MSF Access Campaign
Technical Brief
DECEMBER 2019

FROM GUIDELINES TO REALITY:

Accelerating access to prevention and treatment of paediatric HIV

INTRODUCTION

In 2011, UNAIDS launched the "Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive",[1] endorsed by UN member-state governments to scale up prevention of mother-to-child transmission (PMTCT) services. While this initiative saw the number of new HIV infections in children fall from 280,000 in 2010 to 160,000 in 2018,[2] the rate of decline in the past 3-4 years has plateaued, leaving the goal of only 20,000 new infections per year by 2020 far out of reach. Nine out of 10 of these children live in sub-Saharan Africa.[3] In 2018, 82% of pregnant women living with HIV globally were receiving antiretroviral therapy (ART), but wide regional variations exist, and access to ART for PMTCT ranges from 92% in eastern and southern Africa, to 53% in the Middle East and North Africa.[4] ART coverage for children living with HIV continues to lag behind – in 2018, more than half of children (54%) were still not receiving the lifesaving treatment they needed.[5]

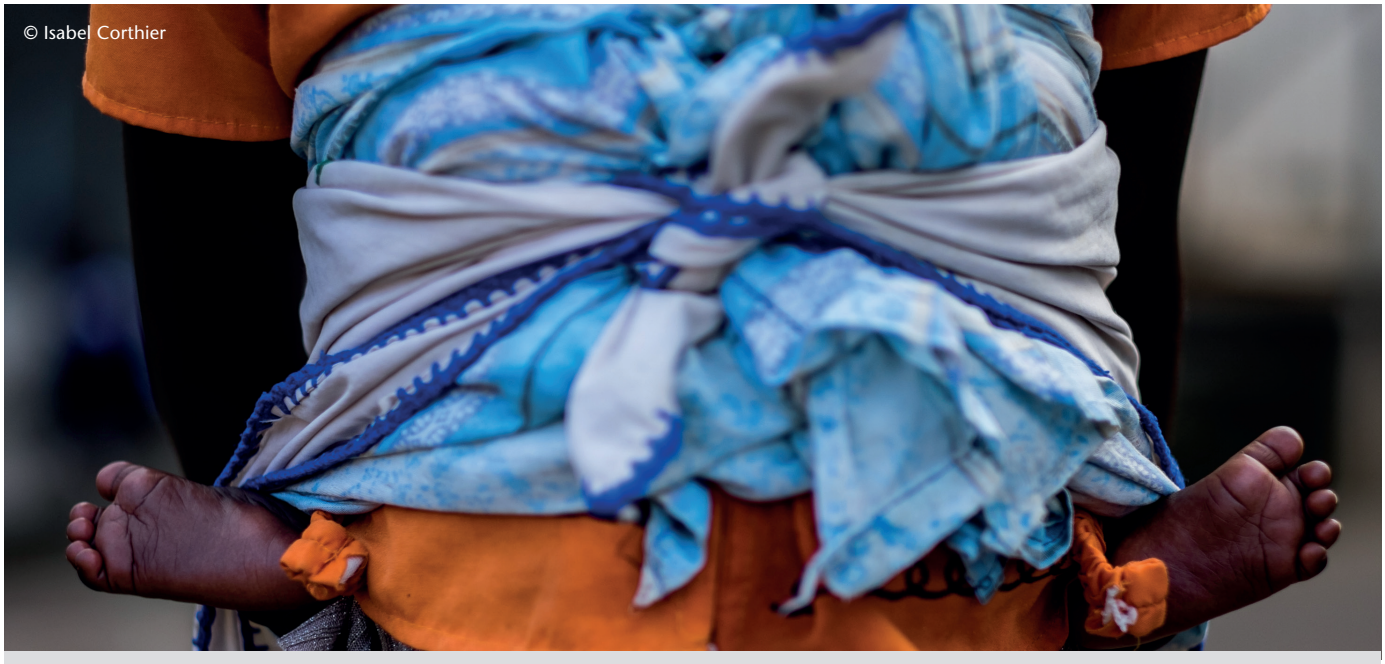
This report examines the barriers to preventing new paediatric HIV infections and to providing timely and optimal treatment where we have failed to prevent transmission.

THE FORGOTTEN PILLARS OF PMTCT

PMTCT interventions have correctly focused on timely diagnosis of women living with HIV, the provision of ART treatment to the mother and prophylaxis to the HIV-exposed infant. However, two key PMTCT pillars have received less attention: preventing infections in HIV-negative women of child-bearing age, particularly those at high risk; and helping HIV-positive women plan their families, both avoiding unwanted pregnancies through the use of effective methods of family planning, and planning pregnancy when HIV positive and virologically suppressed.

Forgotten Pillar #1: Preventing HIV infections in HIV-negative pregnant or breastfeeding women

Women of childbearing age should be assessed for their risk of HIV infection and offered pre-exposure prophylaxis (PrEP) as required. But what about HIV-negative women who are already pregnant and/or breastfeeding? A meta-analysis of data from 19 African studies estimated the pooled HIV incidence rate during pregnancy was 4.7 per 100 person-years, and 2.9 per 100 person-years during the postpartum period.[6]



Mother and child at Arua Regional Hospital, Uganda, where MSF provides HIV care.

Women who are exposed to HIV and seroconvert (to HIV-positive) during pregnancy and/or breastfeeding are at particularly high risk of transmitting the virus to the fetus or breastfeeding infant.[7]

In July 2017, the World Health Organization (WHO) issued specific guidance on the use of PrEP during pregnancy and breastfeeding.[8] This guidance outlines the use of PrEP to complement established HIV prevention strategies as part of a comprehensive package. WHO confirmed that use of PrEP with tenofovir (TDF) and lamivudine (3TC) is safe during pregnancy and breastfeeding. Women identified as high risk using a standardised risk assessment tool, including pregnant women, or those with a HIV-positive partner whose viral load (VL) is unknown or not suppressed, should be offered PrEP.

In an MSF survey of national guidelines in 12 countries where MSF provides HIV care, 10 have adopted the WHO recommendations for PrEP (Table 1), however specific guidance on the use of PrEP in pregnant and breastfeeding women is lacking. Three countries indicate use in these populations. South Africa provides detailed guidance recommending continuation of PreP in pregnancy for women already receiving it, and consideration of PreP for pregnant and breastfeeding women. Where PrEP is specifically mentioned, access to TDF/3TC is primarily through pilot projects run by non-governmental organisation (NGO) implementing partners. As most women in sub-Saharan Africa will breastfeed for up to two years, providing effective prevention strategies for women at high risk must be a priority.

Table 1: National guidelines for PrEP in pregnant and breastfeeding women

Country	PrEP recommended according to risk assessment	Specific PrEP recommendation highlighted for pregnant and breastfeeding women
CAR	Yes	No
DRC	Yes	No
Guinea	Yes	No
India	No	No
Kenya	Yes	No
Malawi	Yes	No
Mozambique	Yes	No (Pilot by NGO)
Myanmar	Yes	No
South Africa	Yes	Yes
Tajikistan	No	No
Uganda	Yes	Yes
Zimbabwe	Yes	Yes

PrEP, pre-exposure prophylaxis; CAR, Central African Republic; DRC, Democratic Republic of Congo; NGO, non-governmental organisation

Forgotten Pillar #2: Family planning

The second forgotten pillar of PMTCT is family planning. Family planning has been shown to reduce both maternal and infant mortality.[9] Family planning is not only about preventing unwanted pregnancies but also about providing the information an HIV-positive woman needs to plan pregnancies when she is well and has a suppressed viral load. Globally, 214 million women of reproductive age in developing countries who want to avoid pregnancy do not have access to effective methods of contraception (Table 2).[9] Access to these contraceptives among women living with HIV is also a challenge. Data from Malawi showed that for 69% of HIV-positive women on ART, their last pregnancy was unintended.[10] In addition, recent data from South Africa demonstrated that unintended pregnancy may predict poor outcomes among women initiating ART during pregnancy.[11]

> **"For 69% of HIV-positive women on ART, their last pregnancy was unintended."**

Table 2: Contraceptive methods and effectiveness rates[9]

Contraceptive Method	Description	Effectiveness in Preventing Pregnancy
Combined oral contraceptives (COCs)	Tablets containing estrogen and progestogen	>99% if used correctly; 92% in real-world setting
Progestogen-only pill	Tablets containing progestogen only	99% if used correctly; 90-97% in real-world setting
Implants	Small rod/capsule with progestogen only, implanted under skin in upper arm	>99%, last 3-5 years
Combined injectable contraceptive	Monthly injectable containing estrogen and progestogen	99% if used correctly; 97% in real-world setting
Progestin only injectable	Progestogen-containing injectable, every 2-3 months	
Contraceptive patch or ring	Skin patch or vaginal ring containing estrogen and progestogen	Newer products but expected to be the same as COCs
Copper-containing intrauterine device (IUD)	Small plastic device containing copper sleeves or wire, inserted into uterus	>99%, lasts up to 10 years
Levonorgestrel-containing IUD	Small plastic device inserted into uterus that releases levonorgestrel	>99%, lasts up to 5 years

Integrating sexual and reproductive health (SRH) services (including family planning) with HIV care (including ART) has long been recommended by WHO. In the 12 countries surveyed by MSF, 11 reported that this recommendation was included in national guidelines but was not systematically implemented. Women could access both services in all settings but not as a one-stop service within the ART clinic. In addition, where ART services for stable clients are provided via a differentiated model of care to reduce the frequency of clinic visits to once or twice per year (e.g. provision of fast-track services, ART clubs, community ART groups), family planning had not been adequately considered or incorporated (Table 3). In the 12 countries surveyed, various family planning options (combined oral contraceptive pills, injectables, implants) were all commonly available but with stockouts frequently reported. Access to intrauterine devices (IUDs) was less common with only six of the 12 countries surveyed where MSF works offering this option.

Table 3: Integration of family planning in ART services

Country	Family planning integration with ART recommended in national guidelines	One-stop service provided in settings where MSF supports services	Family planning systematically integrated into differentiated service delivery models for stable clients on ART
CAR	Yes	No	No
DRC	Yes	No	No
Guinea	Yes	No	No
India	Yes	No	No
Kenya	Yes	No	No
Malawi	Yes	No	No (only teen clubs in MSF sites)
Mozambique	Yes	No	No
Myanmar	No	No	No
South Africa	Yes	No	No
Tajikistan	Yes	No	No
Uganda	Yes	No	No
Zimbabwe	Yes	No	No

ART, antiretroviral therapy; CAR, Central African Republic; DRC, Democratic Republic of Congo

TREATING CHILDREN AT RISK OF OR LIVING WITH HIV

High risk, low risk – the dilemma of prophylaxis to prevent transmission

In the 2016 "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection",[12] WHO recommends that HIV programmes differentiate HIV-exposed infants into those at high or low risk of infection.[a] This should account for any incident HIV infection during pregnancy or breastfeeding, whether or not the mother is on ART, and for maternal viral suppression prior to delivery. Once classified, high-risk infants should receive prophylactic treatment with dual therapy of zidovudine (AZT) once a day and nevirapine (NVP) twice a day for the first 6 weeks of life. Breastfed infants remain at high risk and are recommended to either continue on dual therapy or with NVP alone for a further 6 weeks.

Uptake of these recommendations varies at the national level, with only seven of the countries surveyed by MSF recommending dual prophylaxis for high-risk HIV-exposed infants (Table 4). In Central African Republic (CAR), dual prophylaxis is offered at MSF-supported sites. Due to challenges in defining high-risk infants, some countries such as Mozambique and Kenya have taken a pragmatic approach and recommend dual prophylaxis for all infants for 6 weeks followed by NVP alone in breastfed infants.

[a] High-risk infants are defined as those:
- born to women with established HIV infection who have received <4 weeks of ART at time of delivery; or
- born to women with established HIV infection with viral load >1000 copies/mL in the 4 weeks before delivery, if viral load measurement is available; or
- born to women with incident HIV infection during pregnancy or breastfeeding; or
- identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Feedback from MSF clinicians highlights the challenges in identifying which infants are considered high risk, including a lack of availability of viral load and the challenges in training health workers engaged in the classification of high-risk infants. Ensuring access to both AZT and NVP syrup formulations at the right time in the right place is also a challenge in settings where supply chains are already struggling. This latter challenge is even more problematic in settings where PMTCT care is decentralised, where women do not necessarily access the healthcare system during delivery and where HIV prevalence is low.

Table 4: Dual prophylactic treatment of HIV-exposed Infants

Current National Guidelines	Dual prophylaxis (AZT and NVP) recommended in national guidelines for high-risk HIV-exposed infants
CAR	No
DRC	No
Guinea	Yes
India	No
Kenya	Yes (dual for all for 6 weeks followed by NVP alone until cessation of breast-feeding
Malawi	No
Mozambique	Yes (for all infants born to mothers with HIV)
Myanmar	Yes
South Africa	Yes
Tajikistan	Yes (or triple therapy)
Uganda	No (NVP alone for 12 weeks)
Zimbabwe	Yes

AZT, zidovudine; NVP, nevirapine; CAR, Central African Republic; DRC, Democratic Republic of Congo

These challenges are supported by a study from Harare, Zimbabwe, where dual therapy is in the national guidelines for high-risk infants.[13] Among 197 HIV-positive mothers, only 19 (10%) exposed infants could be defined as high risk, whereas the remaining 90% had inadequate information to classify them. Of these 197 live births, 93% received NVP alone, 15 had no prophylaxis status documented and one infant received dual prophylaxis. The conclusion was that health workers urgently require training both to stratify infants as high or low risk and provide the appropriate prophylaxis.

Available formulations for dual prophylaxis also have the potential to add confusion and compromise results. There is no combined AZT/NVP formulation, nor in development, and AZT alone is mainly available only as a syrup. NVP has been used for many years for prophylaxis and is available for children as dispersible tablets and syrup. The complexity of forecasting supply chain needs for access to AZT and NVP has been a challenge. Due to lack of availability of appropriate formulations, MSF and some country programmes have included in their guidelines the alternative use of adjusted doses of the dispersible fixed-dose combination (FDC) of AZT/3TC/NVP for prophylaxis. This alternative is acknowledged by WHO[14] and aligns with 2018 US guidelines, where empiric triple therapy is recommended in high-risk cases. However, as the first-line regimen transitions away from NVP-based combinations, these FDCs are also less likely to be available. Donors and national programmes must ensure appropriate medicines and formulations are available for PMTCT during transition to newer formulations.

Simplification is needed to provide a pragmatic regimen for all exposed infants that provides the best prophylaxis in settings where diagnostic tests or staff knowledge are not readily available to determine which infants are high risk. Secondly, a simplified regimen is also needed to reduce the number of formulations a national programme should provide for prevention and treatment of paediatric HIV. Harmonisation of neonatal and paediatric treatment drug regimens with exposed infant prophylaxis could provide the opportunity to reduce the number of formulations required, simplify the supply chain, simplify training of health workers who have to provide counselling to caregivers on how to use these multiple formulations, and increase the demand and volume of a treatment product adapted for children, thus incentivising manufacturers to commit to produce.

Transitioning from nevirapine as first-line treatment – where are we now?

In the July 2019 "Update of recommendations on first and second-line antiretroviral regimens",[15] WHO recommends a dolutegravir (DTG)-based antiretroviral (ARV) drug combination (DTG + abacavir [ABC] + 3TC) as the first-line treatment option for children 4 weeks to 10 years old. While WHO's ambitious guidance is welcome, its full implementation is not yet possible: DTG for children under 20 kg is still in development, and the FDC of the three ARVs does not yet exist for children.

For the most part, alternative first-line options (Table 5) have come with considerable supply constraints, and as a result nearly half of children are still taking suboptimal NVP-based treatment options.[16] However, NVP-based regimens should be phased out given that rates of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance are up to 60% in some sub-Saharan African countries,[17] which increases risks of treatment failure, opportunistic infections like tuberculosis (TB), and death. A DTG-based regimen has fewer side effects and offers the best chance to limit drug resistance, given its high genetic resistance barrier. The transition to better treatments is therefore essential and urgently needed.

In countries where MSF provides HIV treatment for children, it is generally done in collaboration with the Ministry of Health, respecting the national guidelines and often using ARVs supplied by the national programme. Overall, across 10 of the MSF countries surveyed where data were available, 82% of children under the age of 14 years were on NNRTI-based regimens (NVP or efavirenz [EFV]). While unsurprising that only a few countries have started using DTG-based treatment (for older children), only 11% are on lopinavir/ritonavir (LPV/r)-based first-line treatment, regardless of national guidelines.

Table 5 highlights the updated 2019 WHO treatment guidelines for infants and children[15] and shows that of the preferred and alternative regimens, only the alternative treatment option for neonates (AZT+3TC+NVP in syrups) is readily available for procurement. (See Annex 1 for detailed information on supply constraints and pricing.) While many countries are in the process of updating guidelines to include DTG for children, Table 6 shows the resultant wide variety of regimens found in national guidelines across the surveyed countries. As of Q3 2019, the ARV Procurement Working Group reports that Cipla and Mylan have scaled up their production of paediatric LPV/r pellet and granule formulations, such that the capacity constraints that have to date limited the supply and implementation of these products should improve considerably in 2020.[18]

The complexity of forecasting multiple paediatric ARV regimens, updating national guidelines, ensuring usage of existing supply before transitioning, changing dosages and formulations as children grow, and continuing to train health workers and caregivers on new combinations of syrups, pellets, granules and dispersible tablets are just a few of the challenges in treating neonates and children with HIV. Simplification of treatment options and continued coordination of the supply of transitioning ARV regimens as new options come into the market are essential to ensuring treatment for children who need it. Although multiple companies are developing paediatric formulations of DTG, drug development takes time, and delays are not uncommon. Given the current rates of resistance to NNRTIs like NVP, countries must transition urgently away from NVP to better options like LPV/r.

Table 5: 2019 WHO-recommended HIV treatment regimens for children

Regimen Type	Neonates	Children
Preferred	**AZT* + 3TC* + RAL†**	**ABC/3TC + DTG‡**
Alternative	**AZT* + 3TC* + NVP***	**ABC/3TC + LPV/r** **ABC/3TC + RAL†** **TAF/XTC + DTG**
Special circumstances§	**AZT* + 3TC* + LPV/r***	**ABC/3TC + EFV§§** **ABC/3TC + NVP** **AZT/3TC + EFV§§** **AZT/3TC + LPV/r** **AZT/3TC/NVP** **AZT/3TC + RAL**

3TC, lamivudine; ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; TAF, tenofovir alafenamide; XTC, either 3TC or FTC (emtricitabine), considered as interchangeable in ARV regimens.

A "+" denotes combination of separate medicines. A "/" denotes availability in fixed-dose combinations (FDCs).

* Syrup formulation
† For the shortest time possible, until a solid formulation of LPV/r or DTG can be used
‡ DTG is only approved above 20 kg
§ In cases where no other alternatives are available
§§ From 3 years of age

Not underlined: Stringent regulatory authority (SRA) or WHO prequalification (PQ) approved and readily available

Underlined: SRA/PQ approved but supply constraints

Double underlined: Product not available or yet approved for entire weight range

Table 6: National guidelines for HIV treatment regimens to start for neonates and children

Country	Neonates	Younger Children*	Older Children*
WHO-recommended regimen	*AZT + 3TC + RAL*	*ABC + 3TC + DTG*	*ABC + 3TC + DTG*
Central African Republic	No specific recommendation for neonates	<3 years: ABC + 3TC + LPV/r	3-10 years: TDF + XTC + EFV
Democratic Republic of Congo	ABC + 3TC + LPV/r (pellets)	<3 years: ABC + 3TC + LPV/r	3-10 years: ABC + 3TC + EFV
Guinea	No specific recommendation for neonates	ABC + 3TC + LPV/r AZT + 3TC + LPV/r	3-10 years: ABC + 3TC + EFV AZT (or TDF) + XTC + EFV
India	No specific recommendation for neonates	AZT + 3TC + LPV/r	3-10 years: AZT + 3TC + EFV >10 years and >30kg: TDF + 3TC + EFV
Kenya	<4 weeks: AZT + 3TC + NVP	4 weeks - 3 years: ABC/3TC + LPV/r	3-14 years: ABC + 3TC + EFV
Malawi	<3kg: no specific recommendation >3kg: ABC/3TC + LPV/r	3-20kg ABC/3TC +LPV/r	>20 kg: ABC/3TC + DTG
Mozambique	3-19.9 kg: ABC/3TC + LPV/r if PMTCT, ABC/3TC/NVP if no PMTCT	3-19.9 kg: ABC/3TC + LPV/r if PMTCT, ABC/3TC/NVP if no PMTCT	>20 kg: ABC/3TC + DTG >30kg: TDF/3TC/DTG
Myanmar	No specific recommendation for neonates	<3 years: ABC (or AZT) + 3TC + LPV/r	3-10 years: ABC/3TC + EFV
South Africa	AZT + 3TC + NVP	<20 kg: ABC + 3TC + LPV/r	<10 years and 20-35 kg: ABC + 3TC + DTG >10 years and 35 kg: Transition to adult regimen
Tajikistan	2 NRTIs + LPV/r or NVP	<3 years old: ABC (or AZT) + 3TC + LPV/r ABC (or AZT) + 3TC + NVP	>3 years: 2 NRTIs + LPV/r or NVP or EFV
Uganda	<3 months: AZT+3TC_NVP	3 months - 3 years, or <40kg: ABC + 3TC LPV/r pellets	3-10 years: ABC + 3TC + EFV (tablets) >10 years and 35kg: TDF + 3TC + DTG
Zimbabwe	AZT + 3TC + RAL	LPV/r, EFV or DTG + 2 NRTIs	LPV/r, EFV or DTG + 2 NRTIs

*Children's regimens are broken down by different age and weight cut-offs that vary by country.

3TC, lamivudine; ABC, abacavir; AZT, zidovudine; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RAL, raltegravir; XTC, either 3TC or FTC (emtricitabine), considered as interchangeable in ARV regimens.

A "+" denotes combination of separate medicines. A "/" denotes availability in fixed-dose combinations (FDCs).

CONCLUSION: WHAT NEEDS TO HAPPEN

In addition to finding, diagnosing and treating children living with HIV, we must do better in preventing new HIV infections in the first place. PMTCT interventions have focused on the provision of maternal ART and prophylaxis for the exposed infant. More investment is needed in the two "forgotten pillars" of PMTCT to ensure primary infection does not occur during pregnancy and/or breastfeeding, and women are able to plan their families to avoid HIV transmission.

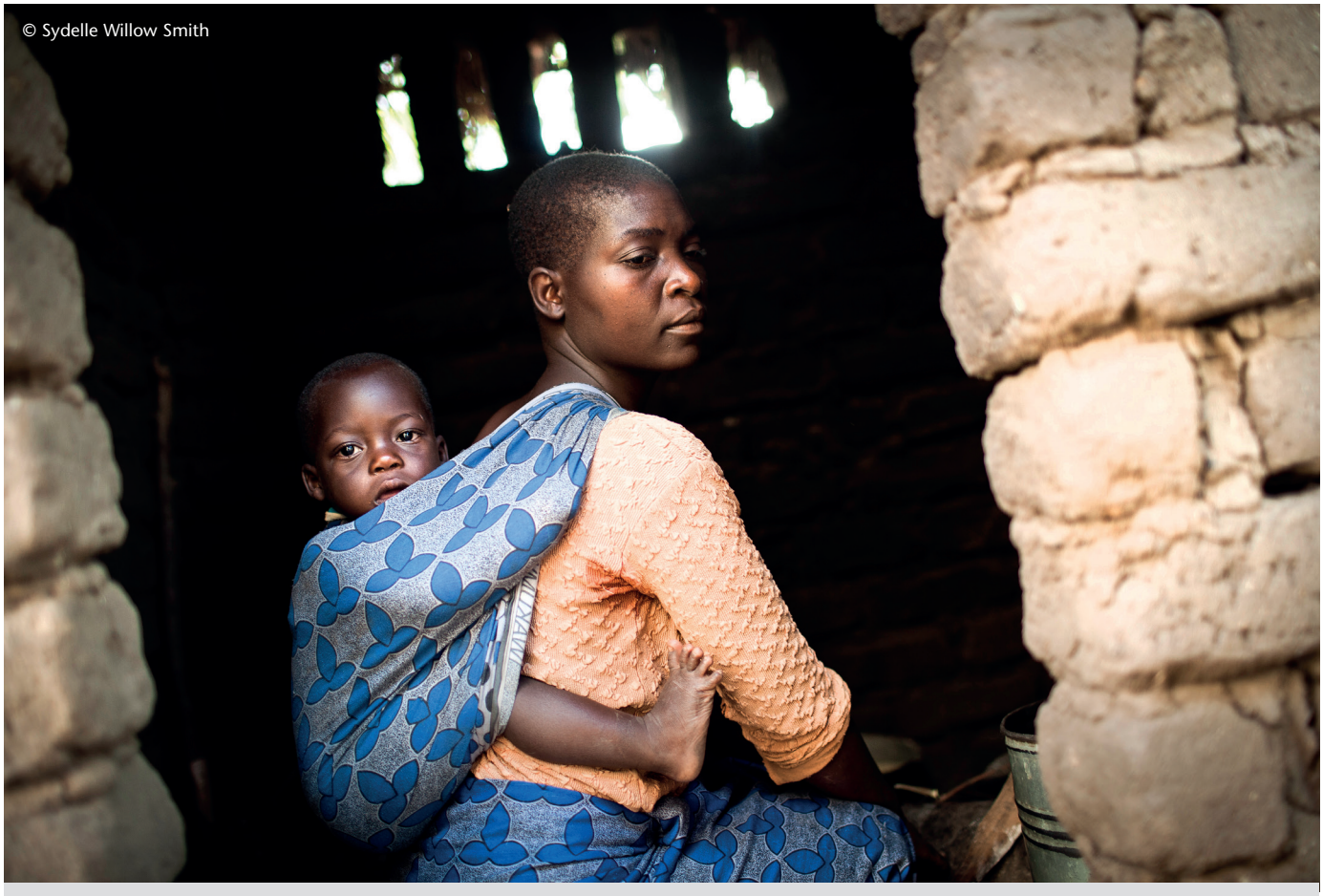
- **PrEP in high-risk pregnant and breastfeeding women should be included in national guidelines and access to PrEP medication ensured.**
- **Family planning should be integrated as a one-stop service within ART services, including in differentiated service delivery models for stable patients. All family planning options including implants and IUDs should be offered with adequate counselling provided to enable women to choose the best option for them.**

Current guidance for prophylactic ARV therapy for HIV-exposed infants is complex, and available formulations are not ideal.

- **Exposed infant prophylaxis regimens need to be simplified to provide the best prevention to all babies, recognising the challenges faced in many settings to stratify into high- and low-risk exposed infants.**
- **Studies should be urgently carried out to consider how harmonisation of regimens for exposed infant prophylaxis and HIV treatment may be possible to simplify forecasting, the supply chain, and the ability to educate health workers to deliver appropriate health education for mothers.**

For paediatric treatment (until DTG is approved for children weighing <20 kg), the number of proposed regimens poses major challenges to supply-chain quantification and delivery.

- **Harmonisation of paediatric and adult regimens moving to DTG including for neonates is urgently needed, with expedited development of appropriate paediatric FDCs to enable actual implementation of the WHO recommendations.**



Jennipher Mwamvera is a mother of four in MSF's PMTCT programme in Thyolo, Malawi.

ANNEX 1. PAEDIATRIC ANTIRETROVIRAL FORMULATIONS – CHALLENGES AND PRICING

Lopinavir/ritonavir paediatric formulations

Product	Pack Size	Price per Unit, US$	Price per Person per Year – 6 kg, US$	Price per Person per Year – 19.9 kg, US$
Cipla LPV/r pellets (40/10mg per cap)	120 capsules per box	19.20	234 (2 caps BID)	584 (5 caps BID)
Mylan LPV/r granules (40/10mg per sachet)	120 sachets per box	18.25	222 (2 sachets BID)	555 (5 sachets BID)
AbbVie LPV/r oral solution (80/20mg/mL)	5x60mL bottles	30.82 per 5x60mL	75 (1 mL BID)	187 (2.5 mL BID)
Generic LPV/r 100/25mg tablets	60 tabs per bottle	5.94 per bottle	Not applicable	145 (2 tabs BID)

Lopinavir/ritonavir (LPV/r; Kaletra, Aluvia) is a protease inhibitor from AbbVie approved by the US Food and Drug Administration (FDA) and on the market since 2000. It is one of the components of first-line treatment for children, and considered as an alternative regimen, though given the lack of formulations of the preferred DTG for children <20 kg, LPV/r becomes the preferred option for children <20 kg.

LPV/r exists as an oral solution from AbbVie for children, which will start to be phased out in 2020, as more child-friendly formulations are scaled up. Generic manufacturers are no longer making quality-assured liquid formulations. Generic drug companies Cipla and Mylan have developed and registered 40/10mg pellet and granule formulations, respectively, which are interchangeable and designed for children <3 years old. While rollout of these newer formulations has been plagued by shortages and delays in supply, the capacity issues are expected to be resolved in early 2020, allowing more programmes to improve treatment options available for children in their countries.

Adding LPV/r pellets and granules into programmes comes with benefits and challenges. They do not require cold chain, and do not contain alcohol – two downfalls of the liquid formulation. However, the taste (unpalatable for children) has not dramatically improved and remains a concern for caregivers, although those with children who have taken the syrup report that children prefer this one.[19] However the most favourable option is to switch to the 100/25mg paediatric tablets as soon as the dose is appropriate and the child can safely swallow them. The additional downfall is the price –these newer formulations cost about three times more than the syrup. The added value of the granule formulation is that it can be used in children as young as 2 weeks.

AbbVie signed a voluntary license with the Medicines Patent Pool in 2014 that covers paediatric formulations of LPV/r up to and including the 40/10mg dose (used in children up to 3 years old), which leaves out the 100/25mg paediatric tablets for children 3 years and older.[20] This is likely because the 100/25mg tablets could be doubled and used in place of the adult 200/50mg tablet formulation in countries where AbbVie maintains its patents and monopoly. However, the voluntary license territory where AbbVie allows generic companies to sell paediatric formulations only covers 102 countries, leaving out many other countries where national HIV programmes could be interested to include the improved LPV/r granules and pellet formulations for children. Furthermore, the only company to have signed the license (Hetero) does not currently market any of the included paediatric LPV/r products. As AbbVie makes plans to phase out production of LPV/r oral solution, they must expand their voluntary-license territory to include all countries who need access to paediatric formulations of LPV/r for the youngest children.

ABC/3TC/LPV/r 4-in-1 granules

For children <3 years old, LPV/r is given as either granules/pellets or syrup, along with ABC/3TC dispersible tablets to make up a WHO-recommended alternative first-line treatment regimen. The 4-in-1 contains 40/10mg of LPV/r and 30/15mg of ABC/3TC, which can be mixed with food, milk, water or breast milk, has a better taste than other LPV/r formulations and is heat stable. The Drugs for Neglected Diseases *initiative* (DNDi) LOLIPOP study in Uganda, which includes children weighing 3-25 kg, will provide crucial data for treatment of HIV in the youngest children.[21] Eventually, this product could ideally be used to align neonatal treatment regimens with prophylaxis regimens in infants at high risk, but will require further studies.

This FDC has been in development as a 4-in-1 granule formulation by two generic companies. Cipla, which has partnered with DNDi to work on this formulation, has filed for registration with the FDA as of mid-October 2019.[22] Ideally, this product could be approved within 6 months and become commercially available in Q3 2020. A second generic source of this combination is in development by Mylan, but not expected to be filed for registration until mid 2020.

Dolutegravir

Formulation	ViiV		Macleods	Mylan
5mg dispersible tablet	In development, pending filing at FDA		N/A	N/A
10mg scored dispersible tablet	N/A		In development, pending filing at FDA	In development, pending filing at FDA
50mg film-coated tablet	Cat 1	Cat 2	N/A	US$46* (0.127)
	US$181 (0.497)	Case by case		

*Lowest price of the tiered pricing provided by Mylan. See Annex 2 for further details.

Dolutegravir (DTG), made by ViiV, is an integrase inhibitor that was approved as 50mg film-coated tablets for adults by the US FDA in 2013,[23] with the first paediatric formulation of 10 and 25mg film-coated tablets approved by the European Medicines Agency (EMA) in 2017 for children >6 years old and weighing >15 kg. However, further studies showed that the pharmacokinetics of this formulation are not ideal in the smaller weight bands,[24] and it is not approved by the FDA for children <30 kg.

The adult 50mg DTG tablets are recommended by the WHO for use in children weighing down to 20 kg. ViiV is developing a 5mg dispersible tablet that will be more suitable for children under 20 kg, which is expected to be filed for registration with the FDA by the end of 2019 for infants and children 4 weeks and older. Generic companies Mylan and Macleods are working on 10mg scored dispersible tablets, potentially available by early 2021.

The bioavailability of the 5 and 10mg dispersible DTG tablet is higher than that of the film-coated tablets, so they will not be interchangeable and dosing would not be the same.[24] To avoid confusion, countries should wait for the dispersible formulations before implementing DTG for children weighing <20 kg.

The WHO-preferred first-line regimen for children is ABC/3TC/DTG, with the dosing ratio for a FDC confirmed as 60/30/5mg per scored dispersible tablet. While multiple generic companies have shown interest in developing this product, its development depends on approval of ViiV's 5mg dispersible tablet. Companies should prioritise the development of this combination to allow children to be initiated or switched to the ideal treatment regimen, avoiding compromised treatment with NVP due to high levels of NNRTI resistance.

RAL granules for oral suspension and chewable tablets (Isentress)

Formulation	Merck Sharpe & Dohme
100mg granules/sachet	US$694 per year for 10-kg child (US$0.95/sachet)
25mg chewable tablet	(US$0.30/tablet)
100mg chewable tablet	(US$0.60/tablet)

Raltegravir (RAL) is an integrase inhibitor approved as 400mg tablets for adults by the FDA in 2007, with the first paediatric formulation of 25 and 100mg chewable tablets approved in 2013. The infant-friendly granules for suspension formulation was approved in 2013.[25] Paediatric RAL is only available from Merck and has a limited recommendation in the WHO HIV guidelines. The RAL granules for suspension require multiple steps for reconstitution into an oral solution but in the absence of a DTG formulation for neonates, they are part of the preferred first-line regimen for treatment of neonates, whereas the chewable tablets are indicated as an alternative option for children weighing <20 kg when LPV/r is not available. Notably, children on RAL should be changed to a LPV/r- or DTG-based treatment regimen as soon as possible, given the potential for resistance to integrase inhibitors with use of RAL.

As of June 2017, Merck has only registered the RAL granules for oral suspension in 33 countries, mainly high-income countries, with the exception of Peru and Argentina. While this product is intended for young children, it is not registered nor readily available in sub-Saharan African countries where the majority of these children live. The registration profile of the 25 and 100mg chewable RAL tablets is not much better. While they are registered in 70 countries, only 18 of these countries are in sub-Saharan Africa.[26] Given the lack of availability in low- and middle-income countries, it is not surprising that only one of the MSF countries surveyed (Zimbabwe) indicated RAL granules in their guidelines for neonates, which is being supported in the country by the Elizabeth Glaser Pediatric AIDS Foundation.

ANNEX 2. ANTIRETROVIRAL DRUG PRICES AND SOURCES, 2019

Developing-country prices are given in US$ per person per year, as quoted by companies. The price in brackets corresponds to the price of one unit (tablet, capsule, mL, etc). Products included in the WHO list of Prequalified Medicines or approved by the US FDA (as of November 2019) are in bold. Paediatric doses are based on 10 kg body weight.

Each originator company applies its own eligibility criteria for discounting ARVs. Countries eligible for a discount from one company may not be eligible from other companies. Usually, companies create two groups of discount-eligible countries, often called Category 1 for countries eligible for the deepest discounts, and Category 2 for countries offered a lower discount.

Paediatric formulations are shaded. Prices for paediatric products are estimated, based on WHO-recommended dosing, for the 10 to 10.9 kg weight band. When not possible to calculate dosing for the 10 kg weight band, the unit price was used.

Global Fund prices have been added as a comparison and additional reference. The prices indicated are the lowest reported for each item in the October 2019 update of the Global Fund's Pooled Procurement Mechanism prices,[27] which accounts for larger pack sizes and cartonless products where applicable.

Generic companies producing DTG or DTG-based FDCs provided price ranges, reflecting the royalties imposed for certain countries as per the ViiV/MPP voluntary license. Companies providing tiered pricing are marked with an asterisk (*) and the lowest price provided is indicated. Royalties paid from the generic company to ViiV vary by country but reflects as follows: 5% in India, Vietnam, the Philippines and Moldova; 7.5% in Indonesia, Egypt, Morocco, Armenia and Ukraine; 10% in Turkmenistan.[28]

ARVs in Alphabetical Order	Daily Dose	Originator Company		Global Fund 2019 PPM Prices	Generic Companies				
Abacavir (ABC)		*ViiV*		*Global Fund*	*Cipla*	*Hetero*	*Micro*	*Mylan*	*Strides Shasun*
20mg/mL oral solution	12 mL	*Cat 1* **412 (0.094)**	*Cat 2*	**132 (0.030)**		**136 (0.031)**			
60mg dispersible tablet	4			**115 (0.079)**	**92 (0.063)**		**121 (0.083)**		
300mg tablet	2			**100 (0.138)**	**134 (0.183)**	**113 (0.154)**	**106 (0.146)**	**100 (0.138)**	**256 (0.350)**
Atazanavir (ATV)		*BMS*		*Global Fund*	*Emcure*	*Mylan*			
		Cat 1	*Cat 2*						
150mg capsule	2	**412 (0.564)**	**412 (0.564)**	**207 (0.283)**	**207 (0.283)**				
200mg capsule	1	**247 (0.677)**	**247 (0.677)**	**122 (0.333)**	**152 (0.417)**				
300mg capsule	1			**207 (0.567)**	**207 (0.567)**	**183 (0.500)**			
Atazanavir/ ritonavir (ATV/r)		N/A		*Global Fund*	*Cipla*	*Emcure*	*Mylan*		
300/100mg tablet	1			**157 (0.430)**	**219 (0.600)**	**207 (0.567)**	**170 (0.466)**		
Darunavir (DRV)		*Janssen*		*Global Fund*	*Cipla*	*Hetero*			
75mg tablet	x	**(0.113)**	Case by case						
150mg tablet	x	**(0.225)**							
400mg tablet	2	**438 (0.600)**		**655 (0.897)**	**548 (0.750)**	**754 (1.033)**			
600mg tablet	2	**657 (0.900)**		**675 (0.925)**	**730 (1.000)**	**779 (1.067)**			
Dolutegravir (DTG)		*ViiV*		*Global Fund*	*Aurobindo*	*Cipla*	*Hetero*	*Mylan*	*Sun*
		Cat 1	*Cat 2*						
50mg tablet	1	**181 (0.497)**	Case by case	**43 (0.117)**	**45* (0.123)**	**43 (0.117)**	**49* (0.133)**	**46* (0,127)**	43* (0.117)

ARVs in Alphabetical Order	Daily Dose	Originator Company		Global Fund 2019 PPM Prices	Generic Companies							
Efavirenz (EFV)		*Merck*		*Global Fund*	*Aurobindo*	*Cipla*	*Hetero*	*Macleods*	*Micro Labs*	*Mylan*	*Strides Shasun*	*Sun Pharma*
		Cat 1	*Cat 2*									
30mg/mL suspension	x	**(0.094)**	**Case by case**									
50mg tablet	x	**(0.114)**		**(0.054)**					**(0.073)**	**(0.040)**		
50mg capsule	x								**(0.067)**			
200mg capsule	3								**52 (0.047)**			
200mg tablet (scored)	3	**394 (0.360)**	**Case by case**	**78 (0.071)**					**82 (0.074)**			
600mg tablet	1	**237 (0.650)**		**31 (0.085)**	**31 (0.085)**	**39 (0.106)**	**35 (0.095)**	**40 (0.11)**	**32 (0.087)**	**37 (0.100)**	**34 (0.093)**	**37 (0.100)**
Etravirine (ETV)		*Janssen*										
		Cat 1	*Cat 2*									
25mg tablet	x	**(0.075)**	**Case by case**									
100mg tablet	4	**438 (0.300)**										
200mg tablet	2											
Lamivudine (3TC)		*ViiV*		*Global Fund*	*Hetero*	*Macleods*	*Micro Labs*	*Mylan*	*Strides Shasun*			
		Cat 1	*Cat 2*									
10mg/mL oral suspension	10 mL	**221 (0.060)**	Case by case	**46 (0.013)**	**34 (0.009)**	**42 (0.011)**						
150mg tablet	2	**144 (0.197)**		**27 (0.037)**	**27 (0.037)**	**33 (0.046)**	**27 (0.037)**	**27 (0.037)**	**30 (0.042)**			
300mg tablet	1				**32 (0.087)**		**28 (0.077)**					
Lopinavir/ ritonavir (LPV/r)		*AbbVie*		*Global Fund*	*Aurobindo*	*Cipla*	*Hetero*	*Macleods*	*Mylan*			
		Cat 1	*Cat 2*									
80/20mg/mL oral solution	4 mL	**150 (0.103)**	**296 (0.203)**	**150 (0.103)**								
40/10mg pellets or granules	4			**467 (0.160)**		**467 (0.160)**			**444 (0.152)**			
100/25mg tablet	3	**108 (0.099)**	**278 (0.254)**	**113 (0.103)**	**137 (0.125)**		**173 (0.158)**	**158 (0.144)**	**131 (0.120)**			
200/50mg tablet	4	**241 (0.165)**	**740 (0.507)**	**219 (0.150)**	**217 (0.148)**	**292 (0.200)**	**304 (0.208)**	**402 (0.275)**	**219 (0.150)**			
Nevirapine (NVP)		*Boehringer Ingelheim*		*Global Fund*	*Aurobindo*	*Cipla*	*Hetero*	*Micro Labs*	*Mylan*	*Strides Shasun*	*Sun*	
10mg/mL suspension	20 mL			**106 (0.015)**	**124 (0.017)**	**91 (0.013)**						
50mg tablet for oral suspension	4			**35 (0.024)**		**35 (0.024)**						
200mg tablet	2						**28 (0.038)**	**27 (0.037)**	**39 (0.053)**	**30 (0.042)**	**27 (0.038)**	
Raltegravir (RAL)		*Merck*		*Hetero*								
		Cat 1	*Cat 2*									
100mg powder/ sachet	2	**694 (0.95)**										
25mg tablet	x	**(0.300)**										
100mg tablet	x	**(0.600)**	**Case by case**									
400mg tablet	2	**675 (0.925)**		**791 (1.083)**								

ARVs in Alphabetical Order	Daily Dose	Originator Company		Global Fund 2019 PPM Prices	Generic Companies					
Ritonavir (RTV)		*AbbVie*		*Global Fund*	*Mylan*					
		Cat 1	*Cat 2*							
80mg/mL oral solution	x	**(0.091)**	**Case by case**							
25mg tablet	x									
50mg tablet	x									
100mg tablet	1	**83 (0.114)**		**83 (0.114)**	**183 (0.250)**					
Tenofovir (TDF)		*Gilead*		*Global Fund*	*Cipla*	*Hetero*	*Macleods*	*Mylan*	*Strides Shasun*	
		Cat 1	*Cat 2*							
Oral powder 40mg/1g	2	**1290 (1.767)**	**Case by case**							
150mg tablet	x	**329 (0.900)**								
200mg tablet	1	**329 (0.900)**								
250mg tablet	1	**365 (1.00)**								
300mg tablet	1	**183 (0.500)**		**29 (0.080)**	**37 (0.100)**	**34 (0.093)**	**40 (0.010)**	**40 (0.108)**	**49 (0.133)**	
Zidovudine (AZT)		*ViiV*		*Global Fund*	*Hetero*	*Micro Labs*	*Mylan*			
		Cat 1	*Cat 2*							
10mg/mL oral suspension	24 mL	**442 (0.050)**		**119 (0.014)**	**82 (0.009)**					
300mg tablet	2			**61 (0.083)**	**61 (0.083)**	**60 (0.082)**	**67 (0.092)**			
ABC/3TC		*ViiV*		*Global Fund*	*Cipla*	*Hetero*	*Mylan*	*Sun*		
		Cat 1	*Cat 2*							
60/30mg tablet	4				**97 (0.067)**		**85 (0.058)**			
120/60mg dispersible tablet	2			**85 (0.117)**	**92 (0.127)**		**85 (0.117)**			
600/300mg tablet	1	**302 (0.827)**		**112 (0.307)**	**152 (0.417)**	**128 (0.35)**	**122 (0.333)**	**122 (0.333)**		
ABC/3TC/DTG		*ViiV*		*Global Fund*						
600/300/50mg tablet	1			**243 (0.667)**						
TDF/FTC		*Gilead*		*Global Fund*	*Cipla*	*Hetero*	*Micro Labs*	*Mylan*	*Strides Shasun*	*Sun*
		Cat 1	*Cat 2*							
300/200mg tablet	1	**243 (0.667)**	**Case by case**	**55 (0.150)**	**61 (0.167)**	**58 (0.158)**	**60 (0.163)**	**64 (0.175)**	**60 (0.163)**	**55 (0.150)**
TDF/FTC/EFV		*Merck*		*Global Fund*	*Hetero*	*Macleods*	*Mylan*	*Strides Shasun*		
		Cat 1	*Cat 2*							
300/200/600mg tablet	1	**613 (1.680)**	**Case by case**	**75 (0.205)**	**81 (0.222)**	**80 (0.220)**	**76 (0.208)**	**83 (0.227)**		
TDF/3TC		*N/A*		*Global Fund*	*Cipla*	*Hetero*	*Macleods*	*Micro Labs*	*Mylan*	*Sun Pharma*
300/300mg tablet	1			**41 (0.113)**	**49 (0.133)**	**44 (0.120)**	**48 (0.132)**	**45 (0.123)**	**52 (0.142)**	**44 (0.122)**
TDF/3TC/EFV		*N/A*		*Global Fund*	*Aurobindo*	*Cipla*	*Hetero*	*Macleods*	*Mylan*	
300/300/400mg tablet	1			**69 (0.190)**				**80 (0.220)**	**73 (0.200)**	
300/300/600mg tablet	1			**69 (0.190)**	**76 (0.208)**	**70 (0.192)**	**72 (0.197)**	**80 (0.220)**	**76 (0.208)**	
TDF/3TC/DTG		*N/A*		*Global Fund*	*Aurobindo*	*Cipla*	*Hetero*	*Macleods*	*Mylan*	*Sun Pharma*
300/300/50mg tablet	1			**64 (0.176)**	**79* (0.217)**	**70 (0.192)**	**74* (0.203)**	**80 (0.220)**	**73* (0.200)**	**74* (0.202)**

ARVs in Alphabetical Order	Daily Dose	Originator Company		Global Fund 2019 PPM Prices	Generic Companies					
AZT/3TC		*Merck*		*Global Fund*	*Cipla*	*Hetero*	*Micro Labs*	*Mylan*	*Strides Shasun*	*Sun Pharma*
		Cat 1	*Cat 2*							
60/30mg tablet	4			**46 (0.032)**	**45 (0.031)**			**80 (0.055)**		
300/150mg tablet	2	**190 (0.260)**		**64 (0.088)**	**67 (0.092)**	**78 (0.107)**	**69 (0.095)**		**68 (0.093)**	**71 (0.097)**
AZT/3TC/NVP		*N/A*		*Global Fund*	*Cipla*	*Hetero*	*Micro Labs*	*Strides Shasun*	*Sun Pharma*	
60/30/50mg tablet	4			**73 (0.050)**	**73 (0.050)**			**73 (0.050)**		
300/150/200mg tablet	2				**85 (0.117)**	**92 (0.127)**	**96 (0.132)**	**89 (0.122)**	**87 (0.120)**	
AZT/3TC + EFV (co-pack)		*N/A*		*Strides Shasun*						
300/150 + 600mg co-pack	1			**49 (0.133)**						

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