (MDR-TB), there are no established treatment guidelines due to the lack of available data and regimens with high success rates. However, for both adults and children, WHO recommends a combination of multiple TB-treatments, including novel treatments such as Johnson & Johnson's bedaquiline (Sirturo®), Otsuka's delamanid (Delyba™) and pretomanid (only recommended for XDR-TB under operational research settings*) developed by the TB Alliance and marketed by Mylan.⁵ Of these three, bedaquiline (Sirturo®) and delamanid (Delyba™) are approved for the use in children, as displayed in table 8.

Two products for MDR-TB offer a lower risk of resistance
There are multiple paediatric FDCs and single treatment options for DS-TB that come in accurate dosing and appropriate formulations when compared to MDR-TB. Yet, there are still gaps in optimal DS-TB treatment options for children weighing less than 5kg.

When it comes to MDR-TB treatments, Johnson & Johnson's bedaquiline (Sirturo®) and Otsuka's delamanid (Delyba™) are the only two novel treatments approved in the last 50 years for the treatment of MDR-TB in patients under the age of 18. They have been conditionally approved for use in children above the age of five and six, respectively. These novel treatments offer the chance to remain effective for longer if used responsibly, because the compounds are not related to existing first-line agents, minimising the risk of cross-resistance. Bedaquiline (Sirturo®) is the only treatment available in a formulation that is suitable for young children and children who cannot swallow pills.

* Revised guidelines expected shortly

TABLE 8 Which companies are making child-friendly TB treatments available on the market?

This table looks at some examples of companies that are making treatments for DS-TB and MDR-TB available on the market, looking at a selection of formulations available for children. The table does not include all MDR-TB treatment options on the market but specifically looks at the most recent novel TB treatments, as they are the most promising in addressing MDR-TB. In the case of DS-TB, the table highlights treatments that take into account specific paediatric needs, such as dispersible tablets and FDCs, as these are more likely to tackle adherence issues across age and weight bands. While not mentioned in the table, these treatments are also available in higher dosage and non-dispersible forms that can also be used for certain ages in the paediatric population.

Companies	Treatment	Formulation
	DS-TB	
Lupin; Macleods	isoniazid/rifampicin	50/75mg fixed-dose combination dispersible tablet
Macleods	isoniazid/pyrazinamide/rifampicin	50/150/75mg fixed-dose combination dispersible tablet
Micro Labs	isoniazid	50mg; 100mg dispersible tablet
Macleods	ethambutol	100mg dispersible tablet
Macleods; Micro Labs	pyrazinamide	150mg dispersible tablet
	MDR/XDR-TB	
Johnson & Johnson	bedaquiline (Sirturo®)	20mg dispersible tablet
Otsuka	delamanid (Delyba™)	50mg tablet

The recommended TB treatments are available for children weighing >5kg in a fixed-dose combination dispersible tablet

Bedaquiline (Sirturo®) and delamanid (Delyba®) are approved for children over the age of 5 and 6, respectively, for the treatment of MDR-TB. WHO guidelines recommend the use of delamanid (Delyba®) for children over the age of 3.

TUBERCULOSIS - R&D INSIGHT

Which companies are developing TB treatments for children?

As current TB treatments become less effective due to resistance, the need to develop new treatments grows more pressing. While progress has been made in the development of new TB treatments for adults such as such bedaquiline (Sirturo®), pretomanid and delamanid (Delyba™), children are often overlooked in this area. To help accelerate the development of appropriate paediatric formulations and reach an evidence-based consensus regarding priority TB treatments, the first WHO-led Paediatric Antituberculosis Drug Optimization Meeting (PADO-TB 1) was held in February 2019. The meeting was convened to build on the experience of the HIV PADO meetings and address the UN General Assembly High Level Meeting on TB targets for treatment and prevention in children, which was held in 2018.⁹ Representatives from high-burden countries and experts from the Global Fund, Unitaid, WHO, MPP, CHAI, the Union, Médecins Sans Frontières (MSF), Global Drug Facility (GDF) and various academic institutions, amongst others, decided on a list of short and long-term priority areas for drug development for children. This section looks at which paediatric products are currently in development, if the industry is actively addressing the identified PADO-TB 1 priorities and how they are addressing future accessibility.

PRIORITISING UNMET NEEDS - PADO PRIORITIES

The WHO-led PADO group identifies priorities for the development of paediatric anti-TB drugs and formulations.[‡]

Short-term (all dispersible scored)	Watch-List
DS-TB	DS- TB
<ul style="list-style-type: none"> Rifampicin Rifapentine 	<ul style="list-style-type: none"> Isoniazid/pyrazinamide/rifampicin/levofloxacin FDC Isoniazid/pyrazinamide/rifampicin/ethambutol FDC
MDR-TB	MDR-TB
<ul style="list-style-type: none"> Bedaquiline † Clofazimine Delamanid Linezolid Pretomanid 	<ul style="list-style-type: none"> Telacebec (Q203) Sutezolid (PNU-100480) Delpazolid (LCB01-0371) Moxifloxacin - taste masked

‡ Preventative treatments are not included.

FIGURE 7 Three projects in the TB paediatric pipeline target PADO priorities*

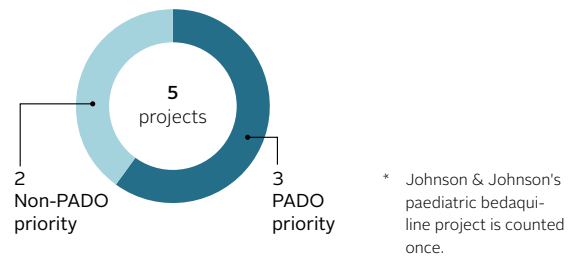


TABLE 9 What is in the paediatric TB pipeline?

The table below provides a breakdown of companies that are developing paediatric DS-TB and MDR-TB medicines and identifies those that are listed on the PADO priority list.*

Company	Phase I	Phase II	Phase III	Approval	Other
Johnson & Johnson**		Bedaquiline (Sirturo®) - MDR-TB - Age: 2-5 years - Dispersible tablet - ☐			
Macleods		Bedaquiline (Sirturo®) - MDR-TB - Age: 0-2 years - Dispersible tablet - ☐ ***			Linezolid – MDR-TB - Age: Paediatric, specific age unknown - 150mg Dispersible tablets - ☐
Otsuka		Delamanid (Delyba™) - MDR-TB - Age: 0-6 years - 25mg Dispersible tablet - ☐			Isoniazid – MDR-TB - Age: Paediatric, specific age unknown - 100 mg Dispersible tablets
Sanofi		Rifapentine/isoniazid paediatric – Preventative treatment - Age: Paediatric, specific age unknown - FDC dispersible formulation			

☐ Listed on the PADO-TB 1 priority list

* This is not an exhaustive presentation of the TB pipeline.
 ** Johnson & Johnson has one phase II project to establish the safety, tolerability and pharmacokinetic profile of bedaquiline in combination with other second-line agents for the treatment of TB in children/adolescents. This study consists of four cohorts. Two cohorts of 12-18 years and 5-12 years, were approved in 2019 and 2020, respectively.

*** Phase II study, cohort not yet enrolled.

† Bedaquiline (Sirturo®) developed by Johnson & Johnson was approved by the FDA in May 2020.

Few projects aimed at children in the pipeline

Overall, the pipeline for paediatric TB treatments is small, including five child-friendly formulations of existing TB medicines, three of which target MDR-TB. Of these five projects, one project is to establish accurate dosages of bedaquiline (Sirturo®) across different age groups for the treatment of MDR-TB. Three projects are identified as PADO-TB 1 priorities including the two paediatric bedaquiline (Sirturo®) projects by Johnson & Johnson; paediatric delamanid (Delyba™) by Otsuka; and paediatric linezolid by Macleods. Otsuka is expecting approval by the European Medicines Agency (EMA) for the expanded paediatric indication of delamanid (Delyba™) in the second half of 2020 and approval of the 25mg dispersible tablet in 2021. Further, the TB Alliance completed a Phase I pharmacokinetics study of pretomanid in 2020 and plans to start dosing paediatric patients in 2021.

Novel paediatric projects

There are two projects in development that are paediatric adaptations of novel TB medicines, bedaquiline (Sirturo®) and delamanid (Delyba™) which are also listed on the PADO-TB 1 priority list. In addition, four companies (LegoChem, Otsuka, Qurient and Sequella) are currently developing four novel late-stage projects targeting MDR-TB in adults that are also identified on the PADO-TB 1 priority list.¹³ Once these products have been approved for sale by the relevant regulatory authority, regulatory obligations will require the companies to study the product in children. However, significant delays often occur between the approval of the adult formulation and children formulations, partially due to waivers or deferral requests by companies and lack of incentives to begin the process prior to approval. Companies should start ahead and refrain from submitting deferrals in order to shorten such delays.

These novel late-stage projects are:

- Otsuka: OPC-167832
- Sequella Inc., & TB-Alliance: Sutezolid (PNU-100480)
- Qurient Co., Ltd: Telacebec (Q203)
- LegoChem Biosciences, Inc: Delpazolid (LCB01-0371)

WHAT VACCINES ARE IN THE PIPELINE?

A total of 14 vaccines are in clinical development for the prevention of TB.¹⁰ Of these 14, two are being developed for neonates and infants and one paediatric vaccine project is in pre-clinical development. Pharmaceutical companies are involved in seven of the 14 vaccine projects in clinical development. One example of a vaccine in development (albeit not yet designed for use in children) is the TB prophylactic vaccine M72/AS01 being developed by GSK. In January 2020, GSK announced that it will license the vaccine to the Bill & Melinda Gates Medical Research Institute for the development and potential use of M72/AS01 in low-income countries affected with a high burden of TB.

TUBERCULOSIS - ENSURING ACCESS

How are companies ensuring access to their current and future treatments for children?

Some of the companies in the pipeline are taking steps to ensure their TB products will be accessible once approved. For example, GSK has licensed its tuberculosis vaccine candidate to the Bill & Melinda Gates Medical Research Institute for continued development. Collaborating with partners that have a clear access agenda is one way to ensure wide access upon approval. Further, Johnson & Johnson has committed to file paediatric bedaquiline (Sirturo®) for registration in the countries where it conducts clinical trials, upon approval.

TABLE 10 What access strategies are companies deploying?

This table provides examples of access strategies that companies and partners apply to their paediatric TB products on the market or projects in the pipeline.

Access strategies	Example of company practice
Registration	Johnson & Johnson registered bedaquiline (Sirturo®) 100mg in 28 low- and middle-income countries.
Affordability	Developed by the TB Alliance and commercialised by Macleods, the FDCs isoniazid/pyrazinamide/rifampicin and isoniazid/rifampicin dispersible tablets were introduced at an average price of USD 15.54 for a full six-month treatment course, which falls below the median price of older paediatric treatments.
Ensuring adequate supply	Since its 2016 agreement with Global Drug Facility (GDF), Otsuka has supplied delamanid (Delyba™) to 89 countries, including 30 with a high burden of multidrug-resistant TB (MDR-TB).
Voluntary licence	In 2019, Otsuka and Mylan announced a licence agreement to commercialise delamanid (Delyba™) for MDR-TB in High-Burden Countries. Otsuka is currently in the process of a technology transfer to Mylan to enable generic manufacturing of delamanid.
WHO-Prequalification	All products displayed in table 8 are WHO-prequalified and/or approved by the Expert Review Panel of the Global Fund, allowing for UN and Global Fund procurement and accelerating the registration process in countries with weak national regulatory authorities.
Access through partnerships	Through the STEP-TB project, the FDCs isoniazid/pyrazinamide/rifampicin and isoniazid/rifampicin dispersible tablets were developed by the TB Alliance and commercialised by Macleods and Lupin. Beyond drug development, the project focused on procurement and regulatory pathways to help ensure the product's accessibility.

TUBERCULOSIS - CASE STUDIES

How companies and organisations are working to develop optimal paediatric TB treatments

Addressing the unmet need for new paediatric TB treatments

MACLEODS, LUPIN, TB ALLIANCE, UNITAID, USAID, WHO

What: Unitaid and USAID in partnership with TB Alliance, the WHO Global TB Programme, and the Department of Essential Medicines and Health Products, launched the STEP-TB project to overcome obstacles in DS-TB paediatric drug-development.

Context: Commercial incentives underpinning the TB market are weak, yet new mechanisms can help encourage the development and availability of treatments.

The need for new paediatric TB formulations

Until recently, paediatric TB programmes were largely dependent on older treatment methods geared mainly towards adults that involved the use of bitter-tasting pills or dispersible tablets in outdated, incorrect dosages.⁸ Often, healthcare practitioners and caregivers would need to break or crush the pills and estimate the correct dosage for their paediatric patients, usually resulting in imprecise dosing.

Developing pathways for childhood TB treatments

To help catalyse the development of new treatments and address the lack of access to existing products, Unitaid in partnership with TB alliance and WHO, launched the Speeding Treatments to End Paediatric Tuberculosis (STEP-TB) project in August 2013. The programme, with an initial investment of USD 16.7 million, received additional support from USAID.⁸

Building on existing treatment guidelines, STEP-TB successfully identified two pharmaceutical companies, Lupin and Macleods, to develop and commercialise two fixed-dosed combination treatments for paediatric DS-TB (isoniazid/pyrazinamide /rifampicin 50/150/75mg and isoniazid/rifampicin 50/75mg) and gain WHO prequalification. Conditions included manufacturing at production scale and ensuring affordability through a global mechanism. What helped achieve this was the absence of patents and established safety of the individual treatments, allowing for the development of a fixed-dose combination. Additionally, TB Alliance offered its expertise throughout the product development and commercialisation process and helped to identify the current and future demand as part of the programme.

Market impact

By identifying market barriers and engaging in innovative industry collaborations, STEP-TB aimed to provide manufacturers with an incentive to develop properly dosed

and affordable paediatric medicines.⁸ Macleods was the first pharmaceutical company that brought the two fixed-dosed combinations to the market and through WHO Prequalification, in 2015 and 2017, respectively. Since then, Lupin has also begun manufacturing and selling isoniazid/rifampicin, having received a positive opinion of the Global Fund ERP and is currently pending WHO Prequalification. In total, more than one million courses of these products have been ordered in 88 countries.

Finding the right MDR-TB treatment for children

STELLENBOSCH UNIVERSITY, TB ALLIANCE, UNITAID

What: BENEFIT Kids project was developed through a grant from Unitaid to Stellenbosch University to produce and evaluate child-friendly treatments for MDR-TB

Context: Address the absence of optimal treatment options for MDR-TB in children

What is BENEFIT Kids?

In 2019, Unitaid granted Stellenbosch University USD 18.9 million to develop and evaluate child-friendly treatments for MDR-TB and assess regimens for the prevention of the disease. The project, "Better Evidence and Formulations for Improved MDR-TB Treatment for Children" (BENEFIT Kids) will run until October 2022.¹¹

How are they enabling future access?

The BENEFIT Kids project is comprised of three components. Firstly, it aims to strengthen the evidence of optimal dosing, safety, efficacy, acceptability and costs of medications for treatment and prevention of MDR-TB in children. Initially, the project will study adjusted formulations of several key MDR treatments to enable clinicians and national programmes to better treat children in the short term. New or improved generic formulations of three treatments will also be developed: linezolid, bedaquiline, and moxifloxacin. This is an important step in creating policies that can impact clinical care. Secondly, it will develop child-friendly formulations for MDR-TB treatment and preventive therapy, taking into consideration the specific needs of children. Thirdly, the project will engage in market shaping activities in order to ensure effective and sustainable roll-out.¹¹

Developing paediatric bedaquiline (Sirturo®) for a wider range of children with MDR-TB

GLOBAL DRUG FACILITY, JOHNSON & JOHNSON

What: Johnson & Johnson is developing a paediatric formulation of bedaquiline (Sirturo®) and aims to build on existing access and stewardship plans that are currently in place for the adult formulation.

Context: Bedaquiline (Sirturo®) is currently approved for children above the age of five, with a 20mg dispersible tablet approved in May 2020.

Johnson & Johnson's breakthrough medicine bedaquiline (Sirturo®) was conditionally approved by the US FDA in December 2012 through fast-track accelerated approval as the first innovative treatment for multi-drug resistant tuberculosis in 40 years. In 2019, bedaquiline (Sirturo®) was approved by the FDA as part of a combination therapy for eligible MDR-TB patients aged 12 years and above. In May 2020, the FDA approved bedaquiline (Sirturo®) 20mg dispersible tablet for children above the age of five. This approval marked the first lower-dose and child-friendly formulation of bedaquiline (Sirturo®) since its approval in 2012.

Developing bedaquiline (Sirturo®) for children across all ages and weight bands

Currently, Johnson & Johnson is developing bedaquiline (Sirturo®) for use across a wider range of age and weight bands. In addition to the newly approved paediatric formulation of bedaquiline (Sirturo®) in the form of a 20mg dispersible tablet for children aged five to 12, a clinical study is currently on-going to evaluate the dispersible formulation and paediatric dosing in children aged two to four years old. Once data is available, Johnson & Johnson has committed to enrol children from zero to two years old.

Expanding existing access and stewardship plans to paediatric bedaquiline (Sirturo®)

By planning ahead while a product is in clinical development – pharmaceutical companies can provide swifter access to new products at affordable prices and have measures in place from day one to ensure new products are used prudently (known as stewardship).

Johnson & Johnson aims to ensure the availability and accessibility of bedaquiline (Sirturo®) through a number of routes: equitable tiered pricing; purchasing via the Global Drug Facility; and through institutional purchasing by international NGOs. The lower tiered price for treatment is available

at a price of USD 400 for a six-month course.¹² The company has committed to build on its existing access pathways that are currently in place for the adult formulation of bedaquiline and apply these to the paediatric formulations upon approval, including ensuring accessibility through the Global Drug Facility. Further, to promote the likelihood of the product being used appropriately and remaining effective over time, current stewardship initiatives will also be expanded to the paediatric formulations.

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