ARV MARKET REPORT

The state of the antiretroviral drug market in low- and middle-income countries, 2016-2021

Issue 8, September 2017

CLINTON HEALTH ACCESS INITIATIVE

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Table of Contents

Acronyms Used

1L	First-line
2L	Second-line
3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
API	Active Pharmaceutical Ingredient
APWG	ARV Procurement Working Group
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BMGF	Bill & Melinda Gates Foundation
CAB	Cabotegravir
CAB LA	Long-acting cabotegravir
CHAI	Clinton Health Access Initiative
CLHIV	Children living with HIV
d4T	Stavudine
DFID	United Kingdom Department for International Development
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EFV	Efavirenz
EID	Early infant diagnosis
EXW	Ex works
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FTC	Emtricitabine
GA	Generic-accessible
GAP-f	Global Accelerator for Pediatric Formulations
HIV	Human Immunodeficiency Virus
HIVST	HIV self-test
IATT	Inter-Agency Task Team for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children
INSTI	Integrase strand transfer inhibitor
LMICs	Low- and middle-income countries
LPV/r	Lopinavir/ritonavir
MoH	Ministry of Health
MSM	Men who have sex with men
NAT	Nucleic acid testing
NDoH	National Department of Health
NGO	Non-governmental organization
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PADO	Pediatric ARV Drug Optimization
PEPFAR	President's Emergency Plan for AIDS Relief
PHTI	Pediatric HIV Treatment Initiative
PI	Protease inhibitor
PK	Pharmacokinetic
PLHIV	People living with HIV/AIDS
PMTCT	Prevention of mother to child transmission
POC	Point-of-care
PPM	Pooled Procurement Mechanism
PPPY	Per patient per year
PrEP	Pre-exposure prophylaxis
RAL	Raltegravir
RPV	Rilpivirine
RSA	Republic of South Africa
SHIMS	Swaziland HIV Incidence Measurement Survey
SOC	Standard of care
SRA	Stringent regulatory authority
SSA	Sub-Saharan Africa
TAF	Tenofovir alafenamide fumarate
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TEE	TDF+FTC+EFV
TLD	TDF+3TC+DTG
TLE	TDF+3TC+EFV
TXE	TDF+(3TC or FTC)+EFV
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
VL	Viral load
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
ZLN	AZT+3TC+NVP

Foreword

The HIV/AIDS community received good news ahead of the 2017 International AIDS Society (IAS) meeting in Paris: for the first time ever, more than 50 percent of people living with HIV were receiving antiretroviral therapy (ART) at the end of 2016 and AIDS-related deaths have halved since 2005. If this trend continues, the world will be on track to meet the UNAIDS Fast-Track targets of 30 million people receiving ART by 2020 – an ambitious, but now attainable, goal.

Two years after the World Health Organization (WHO) recommended that *all* people living with HIV be treated with antiretrovirals (ARVs), regardless of their clinical or immunological status, over 100 nations have incorporated "Test and Treat" policies into their national treatment guidelines – a key step in meeting the Fast-Track goals.

As the number of patients on ART continues to increase, ensuring that patients are on optimal regimens and formulations will be important to improve adherence and meet the "Third 90" goal of 90 patients of patients on treatment being virally suppressed. Dolutegravir (DTG), the standard-of-care drug in many developed nations, is poised to transform the ARV market in low- and middle-income countries (LMICs) in the coming years due to its improved clinical profile and lower costs when compared to current drugs. As of July 2017, over 20 LMICs had initiated procurement of generic DTG singles. In addition, two generic fixed-dose combinations of TDF/3TC/DTG (TLD) were approved by the United States Food and Drug Administration (FDA) in August 2017, with the first orders expected to arrive in countries in Q1 2018. While regulatory approval of TLD represents a significant milestone in the fight to ensure access to the best treatment for all people living with HIV, the announcement at the 2017 United Nations General Assembly of a ceiling price agreement negotiated with manufacturers by the Bill & Melinda Gates Foundation and CHAI ensures that TLD will be available in LMICs at an affordable price.

The pediatric market has seen a flurry of activity around bringing optimal ARVs, such as additional heat-stable LPV/r formulations and fixed-dose combinations of WHO-recommended regimens, to the market. Collaborations between partner organizations, such as the Global Accelerator for Pediatric Formulations (GAP-f), focus on upstream product prioritization and development as well as downstream product introduction and roll-out. Careful consideration will need to be given to long-term sustainability of the pediatric ARV market in light of decreasing need, as prevention of mother-to-child transmission (PMTCT) efforts continue to succeed in reducing new pediatric infections.

Beyond treatment, scaling up prevention efforts is critical to further decreasing the rate of new HIV infections and reaching the Fast-Track goal of 500,000 annual new infections by 2020 (compared to 1.8 million in 2016). Products such as oral pre-exposure prophylaxis (PrEP) continue to generate interest with over 10 LMICs incorporating oral PrEP into their national treatment guidelines as of this report's publication. South Africa became the first LMIC to roll out oral PrEP into their national program in mid-2016, with over 2,300 individuals having been initiated on oral PrEP as of July 2017.

Whereas tremendous progress has been made in reducing the spread of HIV, it has not been equitable. The typical HIV "hot spots" in Eastern and Southern Africa have seen great progress in reducing the rates of new infections, but regions that have received relatively less international attention, such as Central Asia and Eastern Europe, have seen new infections increase by an alarming 60 percent. Additionally, key populations such as adolescent girls and young women, female sex workers, people who inject drugs, and men who have sex with men are still seeing disproportionally high rates of HIV infections.

Much work remains to end the AIDS epidemic as a public health threat. CHAI is focused on meeting this goal by working with Ministries of Health, suppliers and partners to ensure that all patients have access to the best drugs at affordable and sustainable prices, no matter where they live.

2017 ARV Market Report: At-a-Glance

ARV Market Overview

For the first time, over 50% of people living with HIV/AIDS (PLHIV) globally are on treatment

36.7M people living with HIV globally (2016)

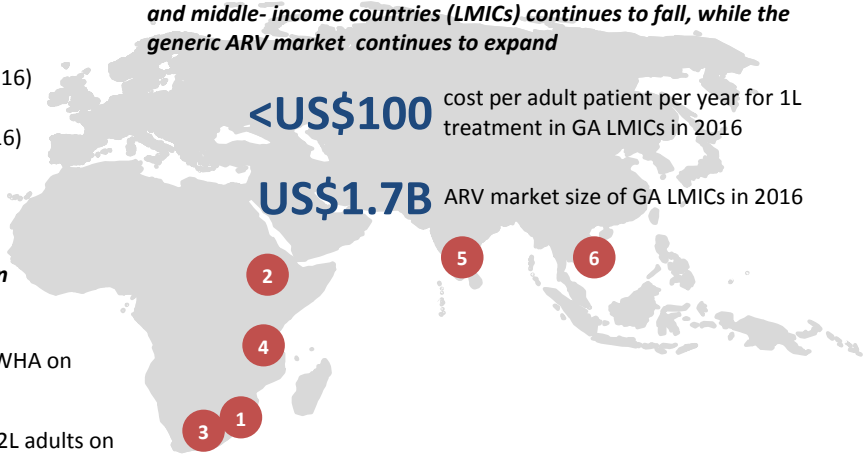
19.5M people on treatment globally (2016)

53% global ART coverage rate (2016)

The cost to treat first-line (1L) adults in generic accessible (GA) low- and middle- income countries (LMICs) continues to fall, while the generic ARV market continues to expand

<US$100 cost per adult patient per year for 1L treatment in GA LMICs in 2016

US$1.7B ARV market size of GA LMICs in 2016



Ministries of Health continue to make great strides in HIV treatment and prevention

1. **Swaziland** doubled the number of PLWHA on ART between 2011 and 2016
2. **Ethiopia** increased the percentage of 2L adults on ATV/r from 32% in Nov. 2015 to 68% in Dec. 2016
3. **South Africa** has initiated in 2,300 individuals on oral PrEP since June 2016
4. **Kenya** has rolled out dolutegravir to 1,400 patients
5. **India** has adopted Test & Treat, making ART available for all patients
6. **Cambodia** has adopted optimal pediatric products such LPV/r oral pellets and ABC/3TC (120/60mg) disp. tablets

Adult Market Trends

Dolutegravir (DTG), as a fixed-dose combination (TLD), is expected to significantly change the 1L adult market

59% forecasted DTG market share in GA LMICs by 2021

US$75 average per patient per year price for generic TLD

2 stringent regulatory authority (SRA) approved generic TLD suppliers; more on the way

20+ LMICs have already initiated procurement for DTG (50mg) singles

Pediatric Market Trends

Existing and pipeline optimal products expected to further drive adoption of WHO preferred regimens

Existing Products

ABC/3TC (120/60mg)

8+ LMICs have initiated procurement

LPV/r Oral Pellets (40/10mg)

20+ LMICs have initiated procurement

Pipeline Products

- **LPV/r Granules (40/10mg)**
  Expected SRA approval: H2 2018
- **ABC/3TC/EFV (150/75/150mg) FDC**
  Expected SRA approval: H2 2019
- **ABC/3TC/LPV/r (30/15/40/10mg) "4-in-1"**
  Expected SRA approval: H2 2019

Prevention

Annual new infections remain high but existing and pipeline technologies expected to bolster prevention efforts

1.8M new HIV infections in 2016

10+ LMICs have adopted oral PrEP guidance

Sample Pipeline Products

-Long-acting injectables
-Implants
-Vaccines

Diagnostics & Lab Services

Testing continues to remain critical for identifying people living with HIV and monitoring effectiveness of treatment

26M forecasted number of viral load tests to be conducted in 2021

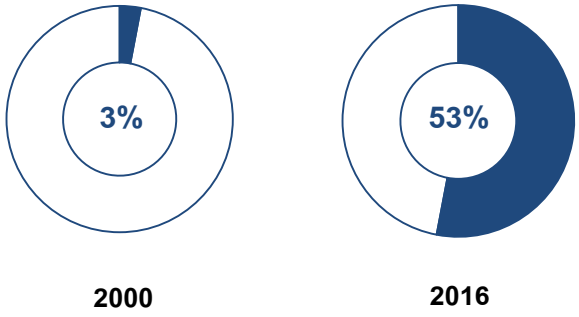
US$2 cost per HIV self-test in LMICs due to pricing agreement

The State of HIV/AIDS Today

For the first time, over 50 percent of people living with HIV globally are on treatment

By the end of 2016, 19.5 million adults and children globally were on antiretroviral therapy (ART). This represents more than half of the nearly 37 million people living with HIV (PLHIV) globally and marks a significant milestone in the fight against HIV/AIDS (Figure 1).[i]

Figure 1: Global ART Coverage Rates (Adults and Children)



Despite tremendous progress over the past few decades, there remains much work to be done before the UNAIDS Fast-Track (90-90-90) targets are met.[1] Treatment disparities still exist among children, adolescents, and key populations such as transgender women. The only way the 90-90-90 targets will be reached is by ensuring *all* people living with HIV, regardless of gender, age, sexual orientation, or geography, have equal access to life-saving treatment.

> **"Now is the time to come together again and finish what we started. Let us seize this opportunity and join the Fast-Track towards ending AIDS as a public health threat by 2030.**
>
> - Michel Sidibé
>
> *Executive Director, UNAIDS*

The global achievements to date are based on the significant efforts at the country-level. A highlight at IAS 2017 was data from Swaziland, the country with the highest HIV prevalence and second-highest incidence among adults 15-49 in 2016 in the world.[ii] Between 2011 and 2016, the number of people on ART in Swaziland rose from around 72,000 to 171,000 (a 2.4 fold increase).[ii] Additionally, data from the latest Swaziland HIV Incidence Measurement Survey (SHIMS 2) found that new infections have nearly halved and rates of viral suppression in adults older than fifteen doubled, from 34.8 percent to 71.3 percent during the same time period (Figure 2).[iii]

Figure 2: Swaziland's Progress, 2011-2016

SHIMS 2	2011	2016
HIV New Infection Rate among Adults	2.5%	1.4%
Viral Suppression *among Adults*	35%	71%

Malawi, Zimbabwe, Zambia, and Lesotho are four other low- and middle-income countries (LMICs) that are nearing epidemiological control of their respective HIV epidemics, according to Population-based HIV Impact Assessments (PHIAs) conducted in each country.[iv]

Swaziland's remarkable progress over a short timeframe is proof that the 90-90-90 goals are achievable, and serves as an inspiration for other LMICs. However, a closer look at the data in Swaziland reveals that even in the context of this remarkable progress, there is significant disparity between adults and youths; treatment and prevention efforts focused on adolescents will need to be a continuing focus here and elsewhere.

While new HIV infections are decreasing globally, a variety of disparities still exist

As part of their annual release of HIV/AIDS statistics, UNAIDS noted in July 2017 that, globally, new infections have decreased by 16 percent since 2010. However, underlying this global decrease in new infections are disparities based on the following factors:

- **Geography:** Traditional HIV "hot spots", such as Eastern and Southern Africa, have seen decreases in new infections, but Eastern Europe and Central Asia have seen a 60 percent *increase* in new infections since 2010 largely driven by the use of injectable drugs and the lack of sufficient HIV treatment services.[v]
- **Age & Sex:** In 2016, new infections among women aged 15-24 were 44 percent higher than young men of the same age. Additionally women aged 15-24 accounted for 26 percent of all new infections in Eastern and Southern Africa in 2016.[v]
- **Key Populations:** HIV incidence among key populations is often substantially higher than it is among the general population across countries. For example men who have sex with men (MSM) accounted for 6 percent of all new infections in sub-Saharan Africa SSA, but 22% of all new infections outside of it in 2015. Overall, key populations and their sexual partners accounted for 25 percent of new HIV infections in 2015 within Sub-Saharan Africa, and 80 percent outside of it.[v]

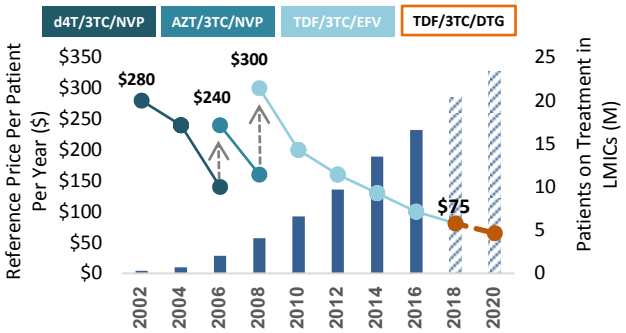
While the overall declines in new infections are certainly cause to celebrate, one cannot ignore the fact that certain geographies and groups of people are being left behind in the fight against HIV/AIDS. These geographies must be a focus and key populations must be targeted and reached with an appropriate mix of prevention and treatment interventions.

[1] *The UNAIDS Fast-Track 90-90-90 treatment targets aim for 90 percent of people infected with HIV knowing their status, 90 percent of those diagnosed with HIV receiving effective treatment, and 90 percent of those treated being virally suppressed by 2020.*

Generic prices for ARVs continued to decrease, making treatment more affordable than ever

The cost of treatment for adults continued to decline over the past year. As an example, the Global Fund Pooled Procurement Mechanism (PPM) reference price for TDF/3TC/EFV (300/300/600mg) tablets (TLE600) fell from US$7.99/pack in Q3 2016 to US$6.75/pack in Q3 2017, essentially costing less than US$85 per patient per year (PPPY) to treat adult patients in most generic-accessible (GA) countries[vi]

Figure 3: Launch Prices for Key 1L Adult Products Since 2012 in Generic-Accessible (GA) LMICs

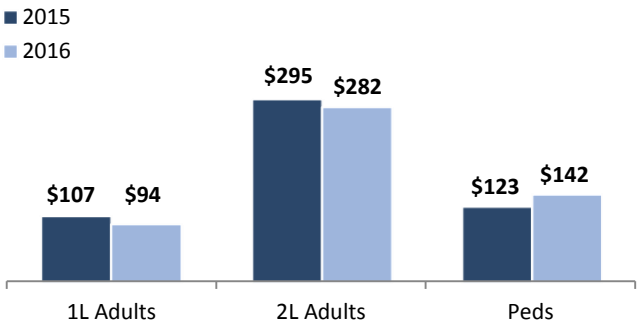


It is difficult to imagine further large declines in prices of current products in a manner that is sustainable for suppliers. However, with the introduction of newer ARVs such as TDF/3TC/DTG (300/300/50 mg) (TLD) and tenofovir alafenamide fumarate (TAF), prices for first-line (1L) products are likely to decrease even further without compromising supplier profitability and market sustainability.

A landmark pricing agreement, announced at the United Nations General Assembly and Global Citizen Festival in September 2017, makes TLD available at an average price of US$75 PPPY in 92 countries covering over 90 percent of PLHIV globally. This marks the first time that a new regimen is launching at a discount to existing therapies (Figure 3).

The continuing decline of ARV prices is notable as the same amount of funding is capable of paying for the treatment of a higher number of patients, which is critical for rolling out test and treat policies worldwide.

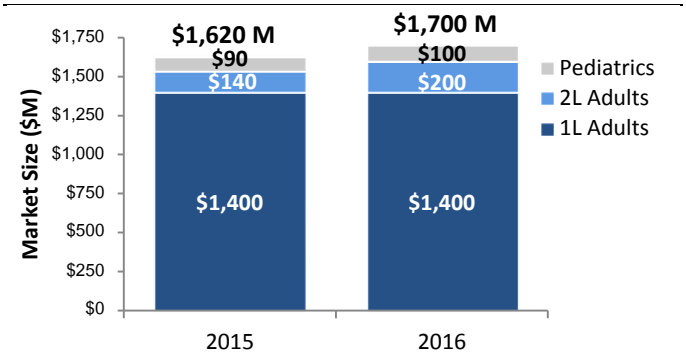
Figure 4: Weighted Average Market Price (USD) for Regimens in GA LMICs, (PPPY)



In 2016, the estimated average cost for second-line (2L) adults in GA LMICs fell slightly year-over-year. To note, the cost to treat children living with HIV increased between 2015 and 2016 (Figure 4) as was the case between 2014 and 2015. This is mostly driven by the desirable shift to more optimal and slightly more expensive LPV/r- and EFV-based regimens in preference to limited-use and non-essential products such as AZT/3TC/NVP (60/30/50mg) dispersible tablets.

Overall, the GA market for ARVs in LMICs continues to grow and reached $1.7 billion in 2016 (Figure 5). Despite falling prices on a per patient basis, the adult 1L market size remained nearly the same year-over-year. The large increase in the number of adults initiated on ART in 2016 offset the decreasing 1L treatment costs.

Figure 5: ARV Market Size (USD) in GA LMICs



Transparency and coordination within the ARV market has helped promote sustainable supply security

The ARV market continues to be supported by a wide range of partners and organizations. The ARV Procurement Working Group (APWG), for example, has played a pivotal role in coordinating procurement, strategically managing demand, and reducing fragmentation of prioritized adult and pediatric products. The APWG consists of procurement agents, donors, and partner organizations who meet routinely to coordinate procurement and share market intelligence. In an effort to promote market transparency further, the APWG now publishes quarterly ARV procurement forecasts that summarize the anticipated volumes (by formulation) across the procurement consortium.[vii]

The November 2016 Buyers and Sellers Forum was another strong example of market coordination. The meeting was hosted by PEPFAR, the Global Fund, and the South Africa Department of Health; the three largest buyers of ARVs, and included 22 generic and innovator manufacturers as well as many partners in the ARV market. Areas of focus during the forum included providing demand visibility through a consolidated forecast across the three buyers, aligning on key supplier performance metrics, and sharing market intelligence.[viii] The next iteration of this meeting is scheduled for November 2017.

Public tenders have been and continue to be a key element of transparency in the ARV market. Over the coming year, there are a few notable tenders due to be floated, representing a large proportion of the market (Figure 6).

To note, South Africa has indicated a switch to a two-year tender for its next tender to allow for more flexibility in procuring newer products as they become available. Additionally, the Global Fund's Pooled

Procurement Mechanism (PPM) has indicated it will extend its current tender until Q3 2018, with their next tender expected to be valid between two and three years. New products can still be introduced during the extension, as was done with DTG 50mg. Combined, these two tenders represent around a third of the number of patients currently on ART.

Figure 6: Upcoming Key Tenders

Entity	Effective Date	Duration	Patients on ART (2016)
Global Fund PPM	Q3 2018	2-3 years	3.4M [ix]
South Africa	Q3/Q4 2018	2 years	3.9M [ii]

Finally, a highlight in the space was the release of CHAI's HIV New Product Introduction Toolkit, which provides Ministries of Health (MoH), partners, and national programs tools and resources to support introduction and scale-up of new ARVs in-country (Figure 7). The toolkit can be found at: https://www.newhivdrugs.org

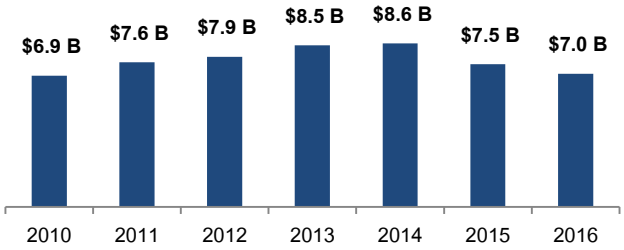
Figure 7: CHAI New Product Introduction Framework

Despite success to date, falling donor spending on HIV threatens to erode current progress

In 2016, donor funding on HIV was approximately US$7 billion USD, which represents its lowest level since 2010.[x]

Although the United States was still the largest donor in 2016 (and represented 70 percent of total global donations), there is uncertainty about funding moving forward (Figure 8).[x]

Figure 8: Donor Government Disbursements for HIV (USD, Billions)x



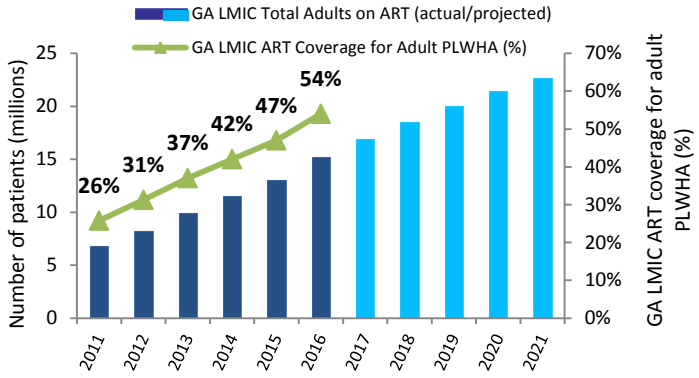
Lagging funding may pose a challenge to achieving the 90-90-90 targets which will require significant scale-up and investments in testing, treatment, and prevention. In fact, a recent analysis by the Bill & Melinda Gates Foundation found an additional 5.6 million people would die by 2030 if global HIV spending were cut by 10 percent.[xi]

Adult ARV Market Trends

18M patients were on ART at the end of 2016, with over 15M in GA LMICs

Over two million adult patients in GA LMICs were put on ART between 2015 and 2016, a remarkable scale-up in a short amount of time.[ii] If current trends continue, nearly 23 million adults are expected to be on treatment by the end of 2021 (Figure 9).

Figure 9: Number of Adults on ART and Adult ART Coverage in GA LMICs[2]

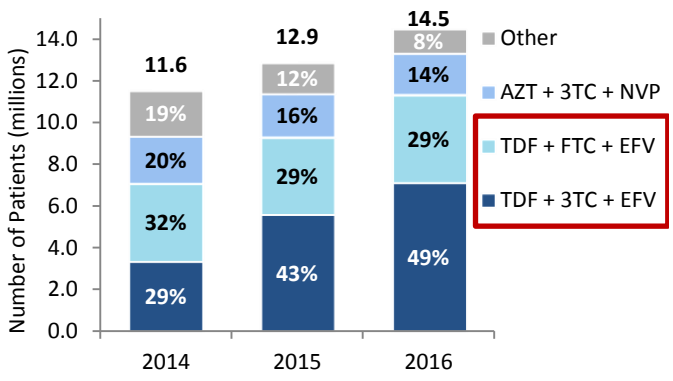


TDF-based regimens continue to dominate the adult first-line market

The WHO still lists TDF+3TC(or FTC)+EFV (TXE) as the preferred regimen for first-line adults, including special populations. Over the course of 2016, more adults were treated with TDF-based regimens in general. TXE in particular made up 78 percent of all 1L adult regimens in 2016, up from 72 percent in 2015 (Figure 10).

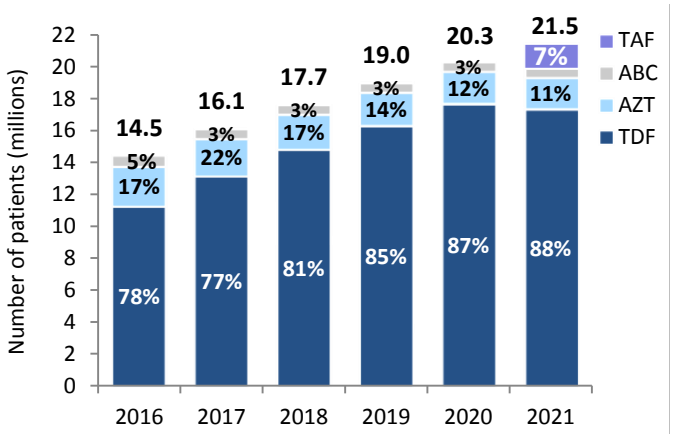
Tenofovir-based regimens are projected to continue to grow in market share (Figure 11). Tenofovir alafenamide fumarate (TAF) is an alternative pro-drug of tenofovir, with the potential to reduce treatment costs. CHAI expects TAF to begin to replace TDF in 2021 – more details on its development are provided in later pages.

Figure 10: First-Line Adult Regimens in GA LMICs, Patient Growth and Share



[2] *Adult ART coverage calculated based on data available in UNAIDS AIDSinfo database as of July 2017 (only includes countries with both ART and PLWHA numbers reported)*

Figure 11: First-Line NRTI Market in GA LMICs, Patient Growth and Share[3]



TLD will significantly impact the first-line market due to improved clinical profiles and lower prices

Dolutegravir (DTG)

The US FDA tentative approvals of DTG-containing fixed-dose combinations (FDCs) with TDF and 3TC (TLD) from Mylan and Aurobindo in August 2017, followed closely by a pricing announcement, may be the most significant ARV-related highlights of 2017 in terms of treatment optimization.[xii,xiii] Patients in LMICs can now access DTG, a clinically superior and less expensive drug (relative to EFV) through a convenient FDC.

In July 2017, as a result of a catalytic procurement of DTG singles by CHAI and Unitaid, Kenya became the first LMIC to offer generic DTG as part of its public HIV program for routine use.[xiv] As of September 1, 2017, Kenya had approximately 1,400 patients on DTG with plans to scale up significantly more patients by the end of the year. The catalytic procurement also brought DTG singles to Nigeria and Uganda, and will be instrumental in helping to determine the key requirements for national DTG roll-out (Figure 12).

Further solidifying DTG as an important and optimal ARV, the WHO added the drug to their Essential Medicines List in 2017, which is a list of medicines the WHO considers essential to strong health systems worldwide.[xv] However, due to a lack of data on DTG use in pregnant women and patients with tuberculosis (TB) co-infections, TLD is listed as an *alternate* adult regimen in the most recent WHO ARV guidelines.[xvi] The exception, noted in the WHO's "Guidelines on the Public Health Response to Pretreatment HIV Drug Resistance" published in July 2017, is that TDF + (3TC or FTC) + DTG (TXD) is listed as the preferred alternative option as a *non-NNRTI-containing* 1L regimen for adults and adolescents.[xvii] The inclusion of TXD as the preferred non-NNRTI-containing regimen is important given high and increasing levels of resistance to NNRTI drugs such as efavirenz (EFV) and nevirapine (NVP) reported in many countries. For example, in Africa, pretreatment NNRTI resistance has been found to be greater than 10 percent in Namibia, Uganda, and Zimbabwe, and 8.1 percent in Cameroon.[xviii] TLD, as a one-pill, once-a-day FDC, will be an important option for such countries in particular.

Figure 12: CHAI-Unitaid Catalytic Procurement Summary

CHAI-Unitaid Catalytic Procurement of DTG Singles

Under the leadership of Ministries of Health in Kenya, Nigeria, and Uganda, CHAI and Unitaid have supported a catalytic procurement of DTG singles to help determine key requirements for national roll-out and to provide a platform for TLD FDC introduction.

H1 2017 Delivery	Key Goals:	
Kenya	• Understand patient preferences and provider training needs	• Inform areas for potential future trainings
Nigeria		• Identify prescriber knowledge gaps
Uganda		

While clinical studies evaluating the use of DTG in pregnancy and TB patients are underway, early data presented at IAS from Botswana (one of the earliest LMIC adopters of DTG), has shown that DTG-based regimens are *just as safe* as EFV-based regimens in pregnant women.[xix] Although more data is needed and expected in the coming years, Botswana's data is an important step in encouraging the uptake of DTG-containing regimens in LMICs.

The TLD pricing agreement announced in September 2017 to make TLD available at around US$75 PPPY should pave the way for rapid access to the medication, and enable overall treatment scale-up through cost savings. The announcement was made by the governments of South Africa and Kenya, together with UNAIDS, CHAI, the Bill & Melinda Gates Foundation (BMGF), Unitaid, the UK Department for International Development (DFID), PEPFAR, USAID, and the Global Fund, with Aurobindo and Mylan (Figure 13). Historically, new 1L FDC market entrants launched at higher prices than the existing market vanguards at the time (Figure 3). Thus, TLD launching at an average price of US$75 PPPY, less than the current cost of TLE, is an exciting and almost unprecedented development for patient access.

Figure 13: TLD Ceiling Price Agreement

TLD Pricing

During the 2017 United Nations General Assembly, a new price for TDF/3TC/DTG (300/300/50mg) tablets was announced.

~$75
per patient per year

"I am excited about this innovative agreement which will allow the government of South Africa to accelerate the introduction… which will greatly benefit our patients due to its superior therapeutic qualities."
– Dr. Aaron Motsoaledi, Minister of Health of South Africa

[3] *shares may not sum exactly to 100 percent due to rounding*

At the 2017 WHO ARV Forecasting Meeting[xx] in Geneva, the Republic of South Africa (RSA) voiced strong interest in switching from TEE to TLD as their preferred 1L adult treatment option in their next tender in 2018. This interest was solidified with the South African Minister of Health stating at the TLD price deal press conference that TLD would be available in his country through the public sector starting in 2018.[xxi] As the largest single market for ARVs, RSA's strong interest in TLD has the potential to rapidly drive volumes and economies of scale for the overall market. Even smaller volume countries such as Laos and Swaziland are moving to make TLD the preferred 1L regimen.

Ministries of Health, funders, and NGOs are not the only groups advocating for the use of dolutegravir in LMICs. PLHIV community groups are advocating access to this new optimal ARV as well. One such group is AfroCAB, the African Community Advisory Board, a network of community HIV treatment advocates across Africa with representatives from over a dozen African nations. AfroCAB ensures that African patient voices are taken into consideration during discussions on ARV drug access. They have been particularly instrumental in advocating for DTG at the patient level.

> "DTG means 'your best foot forward'!
> - Kenly Sikwese
> *Coordinator, AfroCAB*

Learnings from the roll-out of new ARVs, such as DTG 50mg, indicate that involving the patient community early and consistently in the planning process for introduction of new products is critical for ensuring patients have access to accurate information, and improving acceptability and long-term success of transition. It will be important to ensure a continuing dialogue between community groups, Ministries of Health (MoHs), and program implementers as new ARVs are introduced in the future.

Figure 14: Timeline of Major Milestones for DTG-Containing Adult ARV Products

Sep. 2016: FDA approves generic DTG singles (50 mg) from Aurobindo

Apr. 2017: First shipment of CHAI-Unitaid catalytic procurement arrives in Kenya

Aug. 2017: FDA approves two suppliers of a generic TLD FDC, Mylan and Aurobindo

Q1 2018: First deliveries of generic TLD expected to arrive in countries

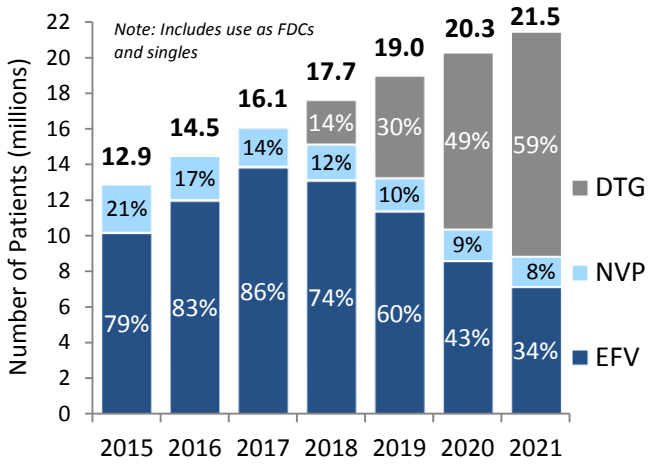
Low-dose efavirenz (TLE400)

Mylan's TDF/3TC/EFV (300/300/400 mg) tablet (TLE400), a variant of TLE600 with a lower dose of efavirenz, was tentatively approved by the FDA in Q1 2017.[xxii] The lower amount of active pharmaceutical ingredient (API) needed reduces the cost of the drug without compromising clinical efficacy.

However, given the FDA approval of two suppliers of TLD, which offers significant clinical, programmatic, and cost benefits over efavirenz-based regimens, programs should carefully consider the implications and complexities of adopting and phasing in TLE400 concurrently. CHAI would not recommend countries adopt TLE400 if it will delay introduction of TLD.

As a further indication of the market preference for TLD over TLE400, PEPFAR has now removed TLE400 from its ARV prioritization list to focus on procurement of TLD, and USAID is supporting market shaping activities to ensure accelerated access to TLD.[xxiii, xxiv]

Figure 15: First-Line NNRTI/INSTI Market in GA LMICs, Patient Growth and Share[4]



Given the excitement around TLD, CHAI expects relatively rapid scale-up in GA LMICs as TLD replaces TLE, TEE, and AZT/3TC/NVP (300/150/200mg) tablets (ZLN) as the preferred 1L drug of choice, albeit more data on pregnant women and TB co-infected patients remains an outstanding need for the WHO to list TLD as a *preferred* (rather than alternate) adult regimen. CHAI's projections based on in-country market intelligence show DTG-based regimens having a 59 percent market share by 2021 (Figure 15).

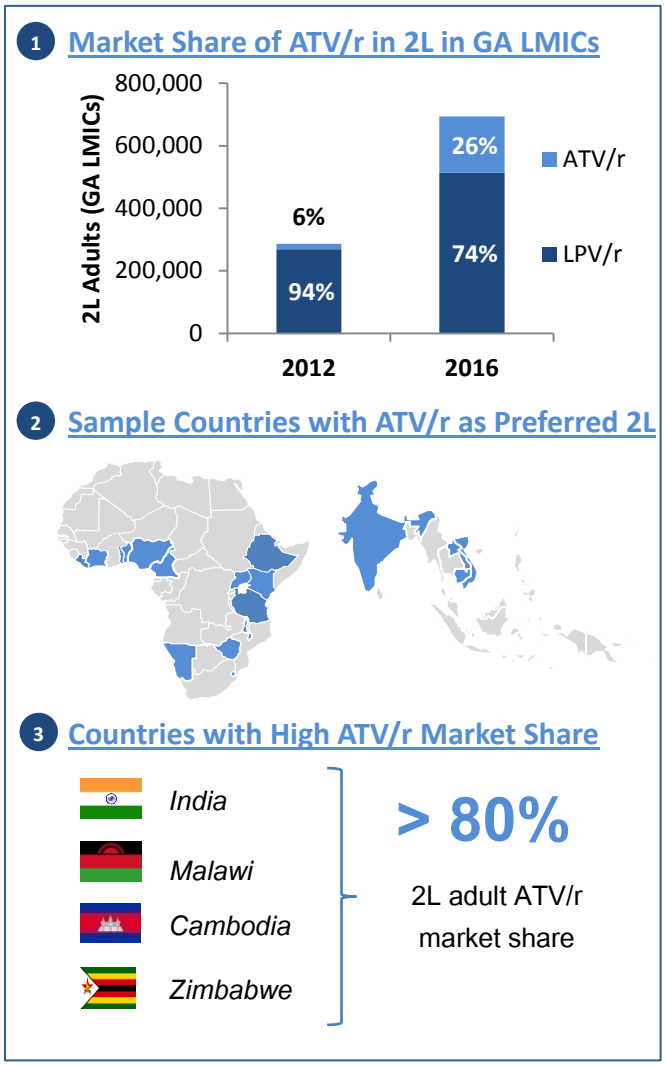
ATV/r is making progress over LPV/r as preferred PI for adult second-line regimens

Ever since the first generic tentative approval of an FDC in 2011, ATV/r's use has been increasing in 2L, due to its lower cost, favorable clinical profile, and lower pill burden compared to LPV/r. In 2016, ATV/r made up over a quarter of PIs used in 2L, compared to just 6 percent in 2012. There are now three stringent regulatory authority (SRA)-approved generic suppliers of ATV/r (Cipla, Emcure, and Mylan), which

[4] *shares may not sum exactly to 100 percent due to rounding*

should alleviate any concerns about supply security in the market that may have hindered uptake in the past.

Figure 16: ATV/r Market Trends in GA LMICs

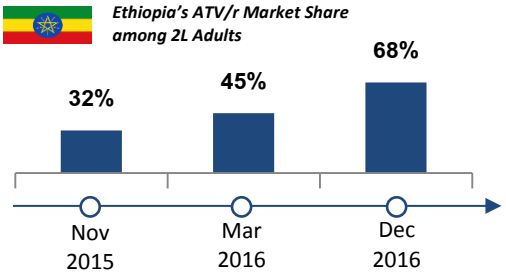


Many high-volume countries are using ATV/r as the preferred protease inhibitor (PI) for 2L patients in their national treatment guidelines. Some of those countries include Nigeria, Kenya, Malawi, Uganda, and Zimbabwe. CHAI anticipates that more countries will promote ATV/r to be the preferred 2L PI in the coming years (Figure 16).

In last year's market report, CHAI profiled Ethiopia's success in improving uptake of ATV/r by issuing a health circular from the Ministry of Health to clinics across the country promoting ATV/r use and conducting clinical mentorship and training activities. Their progress has continued, with ATV/r comprising 68 percent of 2L PI use in 2016, more than doubling of the market share since November 2015 (Figure 17).

Ethiopia's impressive increase in uptake of ATV/r over a short timeframe shows that a concerted effort on the part of Ministries of Health can have a significant impact on the uptake of optimal ARVs. Zambia is another example of a country that was able to make massive strides in ATV/r uptake between 2015 and 2016.

Figure 17: Ethiopia's ATV/r 2L PI Market Share Over Time



Adult pipeline products have potential to further improve clinical outcomes or reduce procurement costs

Darunavir (DRV) and TAF are both widely used ARVs in high-income countries due to their potency and improved side effect profiles. While generic versions are not currently available at affordable prices in LMICs, suppliers, along with CHAI, are working on developing and registering these products with the relevant regulatory authorities (Figure 18).

Figure 18: Overview of Pipeline ARVs: DRV/r and TAF

FDC DRV/r

Overview:
Fixed-dose combination of PI darunavir boosted with ritonavir

Potential Use:
As the preferred 2L PI, also potentially for TB patients

Availability:
Expected SRA approval of two generic suppliers by late 2018

TAF

Overview:
Tenofovir pro-drug that may reduce costs due to lower amounts of API

Potential Use:
As the preferred backbone for 1L adult regimens due to expected cost savings

Availability:
Expected SRA approval of two generic suppliers by mid-2019

While DRV is the most potent PI available, ultimate uptake will depend on multiple factors

While there is interest in DRV use in LMICs due to its improved efficacy and tolerability over available PIs, the ultimate role of DRV in second line is dependent on multiple factors.

- **Availability as an FDC:** DRV/r does not currently exist as an SRA-approved fixed-dose combination
- **Price:** The price of separate DRV and RTV singles is currently above that of both LPV/r and ATV/r (both available as FDCs). Availability of an FDC at a competitive price will be integral to eventual adoption in LMICs
- **Durability of TLD in 1L:** The reported efficacy of TLD as a first-line ARV with a high genetic barrier to resistance may mean that the need for DRV/r is delayed as patients will be stable on TLD for longer than they would be on other 1L ARVs

- **DTG in 2L:** While this topic will be discussed more in-depth in the coming pages, the potential for DTG to be used in 2L may mean DRV/r will ultimately be used as a third-line (3L) ARV for those patients failing EFV-based regimens and moving to DTG in 2L

Results from ongoing clinical trials on TAF required for inclusion in WHO guidelines, eventual LMIC uptake

TAF is a tenofovir pro-drug that has the potential to significantly reduce treatment costs relative to TDF-based regimens due to a significantly lower amount of API required per daily dose (25mg vs. 300mg). However, before national programs implement large-scale switches from TDF-containing FDCs to TAF-containing FDCs, they may await a change in the WHO guidelines for ARV treatment to include TAF-based FDCs as a preferred regimen for 1L therapy. Although TAF has been shown to be as effective as TDF, with potentially marginal safety benefits, further studies on pregnant women and patients being treated for TB with rifampicin-containing regimens are needed for a full WHO guideline change. Three key TAF studies are:

- **ADVANCE:** The ADVANCE study compares TAF+FTC+DTG to TDF+FTC+EFV (WHO preferred 1L regimen) and TDF+FTC+DTG. 48-week endpoint data is expected by the end of Q3 2019, and 96-week endpoint data at the end of Q3 2020
- **IMPAACT2010 (VESTED)**: The IMPAACT2010 (VESTED) study contains the same arms as ADVANCE, but with a target population of pregnant women at 14-28 weeks' gestation. Results are expected by the end of Q4 2020
- **RIFT:** The RIFT study is examining the pharmacokinetic (PK) profile of TAF and other drugs in TB patients. Endpoint data is anticipated by Q1 2018

As such, complete endpoint data is expected to be available for the WHO to review by Q4 2020. Assuming positive results, this would pave the way for adoption of TAF in LMICs beginning in 2021.

DTG in 2L, two-drug regimens, and long-acting ARVs may impact adult market in the future

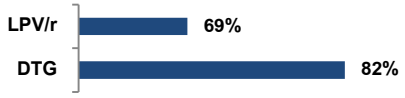
A number of clinical advances may eventually change current treatment paradigms.

DTG in Second-Line

The phase III DAWNING study, which is comparing DTG (+ 2 NRTIs) to LPV/r (+ two NRTIs) for 2L treatment, released preliminary results at IAS this year. At 24 weeks, 69 percent of those on LPV/r had a viral load below 50 copies per mL, compared to 82 percent of those on DTG (Figure 19).[xxv] In fact, the evidence supporting 2L DTG over LPV/r was so strong that patients in the LPV/r arm were offered the option to switch to the more effective DTG regimen, and the LPV/r arm was recommended for discontinuation.

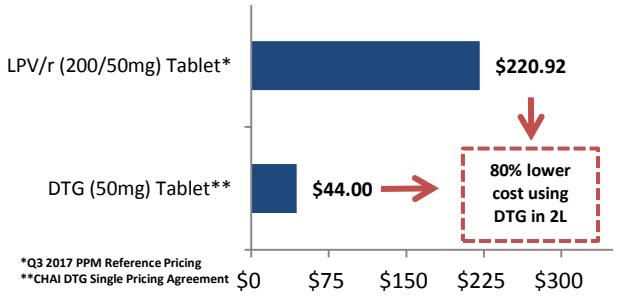
Further evidence supporting the use of DTG in 2L came from results of the NEAT 022 study, which switched virally suppressed patients at high cardiovascular risk from a ritonavir-boosted PI-based regimen to a DTG-containing regimen. The results showed that patients who switched to DTG maintained their viral suppression while also reducing blood lipid levels compared to those remaining on the ritonavir-boosted PI.[xxvi]

Figure 19: Rates of Viral Suppression at Week 24 by 3rd Position Drug in the DAWNING Study xxv



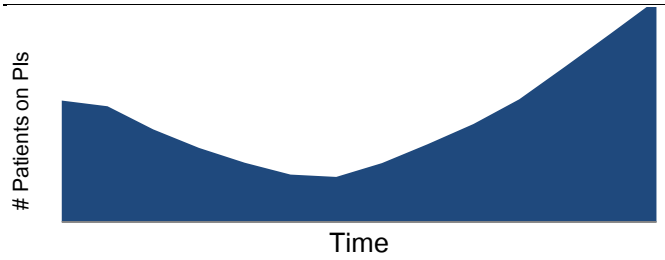
Although the superiority of DTG cannot yet be extrapolated to other PIs, it is important to note that treating adult 2L patients with DTG instead of LPV/r could enable significant cost savings for programs (Figure 20).[vi]

Figure 20: Sample Cost Scenario: DTG vs. LPV/r in 2L Adults



The use of DTG in 2L may mean that in the short-term the need for PIs may decrease. However, there will be a large need for PIs in the long-term as millions of PI-naïve patients begin to eventually fail their DTG-based therapy (whether in 1L or 2L), with DRV/r being the clinically superior option (Figure 21).

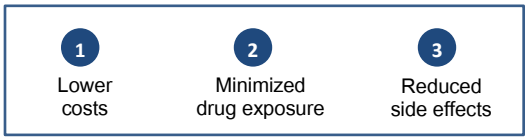
Figure 21: Likely Evolution of Need for PIs



Two-Drug Regimens

The current treatment paradigm of three- or four-drug regimens may one day be replaced with two-drug regimens. SWORD 1 and 2, two phase III clinical trials that are comparing DTG and rilpivirine (RPV) to various three- and four-drug regimens for the maintenance of viral suppression, have found that the DTG and RPV combination was non-inferior compared to triple/quadruple therapy, and even reported improvements in bone density.[xxvii] Studies with DTG+3TC have shown promising results, with more results expected in the near future.[xxviii, xxix, xxx, xxxi] Two drug-regimens have the potential to provide a variety of benefits to patients and national programs (Figure 22).

Figure 22: Potential Benefits of Two-Drug Regimens

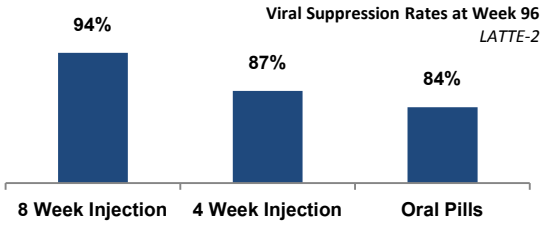


Long-Acting ARVs

Long-acting ARVs, which involve the routine injection or implantation of a drug over a set frequency (e.g., once every eight weeks), are another innovation that may impact the market by changing the way ART is delivered altogether.

The LATTE-2 trial tested long-acting cabotegravir (CAB LA) and RPV injections every 8 and 4 weeks against daily oral abacavir (ABC), lamivudine (3TC), and CAB (ABC+3TC+CAB). The trial found that viral suppression at 96 weeks via long-acting injectable administration was non-inferior to daily oral administration (Figure 23). Phase III studies are now underway with results expected in 2018.[xxxii]

Figure 23: Rates of Viral Suppression at Week 96 among Different ART Delivery Methods from LATTE-2 [xxv]



More details on the ARV pipeline, including longer-term prospects, can be found in the HIV i-Base *Fit for Purpose* report.[xxxiii]

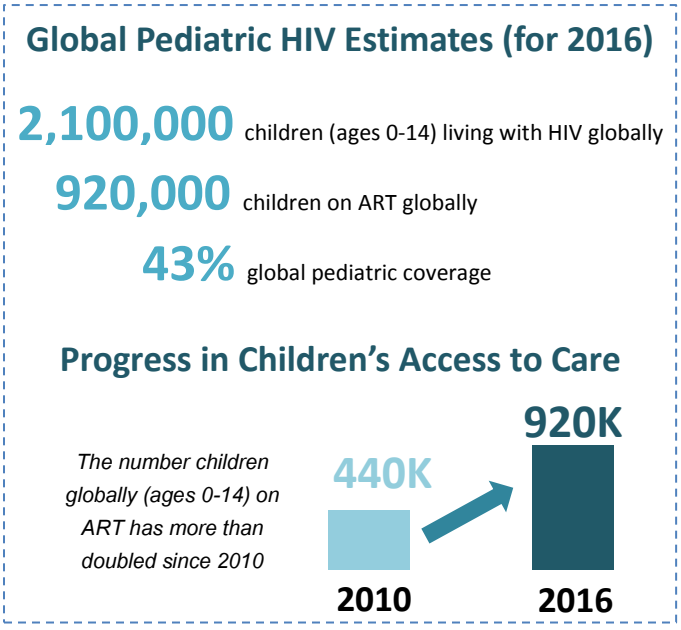
Pediatric ARV Market Trends

Over 900,000 children living with HIV are now accessing treatment

As of the end of 2016, there were more than two million children (ages 0-14) living with HIV (CLHIV) globally. The number of children being newly infected with HIV has decreased year-over-year due in a large part to the success of prevention of mother-to-child transmission (PMTCT) initiatives, in which all pregnant women with HIV are put on ART for life. Since 2009, the number of new infections among children has been halved, with 160,000 new pediatric infections in 2016. In terms of treatment, over 50,000 children were newly initiated on ART in 2016, with just over 40 percent of the world's CLHIV now accessing care (Figure 24).[ii]

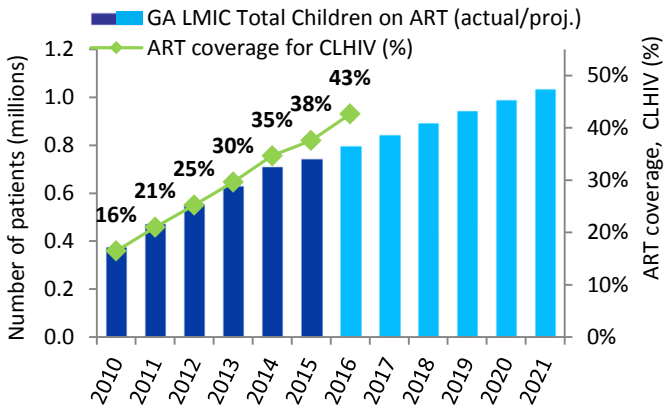
On an annual basis, UNAIDS revises its Spectrum epidemiology model, which produces the CLHIV and other HIV estimates, to reflect the most current HIV-related epidemiological data. In 2016 the model revision resulted in dramatically lower estimates for the number of CLHIV, and thus an effectively higher coverage rate than previously thought. The estimates shifted again with the 2017 revision, with new data on variables such as transmission rates during breastfeeding and fertility among women living with HIV with low CD4 counts, leading to slightly higher estimates of CLHIV than in 2016. This in turn resulted in a slightly lower coverage rate than previously modeled.[v]

Figure 24: Pediatric HIV Treatment Overview in 2016



Of the 920,000 children accessing treatment globally, more than 85 percent live in GALMICs. The number of children on treatment in GA LMICs is projected to increase from ~800,000 in 2016 to ~1 million by 2021 (Figure 25).

Figure 25: Number of Pediatric Patients on ART and Pediatric ART Coverage in GA LMICs[5]



GA LMICs continue to adopt WHO-preferred pediatric regimens and formulations for children on treatment

Since the start of 2016, over a dozen countries, including Botswana, Kenya, Nigeria, Uganda, Zambia, and Zimbabwe, have revised, published, and rolled-out new HIV treatment guidelines. Many of these guidelines reinforced the latest WHO-recommended regimens for 1L and 2L of treatment for children (Figure 26).[xxxix]

Figure 26: WHO-Preferred Pediatric 1L and 2L Regimens

Age	Preferred 1L	Preferred 2L
<3 yrs.	ABC (or AZT) + 3TC + LPV/r	2 NRTIs + RAL
3 - <10 yrs.	ABC + 3TC + EFV	2 NRTIs + (ATV/r or LVP/r)
10+ yrs.	TDF + 3TC (or FTC) + EFV	

Optimal formulations can serve as the foundation of WHO-preferred regimens. The Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children (IATT) periodically produces a pediatric ARV optimal formulary.[xxxiv] The formulations deemed optimal must constitute part of a WHO-preferred regimen, be available in resource-limited settings, have at least one SRA-approved manufacturer, be user-friendly, optimize supply chains, allow for flexible dosing, and can be accessed at comparative costs (the latest optimal list can be found in Appendix C). The IATT formulary has been very effective in serving as a reference to help optimize procurement of pediatric formulations. The synergies between the IATT and APWG have helped decrease the proportion of non-essential products procured via the APWG from roughly 30 percent in 2010 to only 5 percent in 2016, when comparing the prevailing IATT list for the year in question.[xxxv]

Ministries of Health, bolstered in many cases by the momentum of releasing new national HIV guidelines, are expected to continue to make strides in the years ahead toward providing CLHIV the best treatment regimens by using optimal formulations.

ABC is expected to dominate the pediatric NRTI market over the next five years

By 2021, ABC is forecasted to make up more than 60 percent of the pediatric NRTI market (Figure 29). This is largely driven by ABC being part of the WHO-preferred 1L regimens for all children less than 10 years of age. To note, countries such as Kenya, Uganda, and Tanzania are expected to see large increases in ABC-use amongst pediatric patients through continued movement towards preferred regimens. A key asset in driving ABC adoption will be the pill-burden reducing ABC/3TC (120/60mg) dispersible tablets, which have seen further uptake over the past year (Figure 27).

AZT, which is only WHO-preferred for patients less than three years of age, is expected to continue to decline in market share over the next five years (Figure 28). Many programs have historically used AZT for treating children because of the affordable and low pill burden AZT/3TC/NVP (60/30/50mg) dispersible tablets (ZLN disp.). However, in 2016, ZLN disp. was demoted to the limited-use IATT formulary given that AZT+3TC+NVP regimen is no longer a preferred regimen for any age group per WHO guidelines (except infants between 0-2 weeks, for whom oral solutions are recommended).[xxxix, xxxiv]

Figure 27: ABC/3TC (120/60mg) Dispersible Tablet Overview

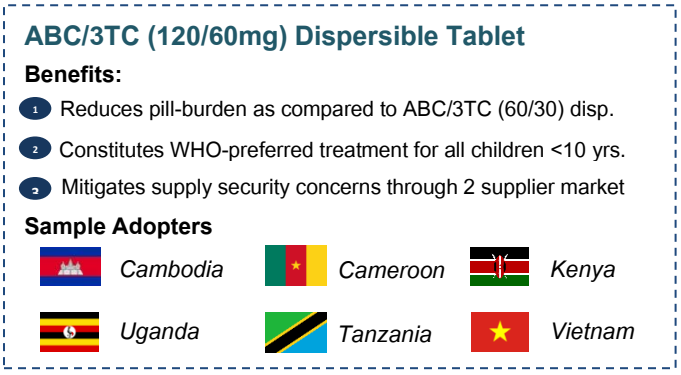
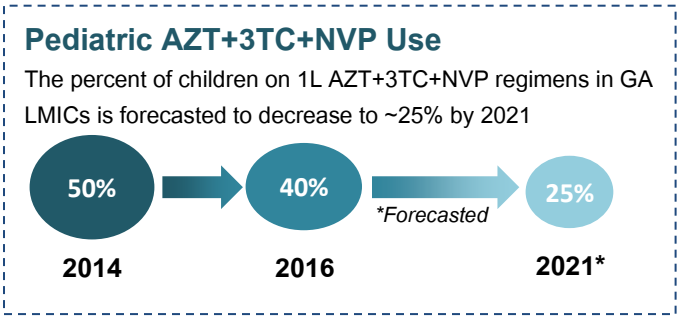


Figure 28: Pediatric AZT+3TC+NVP Regimen Update

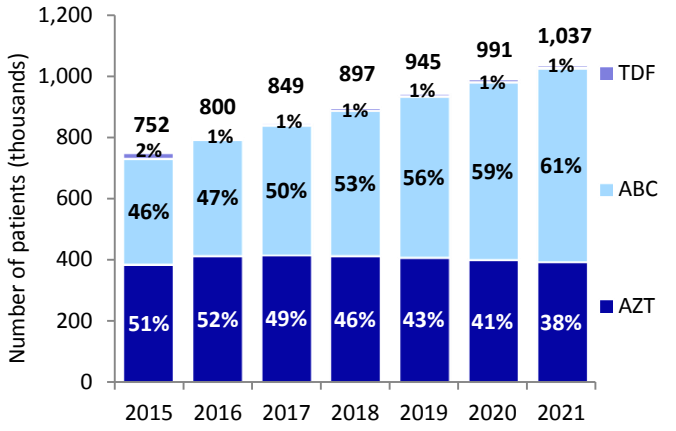


While AZT use is forecasted to decrease, it will not entirely be phased-out of the market given that many pediatric patients will switch to AZT following failure of ABC- or TDF-based 1L regimens.

[5] *ART coverage for adults calculated based on data available in UNAIDS AIDSinfo database as of July 2017 (only includes countries with both ART and PLWHA numbers reported)*

Historically, TDF use has constituted a relatively small percentage of the overall pediatric market. Generally, this is attributable to a lack of an appropriate fixed-dose combination of TDF for pediatric patients, which increases pill burden, as well as concerns about the long term toxicity of TDF in pediatric populations. As such, TDF-based regimens are not recommended as preferred for 0-10 year old children, and TDF single tablets were demoted to the IATT non-essential list in 2016. In 2016, there was a slight decrease in TDF's overall pediatric market share, as Zambia, historically a driver of TDF 200mg use, is phasing out its use.

Figure 29: Pediatric NRTI Market in GA LMICs[6]



Finally, it is important to note that d4T has essentially been phased-out with just a handful of pediatric patients remaining on d4T-based treatment today.

EFV and LPV/r are expected to see further adoption, with NVP expected to be phased-out slowly

LPV/r use, which is the WHO-preferred 1L regimen for children less than 3 years old and also serves as the preferred pediatric 2L regimen in most national programs, is forecasted to increase slightly between 2016 and 2021 (from 23 percent to 28 percent). Historically, LPV/r uptake for young children has been hampered by lack of availability of heat-stable formulations for children less than 3 years. Over the past year, the new heat-stable LPV/r oral pellet product has begun to see significant uptake across many LMICs, which resulted in supply security concerns starting in late 2016 (Figure 30).

EFV, which is part of the preferred 1L regimen for pediatric patients older than 3 years old, is expected to see further uptake in the coming years as MoHs continue to transition away from NVP use. The IATT optimal product EFV (200 mg) scored tablets have helped promote pediatric EFV adoption in over 30 LMICs.[vii] Price, however, tends to be one challenge with the EFV (200 mg) scored tablet. Since Q1 2015, the PPM reference price for EFV (200 mg) scored tablets has remained unchanged at US$9.20/pack.[vi] This formulation would benefit from the entrance of a second and third supplier resulting in more competitive pricing.

For similar reasons to AZT, NVP is expected to see its market share decrease. NVP is no longer a part of preferred WHO-regimens (with the exception being children less than 2 weeks old), and products such as

Figure 30: LPV/r Oral Pellet Market Development Overview

LPV/r Oral Pellet Timeline

May 2015
Cipla received US FDA approval for pellets after many years of development

Mid-2016
After manufacturing pellets only for clinical uses, Cipla began to commercialize product

December 2016
Following low-volume orders for pellets during the first few months of commercial availability, demand began to exceed production capacity

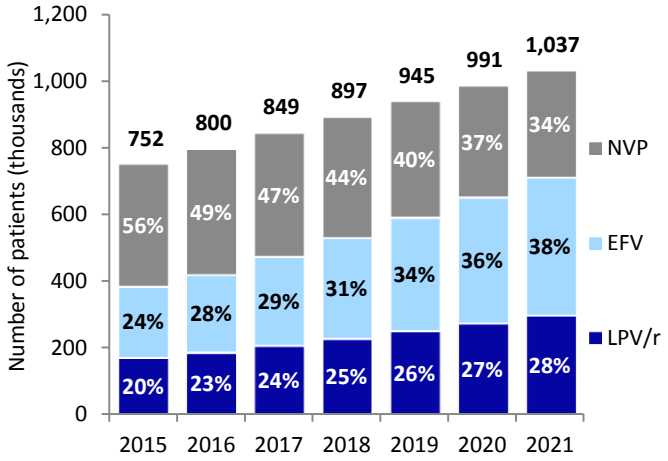
March 2017
After a face-to-face meeting with Cipla and Mylan, the APWG published a memo advising national programs on LPV/r supply security concerns, and advising programs to expect long lead times, stagger larger orders, and carefully quantify need for pellets

April 2017 – Present Day
The APWG has been holding monthly calls with Cipla to ensure supply is able to meet current and future demand, and is monitoring orders through quarterly order cycles

Future Outlook
Cipla is expected to be able to scale-up production capacity in H1 2018. In addition, Mylan is expected to receive SRA approval for its heat-stable granule product in H2 2018

Active monitoring through the APWG will continue until there is sufficient stability in the market

Figure 31: Pediatric NNRTI/PI Market in GA LMICs



[6] *Shares may not sum exactly to 100 percent due to rounding*

AZT/3TC/NVP (60/30/50 mg) dispersible tablets are deemed limited-use by the IATT. As NVP has historically made up more than 50 percent of the NNRTI and PI market, it may take time for the product to be phased-out entirely.

Despite being the preferred 2L drug for patients less than 3 years of age, raltegravir (RAL) has seen very limited uptake in national programs. RAL (100 mg) chewable tablets, the IATT optimal formulation, are not currently generically available and are costly relative to other potential 2L options such as LPV/r (100/25mg) tablets.

New pipeline ARVs are expected to launch in the pediatric market in the coming years

The pediatric ARV market is anticipating the launch of multiple new generic products by 2020, including LPV/r granules and FDCs that provide WHO-preferred regimens in one formulation (Figure 32).

The Pediatric Antiretroviral Drug Optimization (PADO) group, which is led by the WHO and includes clinical expertise from various partner organizations, met in December 2016 to prioritize pipeline ARVs for technical, clinical, and regulatory support. PADO's mid-term priority drugs, which traditionally are 3-5 years away from launching in the generic market, include pediatric formulations such as DTG and DRV/r (the complete list can be found in Appendix D).[xxxvi] While many of these products are a few years away from launching in the GA market, collaboration amongst key partners will be needed to ensure these superior products reach the market in an efficient and timely manner.

Figure 32: Pediatric ARVs Expected to Launch by 2020

LPV/r (40/10 mg) Granules
Use: Another heat-stable, solid formulation alternative to cold chain-dependent LPV/r oral solution
Expected first generic SRA approval: H2 2018

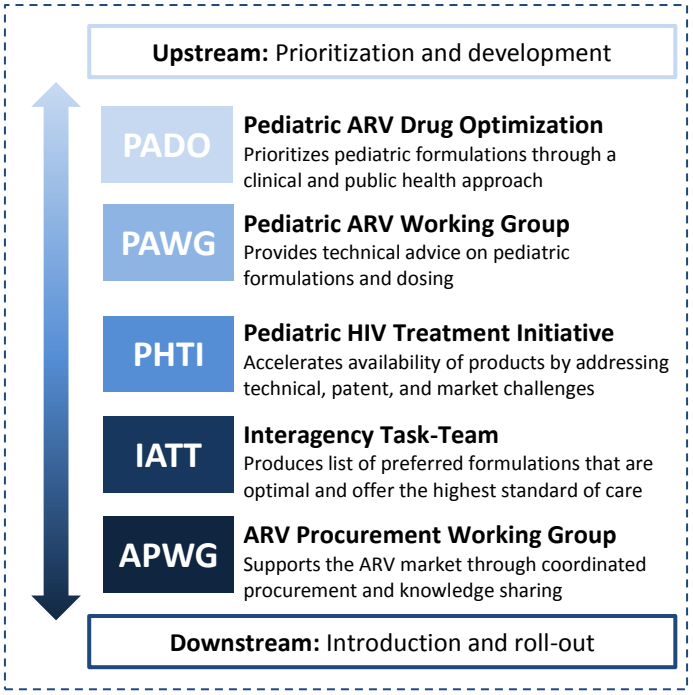
ABC/3TC/LPV/r (30/15/40/10 mg) FDC ("4-in-1")
Use: Provides the WHO-preferred regimen for patients less than 3 years in one formulation (granules)
Expected first generic SRA approval: H2 2019

ABC/3TC/EFV (150/75/150 mg) FDC
Use: Provides the WHO-preferred regimen for patients between 3-10 years old in one dispersible pill
Expected first generic SRA approval: H2 2019

The pediatric market continues to be supported by a range of partner organizations focused on drug optimization

Given the fragile nature of the pediatric market, both due to its small size and complexity around a diverse range of products for different age and weight bands, a number of related collaborations have been created to help bring new optimal ARVs to the market (Figure 33).

Figure 33: Partner Collaborations Supporting Pediatric ARVs



PADO, PAWG, and PHTI have been fundamental in prioritizing and leading the clinical, regulatory, and development initiatives behind emerging products such as the aforementioned ABC/3TC/LPV/r "4-in-1" and ABC/3TC/EFV (150/75/150mg) tablets. Additionally, as discussed earlier, the synergies between the IATT and AWPG have helped drive treatment optimization.

Building on the successes and lessons learned from these partner organizations to date, the Global Accelerator for Pediatric Formulations (GAP-f) is a newer initiative that aims to further catalyze and promote the development and commercialization of novel, optimal pediatric formulations.

The number of children living with HIV is expected to decrease over the coming decade

Unlike the adult market, the pediatric market, in terms of the number of children living with HIV (CLHIV), is expected to decrease in size over the next decade, driven by successful PMTCT initiatives and the "ageing-out" of CLHIV into the adult market. CHAI's analysis shows that the pediatric market may decrease to between 500,000 and 730,000 CLHIV across the 27 highest-burden countries by 2026 (Figure 34).[7] It is important to note that ART coverage for children is less than 50% today, so scale-up efforts must continue to ensure that all CLHIV, regardless of market size, have access to optimal treatment. In the short- to medium- term, the market in terms of CLHIV on ART should grow as more children are put on treatment (Figure 25).

[7] *At IAS 2017, CHAI presented an abstract in which the projected range of CLHIV in 2025 was between 350,000 and 500,000.*[xxxvii] *The latest forecast is based on updated UNAIDS numbers, which now suggest ~400,000 more CHLIV than the 2016 estimate.*

In the decade ahead, it will be critical for partner organizations to prepare for the decreasing pediatric market size. The size of the market will not only dictate the potential demand, but will also inform how the supply side of the market can adequately prepare to support that demand.

Figure 34: CLHIV Population Forecast Through 2026

1 Super Fast-Track targets seek to drastically reduce infections

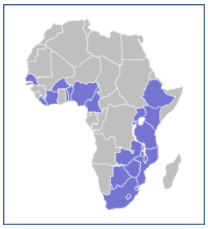
START FREE

Goal: Eliminate new HIV infections among children by reducing the number of children **newly infected to less than** 40,000 by 2018 and **20,000 by 2020.**

2 CLHIV forecasting requires an age-based approach

Provisional age-specific population data for 27 LMICs from UNAIDS was used to forecast CLHIV

- In 2016, the 27 countries represented 90 percent of global CLHIV



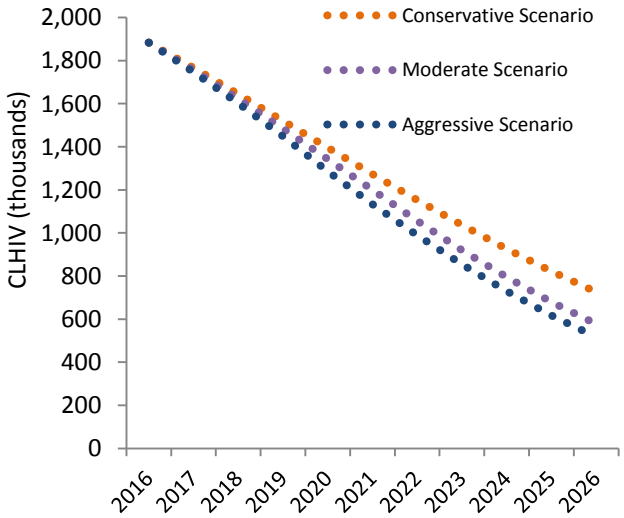
The CLHIV forecast is based on tracking cohorts of children by age and includes modeling on:

- New HIV infections
- Mortality
- "Ageing-out" into adult market

3 Assuming three scenarios….

Aggressive Scenario: Super Fast-Track Targets met by 2020
Moderate Scenario: Super Fast-Track Targets met by 2022
Conservative Scenario: Similar decrease in infections as 2012-16

4 ….the number of CLHIV (ages 0-14) is expected to fall between 500,000 and 730,000 by 2026 for these 27 high-burden LMICs



Prevention

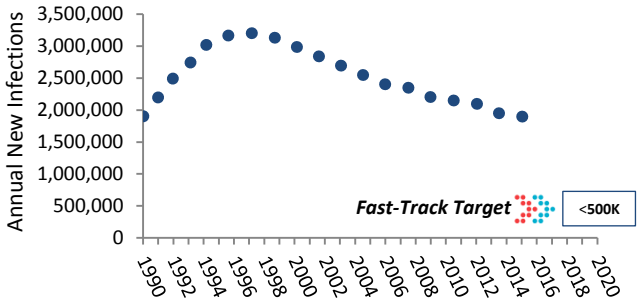
Annual new HIV infections continue to decline, but much work remains to meet Fast-Track Targets by 2020.

Ever since peaking in the mid- to- late 1990s, the number of annual HIV infections has continued to decrease year-over-year from 3.2 million new HIV infections in 1996 to 1.8 million in 2016.[ii]

Previously, UNAIDS had estimated that the number of new HIV infections remained static at about 2 million per year between 2010 and 2015. Newly available epidemiological data, however, led UNAIDS to revise its annual infection estimates in 2017. For example, previously it was estimated that there was a 4 percent decrease in the number of new HIV infections among adults between 2010 and 2016. It was recently determined to be an 18 percent decrease during the same period.[i]

The global Fast-Track Targets currently set a goal of reducing the number of new HIV infections to be below 500,000 by 2020. Despite the modest decrease in the number of new HIV infections each year, the Fast-Track target is not expected to be met based on the current trajectory (Figure 35).

Figure 35: Estimated Annual New HIV Infections Globally Between 1990 and 2016



As mentioned in the "State of HIV/AIDS Today" section, addressing the significant disparities within the HIV infection estimates is key to curbing the epidemic. Focusing prevention efforts toward adolescent girls and young women (ages 15- 24), for example, will be crucial to slow new infection rates in that population. ART scale-up alone will not be enough to meet the Fast-Track targets by 2020. Further work is needed to both ensure access to effective prevention technologies and to enable adherence and usage by all populations, in particular adolescents.

TDF-based oral PrEP sees further adoption in LMICs

Oral PrEP, or the use of daily TDF-based ARVs to help decrease the likelihood of HIV infection, is one prevention option that can help decrease the number of new HIV infections in high-risk individuals. Various phase III trials such as iPrEx and Partners PrEP have shown the use of daily TDF-based regimens to be effective at decreasing the risk of acquiring HIV. In Partners PrEP, for example, TDF+FTC was found to decrease the likelihood of HIV infection by 73 percent in serodiscordant HIV-negative MSM when adherence was above 90 percent.[xxxviii]

The WHO currently recommends oral PrEP be offered to those individuals at substantial risk of HIV infection (defined as HIV incidence greater than 3 per 100-person years). [xxxix] Various LMICs have included guidance on oral PrEP to date (Figure 36).

Figure 36: Oral PrEP Adoption To Date

10+ LMICs have included oral PrEP guidance in national guidelines

Sample LMICs That Have Introduced Oral PrEP Guidance

Botswana *Kenya* *Myanmar* *South Africa* *Zambia*

The initial and continued roll-out of oral PrEP builds upon existing biomedical prevention programs at the country-level, including voluntary medical male circumcision (VMMC) and condom distribution. While these programs have helped drive a reduction in new infections to date, oral PrEP provides an opportunity to expand the number of prevention tools available, particularly for women.

Figure 37: South Africa Oral PrEP Adoption Timeline

Timeline of South Africa's Oral PrEP Roll-Out

September 2015 World Health Organization
The WHO releases updated guidance on use of oral PrEP for HIV prevention

October 2015 health
South Africa's National Department of Health (NDOH) forms an oral PrEP technical working group and drafts guidelines

June 2016
South Africa becomes the first LMIC to introduce oral PrEP through national program

June 2016 – July 2017
The first phase of oral PrEP roll-out primarily focuses on female sex workers. As of July 2017, over 2,300 individuals have been initiated on oral PrEP across 17 sites and within six of South Africa's nine provinces

July 2017 IAS2017
At IAS 2017, South Africa announces intention to continue phased expansion of oral PrEP programming, including university campus clinics

Future Outlook
South Africa is carefully considering additional options for broader program expansion, in particular for adolescent girls and young women

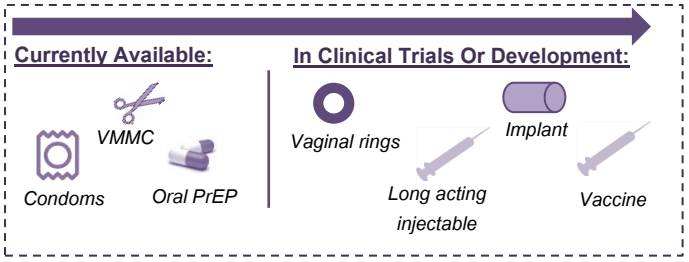
In mid-2016, South Africa became the first LMIC to introduce oral PrEP through a national program (Figure 37). South Africa currently recommends TDF/FTC for oral PrEP and has at least 5 TDF/FTC products currently registered for prevention use.

Looking ahead, national programs will need to carefully consider how they will monitor and evaluate the success of oral PrEP rollout. Unlike treatment, where people living with HIV are expected to take ARVs daily for life, a person taking oral PrEP may cycle on and off usage for varying lengths of time. This makes it more difficult to track oral PrEP effective use and adherence across national programs, and requires innovative models of tracking beyond initiation and continued use to understand what 'uptake' and 'effective use' truly look like.

Numerous prevention technologies are currently at various stages in the research and development pipeline (Figure 38). Beyond decreasing the likelihood of HIV infection, these technologies, such as long-acting cabotegravir (CAB LA) and other injectable and implantable PrEP options, represent a varied set of offerings that could meet the individual needs of diverse populations.

AVAC, a leading global advocacy organization in the field of HIV prevention, has a wealth of knowledge and resources on the pipeline of prevention technologies and its website is a useful asset to understand the future implications of the newer prevention technologies: http://www.avac.org/infographic/2016-17-percolating-pipeline

Figure 38: Current and Pipeline Prevention Technologies

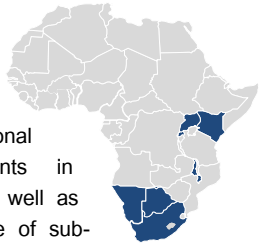


Diagnostics and Lab Services

Viral load testing continues to scale up in LMICs

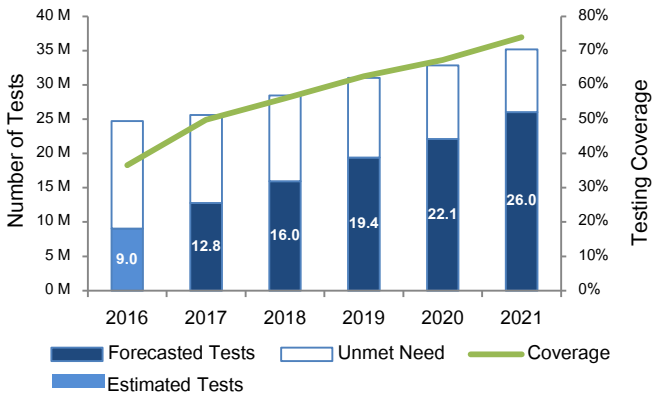
Routine viral load (VL) testing allows national programs to detect cases of treatment failure earlier and more accurately than clinical or immunological monitoring alone. In addition, it provides opportunities to strengthen adherence to 1L regimens instead of unnecessarily switching to more expensive 2L products.[xl] While there are few studies on the impact of VL testing on the number of patients on 2L ART, it is expected that increased access to routine VL testing will generally increase the number of patients moved to 2L as patients already truly undergoing virologic failure are proactively identified in the short-term. At the same time, the changing 1L regimen mix to more durable DTG-based therapy may reduce or delay the net 1L treatment failure rate.

Several countries in sub-Saharan Africa already have public sector viral load programs with high patient coverage rates (including those countries highlighted on the right). More recently, Cameroon, Ethiopia, Nigeria, Swaziland, Tanzania, Zambia, and Zimbabwe have made progress scaling up national VL testing programs through investments in strengthening systems and supply chains as well as leading demand generation activities. Outside of sub-Saharan Africa, India has launched a major tender to support national scale-up, and Brazil already has a well-established viral load testing program.



In addition to increasing VL demand from national programs, the cost of VL testing has decreased over recent years. As an example, in April 2017, the Global Fund shared the results of its VL tender, which included quoted pricing from diverse suppliers such as Abbott, Biocentric, BioMérieux, Cepheid, Diagnostics for the Real World, Hologic, Qiagen and Roche, and ultimately yielded transparency around the scale-up costs that can be accessed by countries.[xli]

Figure 39: Estimated/Forecasted VL Testing Demand in LMICs (2016 – 2021)



Finally, in July 2017, the Xpert® HIV-1 Viral Load assay became the first WHO pre-qualified near-POC VL product. Previously, Xpert® HIV-1 Viral Load assay (in addition to Samba I and II) had only been CE marked. Cepheid GeneXpert allows viral load testing to be decentralized to district hospitals, and may improve efficiency of diagnostic services across diseases given that multiple assays can be run on the same platform.

Given the increasing demand from national programs and decreasing costs, the number of VL tests conducted is projected to increase to approximately 26 million in 2021 (Figure 39).

CD4 testing still has a role, especially in identification of patients with advanced HIV disease

In June 2017, the WHO released *Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy,* which highlights a package of interventions, including screening tests, treatments, and prophylaxis for common opportunistic infections, as well as recommendations for rapid ART initiation and intensified adherence support.[xlii] The WHO strongly recommends that this package is provided to all people living with HIV/AIDS (PLHIV) who present with advanced HIV disease (Figure 40).

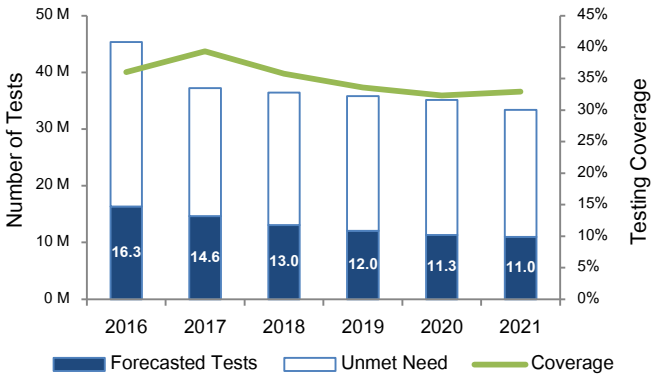
Figure 40: WHO's Definition of Advanced HIV Disease

WHO's Definition of Advanced HIV

Adults and Children (Ages 5+)	***Children (Ages <5)***
CD4 < 200 cells/mm^3 *or* WHO stage 3 or 4	All children under 5 living with HIV

A number of the interventions included in the advanced disease package of care are dependent on the CD4 count of the patient, including use of lateral flow urine lipoarabinomannan assay (LF-LAM) for extra-pulmonary TB diagnosis and Cryptococcal antigen screening, and treatment with co-trimoxazole prophylaxis.

Figure 41: Forecasted CD4 Testing Demand in LMICs (2016 – 2021)



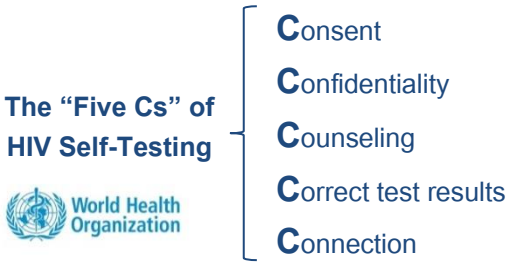
The use of CD4 testing as a trigger for further advanced disease screening and treatment underscores the importance of maintaining access to CD4 testing, even as countries implement Test and Treat policies and scale up VL testing. While access to CD4 testing should no longer be a barrier for treatment initiation, the WHO does still recommend CD4 testing at baseline to identify patients with advanced disease, and to determine the immune status of those with virologic

failure to guide clinical decision-making. However, the demand for CD4 tests is expected to gradually decline (Figure 41).

HIV self-testing (HIVST) gains traction with new WHO recommendations and SRA-approved products

In December 2016, the WHO released supplementary *Guidelines on HIV Self-Testing and Partner Notification*. Under the new guidelines, the WHO strongly recommends that HIV self-testing (HIVST) be offered as an additional approach to HIV testing services, noting that HIVST services should adhere to the WHO's "Five Cs" of HIV testing services (Figure 42).[xliii] This recommendation is supported by evidence that shows HIVST increases uptake of HIV testing among hard-to-reach populations, including male partners of pregnant women and men who have sex with men, and can be conducted safely and accurately by non-health workers without causing potential social harm due to stigma. However, the guidelines do highlight the need for additional research and monitoring and evaluation of linkage to care strategies in order to ensure that users access appropriate prevention, treatment, and care services after testing.

Figure 42: WHO's "Five Cs" of HIV Testing Servicesxliii



The OraQuick® HIV self-test was the first HIVST product to receive WHO pre-qualification (PQ) in July 2017, paving the way for its procurement and use in LMICs. The Bill & Melinda Gates Foundation (BMGF) along with OraSure, the manufacturer of the OraQuick® test, announced a Charitable Support Agreement in 2017 to provide the test at an affordable price to 50 eligible LMICs within Africa and Asia. (Figure 43).[xliv] The reduced pricing is expected to rapidly increase access to HIVST.

Figure 43: Details of BMGF and OraSure HIVST Pricing Agreement

BMGF and OraSure HIVST Pricing Agreement

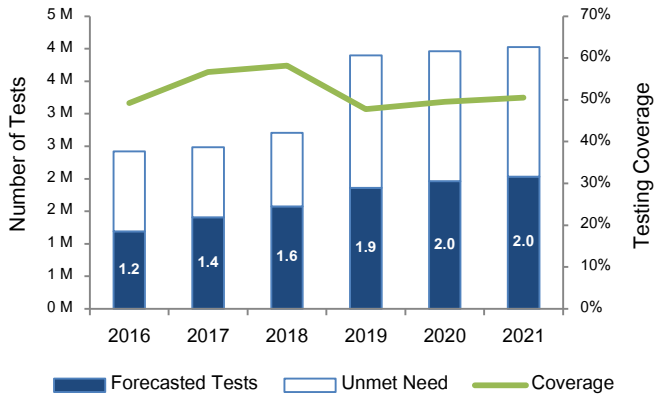
US$2.00	*cost per HIVST*
US$20M	*total BMGF investment*
4 years	*length of agreement*

Further, the Kenyan Ministry of Health has launched a self-testing campaign, with HIVST kits available in select health facilities and pharmacies for approximately US$8.00.[xlv] Kenya's experience launching HIVST for sale outside of health facilities will likely serve as a barometer for other LMICs interested in launching their own self-testing programs.

Despite scaling up of EID testing, coverage is still estimated to be below 50 percent

In 2016, the WHO released new early infant diagnosis (EID) guidelines (as part of the general consolidated HIV guidelines revision) aimed at increasing testing coverage, case finding, and linkage to care. Sample inclusions in the guidelines were the addition of nucleic acid testing (NAT) at birth to existing EID testing approaches, and recommendations on point-of-care (POC) EID testing of infants and children of unknown HIV status in malnutrition, outpatient, and immunization clinics. Ultimately, EID coverage in LMICs was expected to only be 49 percent in 2016 (Figure 44). As the mortality for untreated HIV-positive infants peaks between 2-3 months after birth, identifying and testing HIV-exposed infants as quickly as possible is critical to ensuring HIV-positive children are put on ART right away.

Figure 44: EID Testing Demand in LMICs (2016 – 2021)



Since the impact of POC EID on reducing both result turnaround time, time to treatment initiation, and ultimately increased ART initiation rates were demonstrated, a number of additional countries have registered POC EID platforms for routine use in anticipation of conducting implementation pilots, or have made the decision to scale-up POC EID nationwide. Currently, there are two WHO pre-qualified products available on the market – the Alere™q HIV-1/2 Detect and the Cepheid Xpert®HIV-1 Qual.[xlvi, xlvii] Both of these tests, as well as the SAMBA II HIV-1 Qualitative Whole Blood Test, have CE-IVD marking.

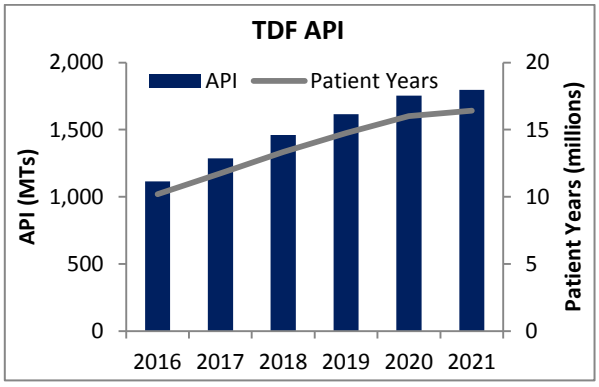
A study presented at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI) found that, in Mozambique, POC EID greatly improved turnaround times for patients to receive results, and shortened time to ART initiation and increased rates of ART initiation as compared to the standard of care (SOC) (Figure 45).[xlviii]

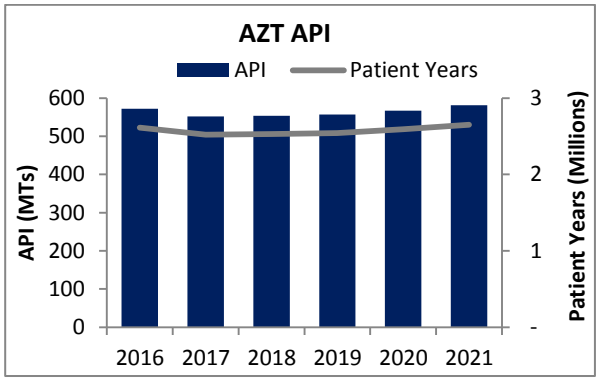
Figure 45: Impact of POC EID on Turnaround Times in Mozambique

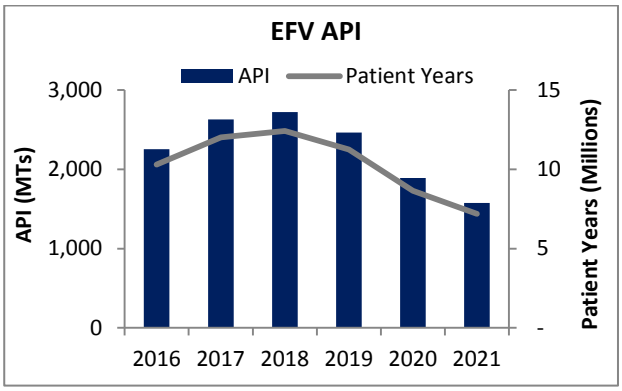
Early Infant Diagnosis	Point-of-care	Standard of care
Infants receiving test results w/in 60 days of sample collection	99.5%	11.8%
Infants starting ART w/in 60 days of sample collection	87.4%	12.8%

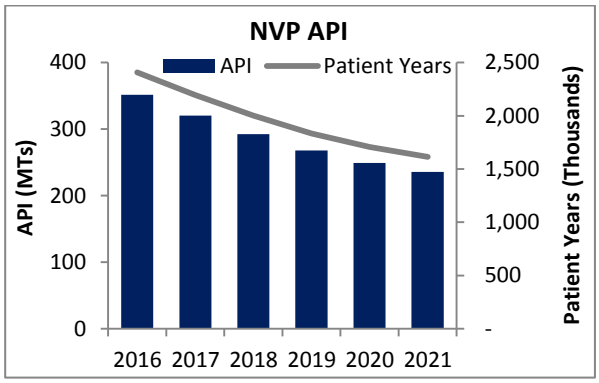
Appendix A: Forecasted API Demand in GA LMICs

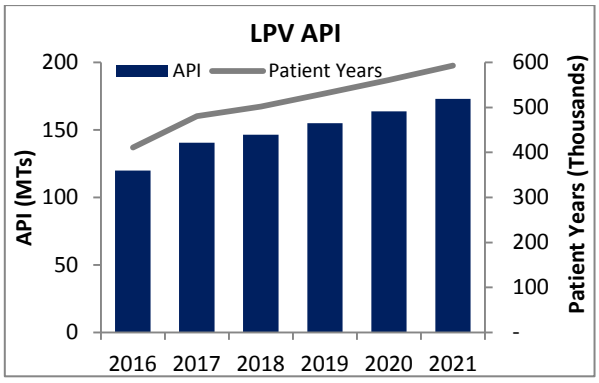
The graphs below show the estimated generic-accessible patient demand and API volume forecast for key adult ARVs. Patient years represent the effective number of patients on treatment for a full year and are used to calculate yearly API demand. Patient years are calculated by assuming newly-initiated patients are on treatment for 6 months on average in the year of initiation, and a 15 percent attrition rate assumed to estimate yearly new initiations. Note that all figures are based on demand for adults only.

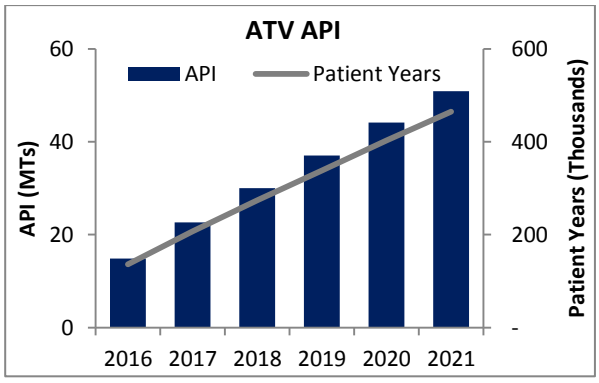


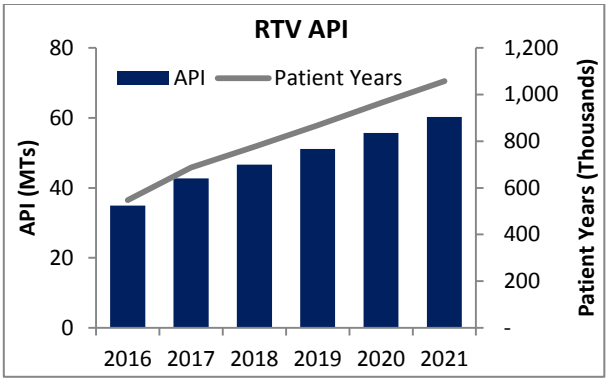


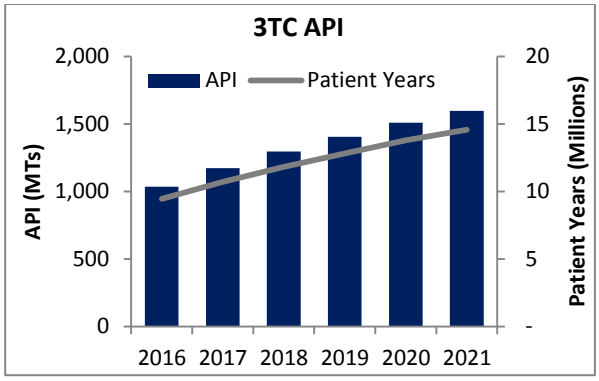









RTV API
API
Patient Years
API (MTs)
Patient Years (Thousands)
0
20
40
60
80
-
200
400
600
800
1,000
1,200
2016
2017
2018
2019
2020
2021


3TC API
API
Patient Years
API (MTs)
Patient Years (Millions)
0
500
1,000
1,500
2,000
-
5
10
15
20
2016
2017
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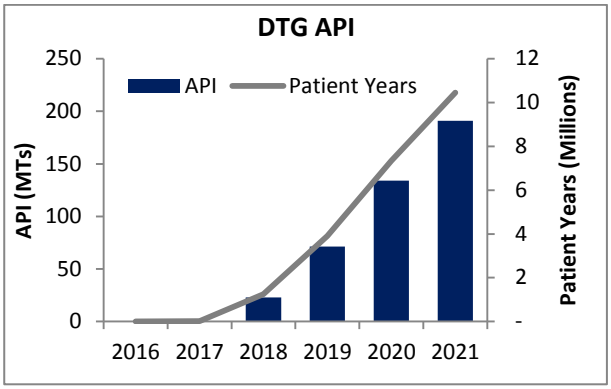
2021


DTG API
API
Patient Years
API (MTs)
Patient Years (Millions)
0
50
100
150
200
250
-
2
4
6
8
10
12
2016
2017
2018
2019
2020
2021

Appendix B: CHAI Benchmark Price Comparison List

The reference price list below provides per pack or bottle prices for key adults and pediatric ARVs. Prices are EXW unless otherwise noted.

Product	Packaging	CHAI Reference Price, 2017 (USD)	MSF Price, July 2017 (USD)[8]	Global Fund PPM Price, Sep 2017 (USD)[9]	2015-2018 RSA Tender Weighted Average Price (USD)[10]
Adult Products					
3TC *(150mg)*	HDPE bottle 60 tablets[11]	TBA	$1.74	$2.25	$1.66
ABC *(300mg)*	HDPE bottle 60 tablets[11]	TBA	$9.48	$11.00	$10.20
ATV/r *(300/100mg)*	HDPE bottle 30 tablets	TBA	$17.01	$15.00	-
AZT *(300mg)*	HDPE bottle 60 tablets[11]	TBA	$4.50	$5.60	$5.63
AZT/3TC *(300/150mg)*	HDPE bottle 60 tablets[11]	TBA	$4.98	$5.10	$7.04
AZT/3TC/NVP *(300/150/200mg)*	HDPE bottle 60 tablets	TBA	$6.48	$6.05	-
DTG *(50mg)*	HDPE bottle 30 tablets	$3.67*	$5.01	$4.00	-
EFV *(600mg)*	HDPE bottle 30 tablets[11]	TBA	$2.46	$3.15	$3.37
LPV/r *(200/50mg)*	HDPE bottle 120 tablets[11]	TBA	$17.76	$18.41	$12.70
NVP *(200mg)*	HDPE bottle 60 tablets[11]	TBA	$1.92	$2.20	$2.35
RTV *(100mg)* heat-stable	HDPE bottle 30 tablets	TBA	$3.42	-	-
TDF *(300mg)*	HDPE bottle 30 tablets[11]	TBA	$2.49	$3.50	$2.45
TDF/3TC *(300/300mg)*	HDPE bottle 30 tablets	TBA	$3.21	$4.15	-
TDF/FTC *(300/200mg)*	HDPE bottle 30 tablets[11]	TBA	$3.99	$5.25	$5.32
TDF/3TC/DTG *(300/300/50mg)*	HDPE bottle 30 tablets	~ $6.25**	-	$6.75	-
TDF/3TC/EFV *(300/300/400mg)*	HDPE bottle 30 tablets	TBA	$6.90	$6.35	-
TDF/3TC/EFV *(300/300/600mg)*	HDPE bottle 30 tablets	TBA	$6.75	$6.75	-
TDF/FTC/EFV *(300/200/600mg)*	HDPE bottle 30 tablets[11]	TBA	$6.75	$6.75	$8.91
Pediatric Products					
ABC *(60mg)* disp.	HDPE bottle 60 tablets[11]	TBA	$4.02	$3.80	$5.13
ABC/3TC *(60/30mg)* disp. scored	HDPE bottle 60 tablets	TBA	$3.48	$4.15	-
ABC/3TC *(120/60mg)* disp. scored	HDPE bottle 30 tablets	TBA	$3.75	$3.50	-
ABC/3TC *(120/60mg)* disp. scored	HDPE bottle 60 tablets	TBA	$7.74	$7.50	-
AZT/3TC *(60/30mg)* disp. scored	HDPE bottle 60 tablets	TBA	$1.74	$1.90	-
AZT/3TC/NVP *(60/30/50mg)* disp. scored	HDPE bottle 60 tablets	TBA	$3.12	$3.25	-
EFV *(200mg)* scored	HDPE bottle 90 tablets	TBA	$9.27	$9.30	-
LPV/r *(40/10mg)* oral pellets	HDPE bottle 120 capsules	TBA	$19.20	$19.20	-
LPV/r *(80+20mg/ml)*	HDPE bottle 5 x 60ml (300ml)[12]	TBA	$30.90	$30.82	$19.70
LPV/r *(100/25mg)*	HDPE bottle 120 tablets	TBA	$11.88	$10.00	-
RAL *(100mg)* chewable scored	HDPE bottle 60 tablets	TBA	$36.00	-	-

**Negotiated price of $44 PPPY. Please refer to the following link for pricing on DTG 50mg singles; ** Average price of around $75 PPPY. Please refer to the following link for pricing on TLD*

[8] Médecins Sans Frontières (MSF), *Issue Brief: HIV & Opportunistic Infection Treatment: Spotlight On Access Gaps*, July 2017; prices shown converted to pack prices from unit prices; generally, the lowest SRA approved supplier reference price shown. Link

[9] Global Fund Pooled Procurement Mechanism Reference Pricing: ARVs, Ex-Works, September 13, 2017; prices shown can be treated as ceiling prices and used for budgeting purposes; lower prices may be accessible. Link

[10] Republic of South Africa 2015-2018 Tender; exchange rate at time of tender award 1 USD = 11.7 ZAR; effective USD prices since fell as the Rand depreciated; prices are on a delivered basis and inclusive of 14% VAT; average prices weighted by volumes allocated across suppliers

[11] RSA is 28 tablet bottle (vs. 30), 56 tablet bottle (vs. 60); 112 tablet bottle (vs. 120)

[12] RSA price provided for 60ml bottle. Multiplied by 5 to get 300ml estimate for comparability purposes

Appendix C: IATT List of Optimal Pediatric Products (2016)

Product	Dosage	Formulation	Stance
ABC/3TC	60/30mg	Tablet (dispersible, scored)	Optimal
ABC/3TC	120/60mg	Tablet (dispersible, scored)	Optimal
AZT/3TC	60/30mg	Tablet (dispersible, scored)	Optimal
EFV	200mg	Tablet (scored)	Optimal
LPV/r	100 mg/25mg	Tablet (heat stable)	Optimal
LPV/r	80/20mg/ml	Oral liquid	Optimal
LPV/r*	40mg/10mg	Oral pellets	Optimal
NVP	50mg	Tablet (dispersible, scored)	Optimal
NVP**	50/5mg/ml (100ml)	Oral liquid	Optimal
RAL*	100mg	Chewable tablet	Optimal

*Additions to the 2016 IATT list

** For infant prophylaxis as part of PMTCT

Appendix D: PADO 3 Priority Pediatric ARVs[xxxvi]

Advance Development
ABC/3TC/LPV/r (30/15/40/10mg) (“4-in-1”)
ABC/3TC/EFV (150/75/150mg)
Mid-Term Priority (3-5 year)
NVP/AZT
DRV/r (120/20mg)
RAL (50mg) scored
DTG (5mg) single tablet
ABC/3TC/DTG (60/30/5mg)
TAF/FTC
TAF/XTC/DTG
DTG/DRV/r
Long-Term Priority (5-10 year)
DTG/3TC
Long acting oral/injectable
Neutralizing antibodies

Appendix E: Notes on Methodology

There are several CHAI analyses from which the majority of figures in this report are derived:

- **ART Patient Forecast:** Each year, CHAI develops a five-year forecast for the total number of patients on ART in generic-accessible (GA) LMICs. 'Generic-accessible' denotes countries where global generic manufacturers can register and supply a large proportion of that country's ARV volume needs. The largest 'generic-inaccessible' countries are Argentina, Brazil, China, and Mexico. For this purpose, GA countries are defined as those LMICs that are covered under voluntary licenses for to generic TDF/TAF to generics. CHAI compiles historic data on the number of patients on ART from UNAIDS Infodatabase. For each country, CHAI assumes that the number of people receiving treatment will increase linearly at the same rate as the linear trend observed in the last four years and will plateau as universal access (under a "Treat All" paradigm) is approached, and then extrapolates to the rest of the world.

- **ARV Demand Forecast:** CHAI collects aggregate country data on patient regimens, formulations used, national guidelines, and anticipated future trends from CHAI's country teams and published literature each year. CHAI uses the data, an internally developed forecasting model, and the ART patient forecast (above) to project ARV demand in LMICs over the next five years. This year CHAI received data from: Benin, Brazil, Cambodia, Cameroon, Ethiopia, India, Kenya, Laos, Lesotho, Malawi, Mozambique, Nigeria, Papua New Guinea, Senegal, Togo, South Africa, Swaziland, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe. The countries included represent 83 percent of the patients on ART in GA LMICs in 2016.

- **Market Sizing Analysis:** Each year, CHAI combines known regimen and formulation splits by country with pricing data to calculate the current size of the ARV market in dollar terms and to calculate the average cost of treatment for first- and second-line adult and pediatric patients. The assumed price paid for ARVs is informed by two sources. South Africa procurement informs the weighted average price paid for each respective formulation within a given year only for South Africa regimens and formulations. For all other countries, average Global Fund Pooled Procurement Mechanism (PPM) reference pricing across 2016 is used.

- **Pipeline ARV Forecast:** CHAI's global pipeline drug forecast model accounts for country-specific uptake at the regimen level. The global forecast is divided into two segments, twelve high-volume countries and the generic-accessible (GA) rest of world (RoW), which were both used to estimate global uptake for adult pipeline products. New product uptake assumptions were based on three main factors: 1) anticipated price differential between new and current products, 2) relative clinical improvement of new product relative to current, and 3) anticipated launch year (i.e. likely first availability of product in country post-SRA and NDRA approval, inclusion in national guidelines and procurement plans), with the expectation that WHO guideline inclusion would have already occurred. Based on these three variables, uptake curves were then selected for each of the twelve focal countries based on CHAI's country intelligence, and one set of global uptake assumptions for GA RoW, separately for existing and newly initiating patients. These uptake curve choices for new products relative to current products estimated the total number of patients in a given year in GA LMICs.

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