HIV MARKET REPORT

The state of the HIV treatment, testing, and prevention markets in low- and middle-income countries, 2017-2022

Issue 9, September 2018

CLINTON HEALTH ACCESS INITIATIVE

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Acronyms Used

1L	First-line
2L	Second-line
AfroCAB	African Community Advisory Board
AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal care
API	Active pharmaceutical ingredient
APWG	ARV Procurement Working Group
ART	Antiretroviral therapy
ARV	Antiretroviral
ASLM	African Society for Laboratory Medicine
ATV/r	Atazanavir/ritonavir
BMGF	Bill & Melinda Gates Foundation
bNAbs	Broadly neutralizing antibodies
CAB	Cabotegravir
CADO	Conference on Antiretroviral Drug Optimization
CAGR	Compound annual growth rate
CHAI	Clinton Health Access Initiative
CLHIV	Children living with HIV
CROI	Conference on Retroviruses and Opportunistic Infections
DFID	United Kingdom Department for International Development
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EDL	Essential Diagnostics List
EFV	Efavirenz
EID	Early infant diagnosis
EMA	European Medicines Agency
ERP	Expert Review Panel
US FDA	United States Food and Drug Administration
FDC	Fixed-dose combination
FSW	Female sex worker
FTC	Emtricitabine
GA	Generic accessible
GAP-f	Global Accelerator for Pediatric Formulations
GHSC-PSM	Global Health Supply Chain Program-Procurement and Supply Management
HBDC	High-burden developing country
HBV	Hepatitis B
HCV	Hepatitis C
HCW	Healthcare worker
HIV	Human immunodeficiency virus
HIVST	HIV self-test
HPV	Human papillomavirus
INSTI	Integrase strand transfer inhibitor
IVD	In vitro diagnostic device
LA	Long-acting
LAIs	Long-acting injectables
LMIC	Low- and middle-income country
LPV/r	Lopinavir/ritonavir
MOH	Ministry of Health
MSM	Men who have sex with men
NAT	Nucleic acid testing
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NTD	Neural tube defect
NVP	Nevirapine
OS	Oral solution
PADO	Pediatric ARV Drug Optimization
PAWG	Paediatric ARV Working Group
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease inhibitor
PK	Pharmacokinetic
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission
POC	Point-of-care
PPM	Pooled Procurement Mechanism
PPPY	Per patient per year
PQ	Prequalification
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
R&D	Research and development
RAL	Raltegravir
RDT	Rapid diagnostic test
RfP	Request for proposal
RIF	Rifampicin
RPV	Rilpivirine
RSA	Republic of South Africa
RTV	Ritonavir
SRA	Stringent regulatory authority (US FDA (full or tentative), WHO PQ, or Global Fund ERP)
SSA	Sub-Saharan Africa
TAF	Tenofovir alafenamide fumarate
TasP	Treatment as prevention
TB	Tuberculosis
TLD	TDF+3TC+DTG
TLE	TDF+3TC+EFV
TLE400	TDF+3TC+EFV400
TLE600	TDF+3TC+EFV600
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
VL	Viral load
VMMC	Voluntary medical male circumcision
WCA	West and central Africa
WHO	World Health Organization
WRHI	Wits Reproductive Health and HIV Institute

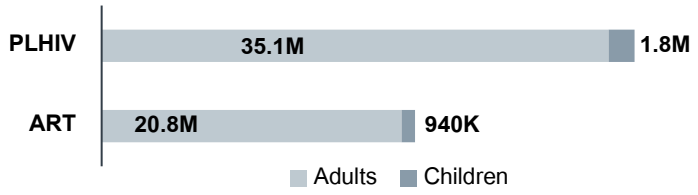
2018 HIV Market Report At-a-Glance

HIV Data Overview, 2017

36.9M People living with HIV globally

21.7M People on treatment globally

59% Global ART coverage rate



New WHO Treatment Guidelines

Adults & Adolescents

- **DTG preferred first-line for all adults and adolescents** except for women and adolescent girls of childbearing potential who wish to become pregnant or do not have access to effective contraception
- **DTG preferred second-line** for those failing non-DTG-based regimens, including NNRTIs

Pediatrics

- **DTG preferred first-line** for children > 4 weeks, RAL preferred for neonates
- **DTG preferred second-line** after NNRTI or PI failure
- **DTG (50 mg)** can be used down to **25kg**
- **Avoid NNRTIs** except for special circumstances

Key ARV Approvals*

TDF/3TC/DTG (300/300/50 mg)	DTG (50 mg)	ATV/r (300/100 mg)	LPV/r (40/10 mg)
Mylan	Mylan	Mylan	Mylan
Hetero	Cipla	Cipla	Cipla
Aurobindo	Aurobindo	Emcure	
Cipla (ERP)	Hetero (PQ)		
Macleods (ERP)			
Sun Pharma (ERP)			

*All tentatively FDA-approved except when specified otherwise.

Prevention

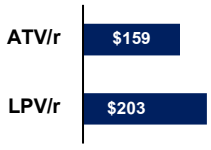
1.8M
New HIV infections were reported in 2017

<500K
New HIV infections by 2020 to meet Fast-Track targets

~350K
Total global oral PrEP initiates to date

HPTN 084
Trial launched in Dec. 2017 testing safety/efficacy of long-acting CAB in women 18-45

Major Pricing Updates

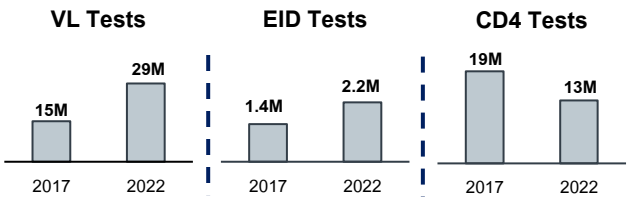


US$43.80 PPPY
Estimated annual savings per patient from **switching from LPV/r- to ATV/r-based** adult second-line regimens

US$12.00
per patient sample
Price per patient sample negotiated by CHAI, Unitaid, and other partners for **conventional virologic tests run on the Hologic Panther**. Includes HIV, HBV, HCV, HPV

US$14.90
per cartridge
EXW price for **HIV, HCV, and HPV GeneXpert test cartridges for 130 LMICs** in Cepheid's High-Burden Developing Country (HBDC) program

Diagnostics and Lab Services



The WHO released its first-ever **Essential Diagnostics List**, and included an HIV self-test on the list

9 months
Age at which the WHO now recommends second NAT test for HIV-exposed infants

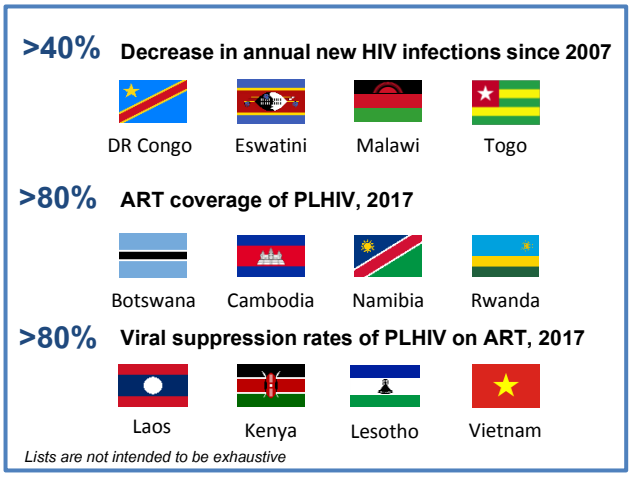
The State of HIV/AIDS Today

As 2020 nears, the world is at risk of missing Fast-Track targets despite impressive country-level successes

Globally in 2017, 21.7 million people living with HIV (PLHIV) were on antiretroviral therapy (ART), meaning close to 60 percent of all those infected were on treatment. AIDS-related deaths have been cut in half since 2007. Further still, 80 percent of pregnant women living with HIV were on treatment, and three in four PLHIV knew their status in 2017.[i]

These global successes stem from significant work at the country-level. Many nations have made significant progress in their fight against HIV/AIDS (Figure 1).

Figure 1: Sample Country Highlights on Progress against HIV



South Africa, the nation with the largest HIV burden, is close to meeting 90-90-90. In 2017, 85 percent of PLHIV in South Africa knew their status, 71 percent of people who knew their status were on ART, and 86 percent of people accessing treatment had suppressed viral loads.[ii]

Despite these tremendous successes, the global HIV community is at risk of missing the 90-90-90 Fast-Track targets. HIV infections are not decreasing fast enough. Children have been left behind, with nearly half of children living with HIV (CLHIV) globally still not on treatment. Further, about 20 percent of PLHIV on ART were not virally suppressed in 2017.[i] Additionally, the global HIV community can only make rapid progress against HIV/AIDS if it invests in addressing disparities across geographies and populations (Figure 2).[i,iii]

> **"We are, in my view, at the highest risk ever of losing control of the epidemic since all of this began.**
>
> **- Mark Dybul**
>
> *Former Executive Director of the Global Fund and former U.S. Global AIDS Coordinator*

Global funding remains a constraint

Although total donor government disbursements for HIV increased from US$7 billion in 2016 to US$8.1 billion in 2017, the increase is largely attributable to the timing in disbursements and not an underlying increase in actual funding (Figure 3). US government disbursements, for example, increased by over US$1 billion in 2017 but the trend is not expected to continue given allocations for funding largely remain unchanged.[iv]

Figure 2: Geographical, Age & Sex, and Key Population Disparities

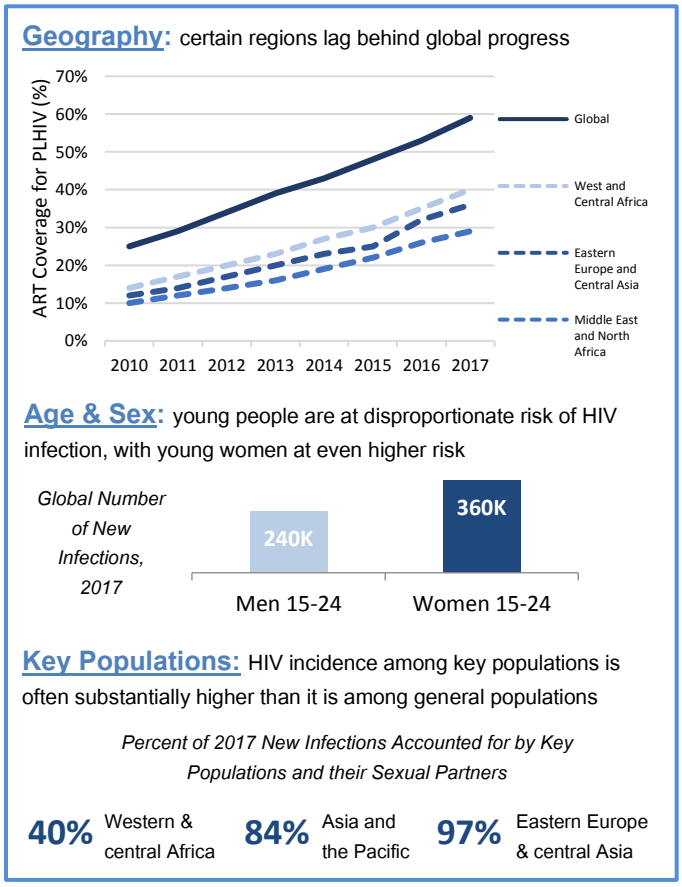
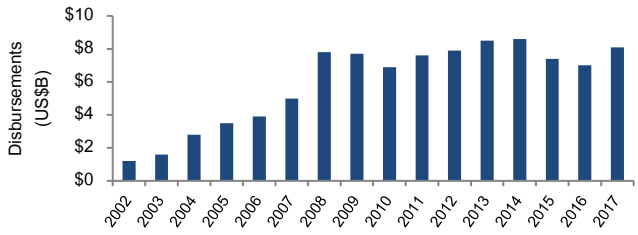


Figure 3: Donor Government Disbursements for HIV, 2002-2017



At the low- and middle-income country (LMIC)-level, the estimated total resources available for HIV increased from US$19.1 billion in 2016 to US$21.3 billion in 2017.[v] LMIC domestic funding has increased since 2009 and represented 56 percent of overall HIV resources in 2017.[iii] However, the sustainability of these increases is unclear.[vi]

Given funding constraints across the HIV continuum, LMICs will need to continue to identify innovative ways to do more with limited resources.

Despite challenges, 2018 could be a transformational year in making progress against the epidemic

2018 could be a notable year given major global developments across the HIV cascade (Figure 4).

Figure 4: Major 2018 Developments across the HIV Cascade

Treatment

WHO now recommends **DTG as the preferred regimen for nearly all PLHIV**, with special guidance for women living with HIV (WLHIV) of childbearing potential

New **Optimal Formulary** reflects latest pediatric guidelines, serves as a **benchmark for continued optimization**, and has a special provision for pediatric DTG products

First deliveries of TLD occurred in 2018, with widespread adoption and rollout expected

Diagnostics

Breakthrough pricing agreement allows public sector to access Hologic Panther system at **US$12 per patient sample**

Prevention

Over 50 countries have adopted oral PrEP

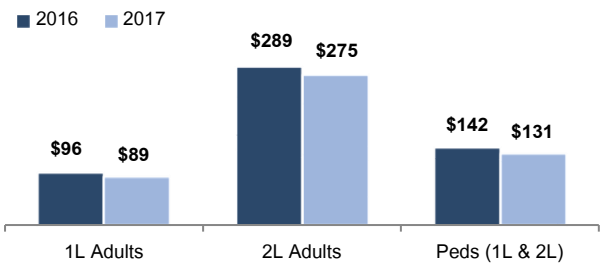
These global developments can continue to build the momentum needed to meet 90-90-90. The only way the Fast-Track targets will be reached is by ensuring all PLHIV, regardless of gender, age, sexual orientation, or geography, have access to effective HIV prevention and treatment services. CHAI is eager to continue meeting this goal by working with Ministries of Health (MOHs), communities, suppliers, funders, and partners to ensure the end of HIV/AIDS as a public health threat.

ARV Market Trends

Treatment costs continue to decline, while the overall "generic-accessible" (GA) LMIC market still grows[1]

The annual costs of adult and pediatric treatment fell in 2017 (Figure 5).

Figure 5: GA LMIC Weighted Average Regimen Price (USD, PPPY)

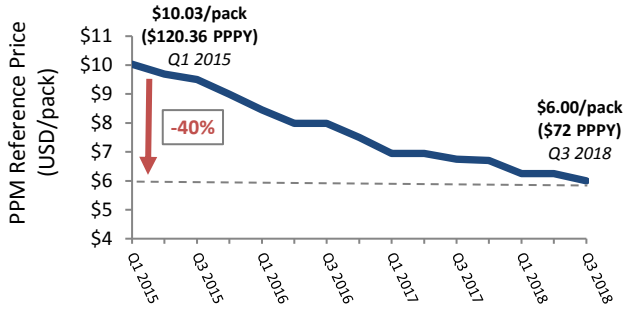


[1] *'Generic-accessible' denotes countries where global generic manufacturers can register and supply a large proportion of a country's ARV volume needs. Large 'generic inaccessible' countries: Argentina, Brazil, China, Mexico*

Adult First-line (1L) Cost

In 2017, the weighted average price of adult 1L treatment fell below US$90 per patient per year (PPPY) for the first time, driven by continued price erosion of high-volume antiretrovirals (ARVs), such as TDF/3TC/EFV (300/300/600 mg) tablets (TLE600) (Figure 6).[vii]

Figure 6: Decline in Price of TLE600 Since 2015



The launch of TDF/3TC/DTG (300/300/50 mg) tablets (TLD) put further price pressure on TLE600. A breakthrough agreement announced in September 2017 marked the first time a new optimal product launched at a price less than or equal to the standard of care.[viii]

In the near-term, stringent regulatory authority (SRA) approval of additional suppliers and increasing demand are expected to further lower the price of TLD and thus adult 1L treatment cost. In the longer-term, tenofovir alafenamide fumarate (TAF)-based ARVs have the potential to help lower the cost of treatment further (discussed in detail later).

Finally, rather than packaging ARVs with the traditional mono-carton shell, suppliers now offer carton-less ARV bottles that provide many benefits to national programs including lower cost per product pack, reduced transport costs, and more efficient storage.[ix,x]

Adult Second-line (2L) Cost

The weighted average adult 2L cost for treatment also fell in 2017. Driving the decrease were:

- **Higher use of ATV/r for 2L.** Adult atazanavir/ritonavir (ATV/r) tablets, as covered in more depth later, cost much less than adult lopinavir/ritonavir (LPV/r) tablets.
- **Lower NRTI dual prices.** The cost of the most commonly-used nucleoside reverse transcriptase inhibitors (NRTIs) for 2L, adult zidovudine/lamivudine (AZT/3TC) tablets and tenofovir disoproxil fumarate/lamivudine (TDF/3TC) tablets, fell in 2017, with the former by over US$15 PPPY in 2017.[vii]
- **Less reported ABC/3TC use in 2L.** Adult abacavir/lamivudine (ABC/3TC) tablets are generally twice the cost of other adult dual NRTIs.[x]

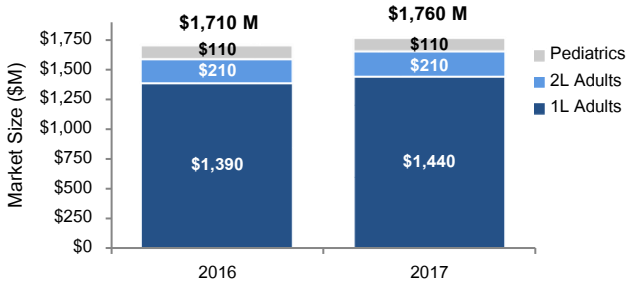
Pediatric ART Cost

Despite increasing use of optimal pediatric formulations, which tend to be more expensive than commonly used AZT/3TC/NVP dispersible tablets, the weighted average cost of pediatric treatment fell in 2017. The year-

over-year decrease was driven by further optimized use of optimal formulations based on the age and weight of patients (e.g., less use of more expensive LPV/r oral solution (OS), coupled with higher use of more affordable LPV/r (100/25 mg) tablets and EFV (200 mg) scored tablets). Formulation optimization based on a child's age and weight can lead to national cost savings.[xi] Kenya, for example, updated its national pediatric forecasting with revised weightband data in 2017, greatly lowering LPV/r OS use in older children and, thus, costs. Dolutegravir (DTG) will likely reduce the costs even further (discussed in *Pediatric Market Trends).*

Even with falling prices, the overall market still grew 3 percent to US$1.76 billion due to large increases in the number of PLHIV on ART (Figure 7).

Figure 7: ARV Market Size (USD) in GA LMICs



Large funders' tenders and product prioritizations serve as a compass for future treatment trends

Collectively, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (the Global Fund), the President's Emergency Plan for AIDS Relief (PEPFAR), and the Republic of South Africa (RSA) are the three largest buyers of ARVs in the GA LMIC market and represent a significant share of ARVs funded and procured by LMICs. Tracking their activities provides a guide to future trends in the space (Figure 8).

Figure 8: Developments across Largest ARV Buyers[2][i,xii,xiii,xiv,xv,xvi]

PEPFAR U.S. President's Emergency Plan for AIDS Relief **13.3M** *PLHIV were on ART as of Sep 30, 2017 because of PEPFAR support*

Since 2017, PEPFAR has been advocating for TLD roll-out and recommending the broad switch of eligible adult 1L and 2L.

TheGlobalFund **11M** *PLHIV on ART through Global Fund-supported programs in 2016*

In July 2018, the Global Fund announced it had signed multi-year framework agreements with 14 supplier, representing US$1.2 billion over next four years. 98 percent of ARV spend is allocated for 30 1L and 2L products that can fulfill WHO preferred or alternative regimens.

health Department: Health REPUBLIC OF SOUTH AFRICA **4.4M** *PLHIV on ART in South Africa in 2017*

In August 2018, South Africa advertised a new tender for ARVs, including TLD, with an effective start date of April 2019.

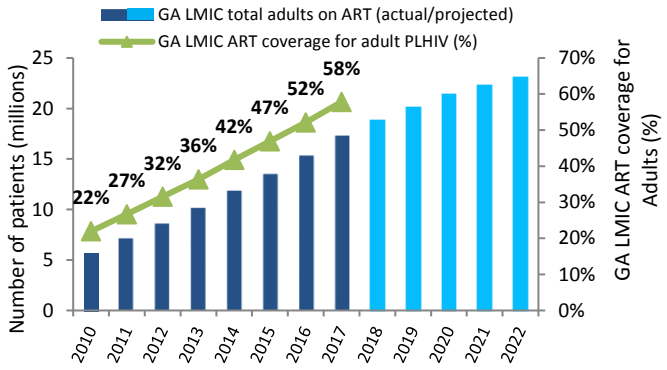
In a continued effort toward market transparency, the three large buyers publish consolidated demand forecasts across high-volume adult and pediatric products, and the ARV Procurement Working Group (APWG) publishes its forecast of pediatric ARVs, low-volume adult ARVs, and adult products in transition on a quarterly basis.[xiii,xvii]

Adult Market Trends

Nearly 21 million adults were on treatment in 2017, with over 17 million in GA LMICs

The number of adults on ART has more than tripled since 2010 in some LMICs, such as D R Congo, Mozambique, Myanmar, Uganda, and Tanzania.[i] At current ART scale-up rates, over 23 million adults in GA LMICs can be expected to be on ART by 2022 (Figure 9).

Figure 9: Adults on ART and Adult ART Coverage in GA LMICs[3][xviii]



The WHO now recommends DTG as the preferred treatment option for adults (with special considerations for women of childbearing potential)

At AIDS 2018, the World Health Organization (WHO) issued updated 1L and 2L treatment recommendations for adults, adolescents, and children living with HIV (the *Pediatric Market Trends* section covers the pediatric guidelines in more detail).[xix] The WHO's next full HIV guidelines review process is expected to start in 2019.[xx]

Figure 10: 2018 WHO 1L Guidelines: Adults and Adolescents

Adult Population	Preferred 1L Regimen
Adult men and adolescent boys	TDF + 3TC + DTG
Pregnant (from eight weeks after conception) and breastfeeding women and adolescent girls	
Women and adolescent girls with effective contraception or not of childbearing potential	
Women and adolescent girls of childbearing potential who want to become pregnant and have no effective contraception	TDF + (3TC or FTC) + EFV600

[2] Estimates for PEPFAR and the Global Fund are not mutually exclusive because of the multifaceted nature of their funding

[3] Adult ART coverage calculated based on data available in UNAIDS AIDSinfo database as of July 2018 (only includes countries with both ART and adult LHIV numbers reported)

For nearly all adults and adolescents, the preferred 1L regimen is now TDF+3TC+DTG (Figure 10). DTG replaces EFV as the preferred drug option for adults because of benefits such as faster viral suppression, a higher genetic barrier to resistance, and fewer side effects. DTG is particularly important in light of emerging data on HIV drug resistance: a 2017 WHO report found that half of the 11 surveyed countries had levels of NNRTI pretreatment resistance above 10 percent.[xxi]

DTG is currently not recommended as preferred for women and adolescent girls of childbearing potential who want to become pregnant and are not able to access effective contraception. The main driver for the recommendation was the Botswana safety signal (Figure 11).

Figure 11: Botswana Safety Signal: Timeline of Key Events[xix,xxii,xxiii,xxiv]

Botswana Safety Signal

In May 2018, data from a preliminary unscheduled analysis of the ongoing observational Tsepamo study in Botswana found four cases of neural tube defects (NTDs) out of 426 women who became pregnant while taking DTG. The resulting rate of 0.9% compares to a 0.1% risk of NTDs in infants born to women taking other ARVs at the time of conception.

Drug Safety Alerts

The WHO, US FDA, and EMA issued drug safety alerts for DTG use in women of childbearing age. The WHO's statement advised treatment for women of childbearing age, including pregnant women, should be based on drugs with adequate efficacy and safety data available, noting EFV-based regimens are safe.

Community's Response

As national programs grappled with these alerts, civil society groups, such as AfroCAB, reacted swiftly. AfroCAB issued a statement calling for TLD to be "made available urgently across the continent with everyone having access, and the appropriate education and support with regard to pregnancy (and the option of using TLE) and TB, for all stakeholders."

New WHO Guidelines

At AIDS 2018, the WHO issued new treatment guidance recommending DTG as the preferred adult treatment option, with special considerations for women of childbearing potential. WHO echoed the community in advocating for a woman-centered approach in the design of ART programs.

Additional Data & Future Monitoring

Latest data from the Tsepamo study presented at AIDS 2018 showed no NTDs across 170 additional DTG pre-conception exposures, translating to an updated risk of 0.67% (still outside of confidence interval of non-DTG regimens). 1,226 additional births from DTG pre-conception exposures expected by end of March 2019 will add to the evidence base.

Drug safety alerts serve a different purpose than guidelines, and thus tend to be more drug-centered and restrictive. The risk with these alerts in particular was that, in the absence of other guidance, WLHIV who could benefit from DTG might be denied access. Following the safety alerts, the African Community Advisory Board (AfroCAB), supported by CHAI and Unitaid, convened a gathering of WLHIV from 18 countries in sub-Saharan Africa ahead of AIDS 2018 to canvass opinions from the population most impacted and issued the statement in Figure 12.[xxv]

Figure 12: Community's Response to the Botswana Safety Signal

"We strongly urge key stakeholders – especially national programmes and global partners – to **respect the voices of those affected** by HIV. The actual **women living with HIV must be consulted**…[and] we are calling for TLD to be made available urgently across Africa, **with everyone having access, regardless of gender or reproductive capability,** and with **integration of sexual and reproductive health** services. It is critical to **not just view a pregnant mother**, or any woman of childbearing potential, **as a vessel for a baby, but as an individual** in her own right, who deserves access to the very best, evidence-based treatment available and the **right to be adequately informed to make a choice** that she feels is best for her."

Excerpt from the *Communique of the Kigali dolutegravir stakeholder meeting of African WLHIV*

Recognizing that communities' voices and preferences are critical to the global HIV response, the WHO's new guidelines advocated for a woman-centered HIV treatment approach, including using "childbearing *potential*" rather than "childbearing *age*" in its language.[xix]

The Botswana safety signal and the WHO's woman-centered health approach recommendation served as a reminder that national programs should continue to integrate public health offerings such as treatment and family planning services. Some sub-Saharan African (SSA) nations have already started mapping ARV and family planning facilities nationally to identify potential areas for strengthening both programs.

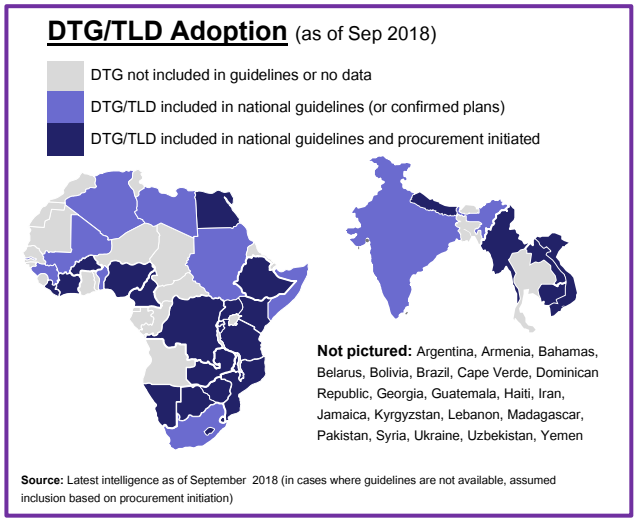
When deciding to switch existing eligible patients to TLD, viral load (VL) testing is encouraged where possible and considered good practice, but should not be a barrier to TLD adoption. PEPFAR has stated that they support the switch to TLD even if VL is not available.[xxvi]

Finally, the WHO recommended twice daily dosing of DTG for tuberculosis (TB) coinfected patients treated with rifampicin (RIF), given drug interactions. The recommendations are based on 24-week interim results from the INSPIRING study that were presented at CROI 2018.[xxvii]

TLD expected to replace TLE600 as the most-prescribed ARV in GA LMICs

Dolutegravir

Figure 13: Inclusion of DTG in National Treatment Guidelines



It is abundantly clear that the GA LMIC market is moving toward DTG. Over two dozen high-burden LMICs have already included or are planning to include DTG-based regimens in their national HIV treatment guidelines, a critical first step for new product introduction (Figure 13).

Broad DTG adoption will build off lessons learned from early adopter countries like Botswana, Brazil, Kenya, Nigeria, and Uganda (Figure 14).

Figure 14: Early Adopters of DTG[xxviii]

Kenya **Nigeria** **Uganda** Unitaid

Under leadership of MOHs in Kenya, Nigeria, and Uganda, CHAI and Unitaid supported a **catalytic procurement of DTG singles** to help determine key requirements for national rollout and to provide a platform for TLD introduction. By end of 2017, **over 9,000 PLHIV were on DTG-based regimens**.

DTG operational research in Nigeria and Uganda, which aims to **describe the experience and acceptability of using DTG** as part of 1L ART from the patient and provider perspectives, shows very positive early results in terms of acceptability, which will be presented at the 2018 HIV Glasgow Therapy Congress.

Botswana became one of the first LMIC adopters of DTG in 2016 and by the end of 2017 had an estimated 52K PLHIV on DTG. Early lessons from Botswana, including use of DTG at conception, have been critical in informing the global community.

In 2017, **Brazil** began to offer DTG for PLHIV. As of May 2018, ~113K PLHIV were on DTG-based regimens.

As of September 2018, over 20 LMICs have initiated procurement for TLD. Kenya, Malawi, Nigeria, Uganda, and Zambia are some of the 15+ LMICs who have already received first shipments of TLD.

Zambia, for example, began rolling out TLD in July 2018. Zambia rapidly responded to the Botswana safety signal to create treatment algorithms that allow WLHIV of childbearing potential access to DTG if on reliable contraception (and meet additional initiation criteria). A three-phased approach was taken (Figure 15).

Figure 15: Zambia's TLD Phase-in Approach

Zambia TLD Rollout Plan

To ensure a smooth transition to TLD, Zambia designed a three-phase rollout strategy:

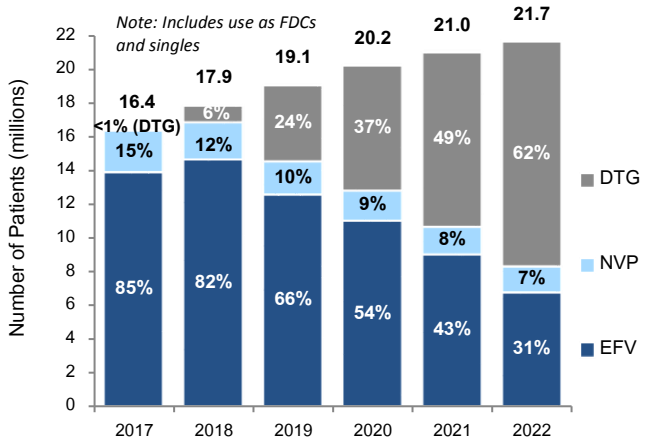
'Pathfinder' Sites: *Mid-July 2018*
Zambia began TLD rollout at six high-volume, high-capacity facilities in four provinces starting in mid-July 2018. The facilities serve ~36K total PLHIV on ART and helped generate early lessons learned for broader TLD rollout.

'First Wave' Sites: *August-December 2018*
Following the Pathfinder sites, the 'First Wave' of facilities, representing ~440K total PLHIV on ART, will transition to TLD on a rolling basis. These 153 sites are expected to complete their TLD transition by year-end 2018.

'Second Wave' Sites: *January 2019-Onward*
Starting in 2019, the remaining facilities will transition to TLD. Upon completion of the 'Second Wave', all sites within Zambia will have transitioned to TLD.

With strong momentum toward adoption based on WHO guidance and PEPFAR policy, DTG-based regimens are projected to represent 62 percent of the adult 1L market in GA LMICs by 2022 (Figure 16).

Figure 16: 1L NNRTI/INSTI Use in GA LMICs, Patient Growth and Share[xviii]



Reliable supply and sufficient capacity can help ensure a smooth transition to TLD. In early 2018 there were some capacity concerns, mostly driven by delays in expected SRA approvals of process variations that helped increase capacity. The APWG arranged routine calls with the two suppliers of TLD in response to the supply security concern, mapped known TLD demand against suppliers' books, and allowed for a clear centralized communication channel between supply and demand. The TLD supply has since stabilized and the APWG will continue to monitor the supply and demand during the transition to TLD. As of September 2018, three generic suppliers have received tentative US FDA approval (Aurobindo, Hetero, Mylan), with an additional three having received Global Fund ERP approval (Cipla, Macleods, Sun Pharma).

Low-dose efavirenz (TLE400)

The WHO currently lists TLE400 as an alternate regimen for adults and adolescents and can be used in pregnancy and with TB therapy. EFV-based products such as TLE400 will likely maintain a place in certain contexts and national programs, including as an alternate therapy for adults who are unable to take DTG – a strategy that countries may consider, particularly if TLE400 has a cost advantage over TLE600.

Mylan is currently the only supplier with SRA approval for TLE400 (tentative US FDA approval). To date, most procurement for TLE400 has been for Zambia and Zimbabwe. Zimbabwe plans to switch all TLE600 patients over to TLE400 in 2018, and initiate a broad rollout of TLD starting in 2019. Zambia plans to use TLE400 as an alternate regimen for patients who cannot take TLD.

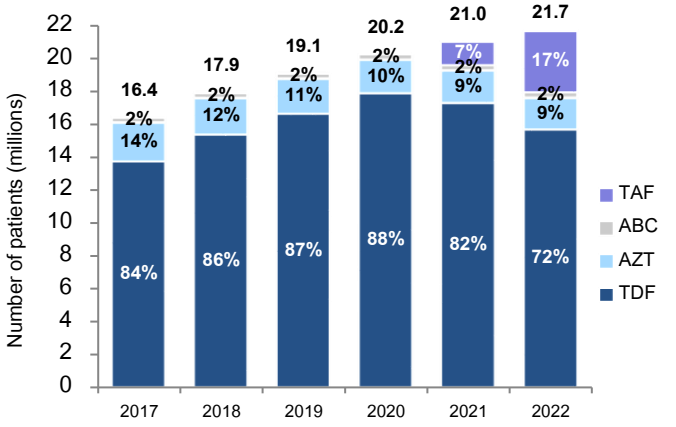
Tenofovir alafenamide

TAF is a tenofovoir pro-drug that could replace TDF in formulations such as TLD. Interest in TAF is largely based on potential cost savings relative to TDF-based regimens given a lower required dose (TAF 25mg vs TDF 300mg). Mylan received tentative US FDA approval for its TAF/FTC/DTG (25/200/50 mg) product in Q1 2018, but is expected to be the sole supplier until at least mid-2019.

The WHO guidelines currently do not recommend TAF-based regimens for treatment at all, whether as preferred or alternate. Although TAF has been shown to be as effective as TDF, studies on use in some key populations, such as pregnant women, are ongoing. In terms of TB, data presented at CROI 2018 from the RIFT study showed that TAF dosed 25mg daily is effective with RIF.[xxix]

Full data to inform WHO review and inclusion in guidelines is not expected until 2020. Thus, uptake of TAF-regimens is only forecasted to begin in 2021 (Figure 17).

Figure 17: 1L NRTI Market in GA LMICs, Patient Growth and Share[4][xviii]



DTG, DRV/r expected to have increasing role in adult 2L

The 2L adult market in GA LMICs has predominately been driven by two protease inhibitors (PIs) to date: ATV/r and LPV/r. New recommendations on 2L were included with the 2018 WHO guidelines (Figure 18). DTG-based regimens are now preferred following NNRTI failure, while ATV/r or LPV/r are only preferred following failure of a DTG-based 1L regimen.

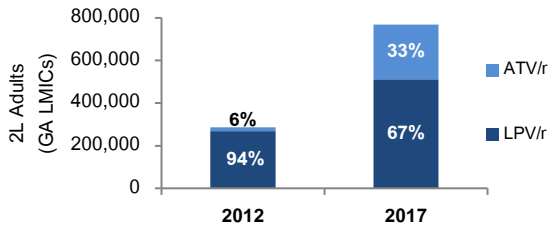
Figure 18: 2018 WHO Guidelines for 2L: Adults and Adolescents

Failing 1L Regimen	Preferred 2L Regimen	Alternate 2L
2 NRTIs + DTG	2 NRTIs + (ATV/r or LPV/r)	2 NRTIs + DRV/r
2 NRTIs + EFV (or NVP)	2 NRTIs + DTG	2 NRTIs + (ATV/r or LPV/r or DRV/r)

ATV/r

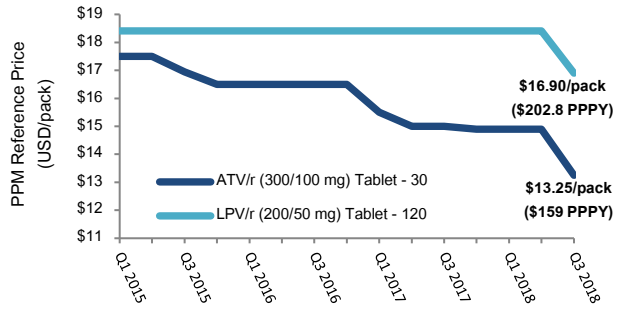
Since 2012, ATV/r has seen increasing use, with about one in three adults on 2L ART in GA LMICs on the regimen by year-end 2017 (Figure 19).

Figure 19: ATV/r's Market Share Increase in GA LMICs since 2012



ATV/r offers many benefits over LPV/r including its lower cost, favorable clinical profile, and lower pill burden. While LPV/r (200/50 mg)'s reference price has remained mostly constant over the past three years, ATV/r's price has consistently declined since 2015 (Figure 20).[vii] There are now three tentative US FDA-approved suppliers (Cipla, Emcure, Mylan), providing reassurance of supply security. Several countries have over 60 percent of 2L patients on ATV/r, including Cambodia, Cameroon, Ethiopia, India, Laos, Lesotho, Malawi, Rwanda, Togo, and Zimbabwe.

Figure 20: ATV/r's Price Decline Since 2015[vii]



DRV/r

DRV has superior clinical efficacy, a favorable tolerability and toxicity profile, and high genetic barrier of resistance relative to the other PIs on the market. However, the WHO still lists DRV/r as an alternate 2L option for adults failing integrase strand transfer inhibitor (INSTI)- or NNRTI-based regimens. A key reason for this is that DRV is not available as a generic FDC with ritonavir yet. Generic companies are working on such an FDC (DRV/r (400/50 mg)) and some have even filed for regulatory approval.

Affordability is another key barrier to DRV/r's uptake in GA LMICs. Currently, treatment with separate tablets of DRV and RTV collectively cost over three times the cost of the other boosted PI options.[x]

To help accelerate the affordability of a DRV/r FDC, CHAI and Unitaid released an RfP in December 2017. The first SRA approval for a DRV/r FDC is expected by the end of 2018.

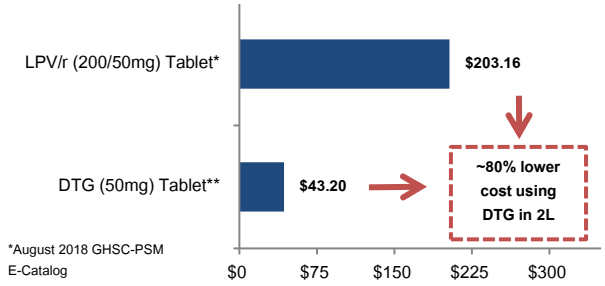
Dose optimization may also provide a pathway to cost competitiveness. Generally, the DRV/r dose recommendation for PI-naïve patients is 800/100mg once daily.[xxx] 48-week data from the Wits Reproductive Health and HIV Institute (WRHI) 052 study presented at AIDS 2018 showed that switching virally suppressed patients from LPV/r to DRV/r (400/100mg) once daily was non-inferior to continuing on LPV/r.[xxxi] However, data on using the lower dose in PI-naïve patients failing 1L is still needed before it can be recommended broadly.

DTG in 2L

A noteworthy update in the 2018 WHO guidelines was the recommendation of DTG-based regimens as the preferred 2L option for those failing 1L NNRTIs. The recommendation builds on positive results from the phase III DAWNING study and NEAT 022. Beyond many clinical benefits for 2L patients, DTG can offer significant cost savings for national programs (Figure 21).

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

Figure 21: Annual Cost of DTG vs LPV/r in 2L Adults (USD)



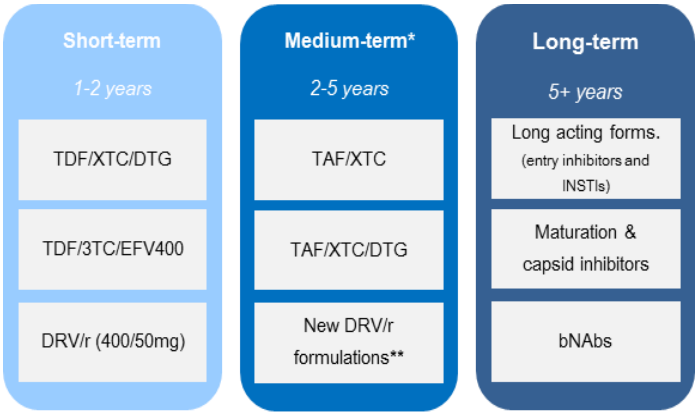
As mentioned earlier, PEPFAR is advocating for broad TLD rollout for eligible 2L patients. At the time of publication, only a few LMICs have DTG listed as a preferred option following NNRTI failure in their guidelines. Of note, Myanmar had already included DTG and DRV/r as alternates for 2L use in its 2017 national treatment guidelines. Several high-burden countries are considering switching stable 2L patients from a PI-based regimen to DTG.

The use of DTG in 2L may mean that the number of individuals on PI-based therapies decreases in the short term. In the long term, the need for PIs will increase as individuals failing DTG-based 1L and 2L regimens will ultimately need a PI. CHAI modeling on the evolution of the PI market will be presented at the upcoming 2018 HIV Glasgow Drug Therapy Congress.

Long-acting formulations, maturation and capsid inhibitors, and bNAbs on the horizon

In December 2017, the third Conference on ARV Drug Optimization (CADO3) was held in Johannesburg, South Africa.[xxxii] One of the key outputs from the meeting was a prioritized list of optimized products and formulations desired for treating adults (Figure 22).

Figure 22: CADO3 Prioritized List of Optimized Products and Formulations for Adults on ART



*Other lower priority products might be considered in the future if the data suggests superiority to existing priorities

**Low dose standard formulations (400/100mg) or standard dose nanoformulations (800/100mg)

Many of the short-term and medium-term products have been discussed in great detail already, but the long-term products (5+ years away from market) highlight what is on the horizon for the HIV treatment landscape for adults. A summary of these can be found in Figure 23.

Figure 23: Potential Long-Term HIV Treatment Offerings[xxxiii,xxxiv,xxxv]

1. **Long-acting formulations**
   Long-acting ARVs involve the routine injection or implantation of a drug over a set frequency (e.g., once every eight weeks). The ATLAS study, a phase III trial testing the efficacy of CAB and RPV injections, announced 48-week data in August 2018. Amongst virally suppressed patients, switching to monthly injections of CAB and RPV was found to be non-inferior at 48-weeks to maintaining their current oral regimen of 2 NRTIs + (PI or INSTI or NNRTI).
2. **Maturation and capsid inhibitors**
   Like other ARVs, maturation and capsid inhibitors disrupt key steps of the HIV virus' development and lifecycle. Gilead's capsid inhibitor GS-CA1 is in preclinical studies, and ViiV's maturation inhibitor GSK3640254 is currently in phase 1 studies.
3. **Broadly Neutralizing Antibodies (bNAbs)**
   bNAbs are antibodies that can be used to fight multiple strains of HIV. Ibalizumab became the first monoclonal antibody approved by the US FDA to treat multi-drug resistant HIV. Ibalizumab requires infusions once every two weeks and costs US$118K per year (not including infusion costs). Much work will need to be done to ensure bNAbs can be administered with ease and at a lower cost, but they could be an option for PLHIV with multi-drug resistance who don't respond to other ARVs on the market.

More details on the new pipeline treatment offerings can be found in the HIV i-Base Fit for Purpose and HIV Pipeline reports.[xxxiv,xxxvi]

Pediatric Market Trends

Nearly 900,000 pediatric patients in GA LMICs were on ART in 2017, but coverage still only at ~50 percent

UNAIDS currently estimates that globally in 2017 there were 1.8 million CLHIV with approximately 940,000 on treatment. Approximately 94 percent of children on ART globally were in GA LMICs, where ART coverage was ~50 percent (Figure 24). An estimated 180,000 pediatric patients were newly infected with HIV in 2017. While this is an improvement from an estimated 340,000 in 2007, reductions have been relatively flat since 2015 (Figure 25).[i]

Figure 24: Number of Pediatric Patients on ART and Pediatric ART Coverage in GA LMICs[xviii]

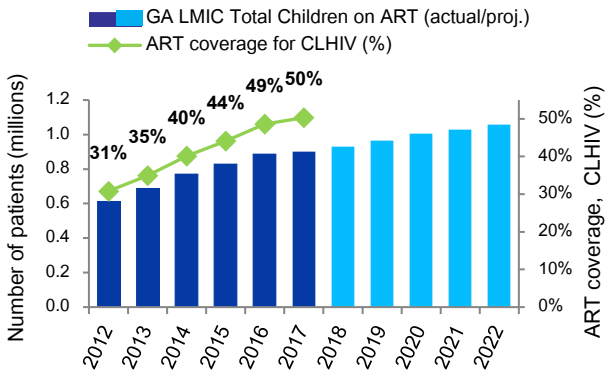
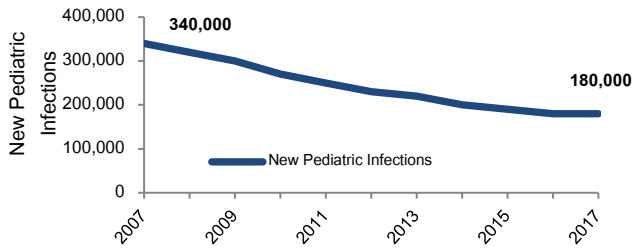
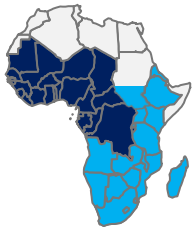


Figure 25: Global Number of New Pediatric Infections Since 2007[i]



The global view masks vast regional differences in pediatric treatment coverage rates. As is also true for adults, certain regions of the world, especially west and central Africa (WCA), are being left behind when it comes to putting CLHIV on treatment (Figure 26). (See the *Diagnostics and Lab Services* section for more discussion on pediatric case finding).

Figure 26: Pediatric ART Coverage in Sub-Saharan Africa, 2017[i]



2017 Pediatric ART Coverage

West and central Africa **26%**

East and southern Africa **59%**

As part of its annual release of HIV/AIDS data, UNAIDS also updates its Spectrum epidemiology model. As was the case last year, this year's update resulted in lower estimates of the global number of CLHIV. For example, India saw its estimate of CLHIV in 2016 decrease 50 percent between 2017 and 2018, while Malawi's decreased 33 percent. The variability in these estimates highlights the challenges the global community faces when setting targets for pediatric HIV on the ground.

Updated WHO treatment recommendations prioritize dolutegravir and serve as beacon for pediatric regimen optimization and simplification efforts

At AIDS 2018, the WHO released updated guidance on pediatric HIV treatment outlining new preferred and alternative regimens. The updated guidance makes large strides toward optimizing and simplifying preferred treatment regimens for pediatric patients, with a strong focus on DTG (Figure 27). DTG is especially important for children given data on NNRTI resistance in pediatric populations.[xxxvii]

Figure 27: Major Takeaways from Updated WHO Guidance on Pediatric Treatment[xix]

DTG listed as preferred 1L for all children at least four weeks old (when approved dosing/products available for small children), with RAL preferred for neonates, replacing previous focus on LPV/r and EFV for pediatrics. DTG also recommended as 2L therapy for children failing NNRTI- or PI-based 1L

DTG (50 mg) tablets can be used down to 25kg, although US FDA and European Medicines Agency (EMA) labels still list 40kg as the minimum weight for this dose (see Figure 36 for more on pediatric DTG dosing)

DTG to be introduced as soon as possible to ensure children have access to the best medicine available

NNRTIs should only be used in special circumstances in children, replacing previous guidance where EFV was preferred for patients aged 3-10

Compared to previously recommended treatment regimens, these updates dramatically simplify the pediatric treatment landscape in terms of the number of preferred and alternative regimens, and dosing structure and schedule (Figures 28, 29). In particular, children greater than 25kg can use the DTG (50 mg tablet) which is already generically available and in country supply chains. These updates are particularly forward-looking in indicating DTG as preferred for all children over four weeks even in advance of formulation and dosing availability. These simplified guidelines will help countries streamline their own treatment programs and procurement, while also ensuring that children are on the most effective and tolerable products as soon as they are available.

Figure 28: Updated Preferred First-Line Pediatric Treatment Regimens, WHO, 2018[xix]

	Neonates	Children
Preferred 1L	AZT + 3TC + RAL	ABC + 3TC + DTG
Alternative 1L	AZT + 3TC + NVP	ABC + 3TC + (LPV/r or RAL)
Special Circumstances	AZT + 3TC + LPV/r	ABC (or AZT) + 3TC + EFV (or RAL) AZT + 3TC + (LPV/r or RAL or NVP)

Figure 29: Updated Preferred Sequencing of Pediatric Treatment Regimens, WHO, 2018[xix]

Population	1L Regimens	2L Regimens	3L Regimens
Children	Two NRTIs + DTG	Two NRTIs + (ATV/r or LPV/r)	DRV/r + DTG + 1-2 NRTIs (if possible, consider optimization using genotyping)
	Two NRTIs + LPV/r	Two NRTIs + DTG	
	Two NRTIs + NNRTI	Two NRTIs + DTG	

Significant changes to Optimal Formulary accompanied WHO guideline updates

In 2018, the WHO released a new Optimal Formulary and Limited-Use List for Paediatric ARVs (formerly known as the IATT Paediatric ARV Formulary and Limited-Use List) (Appendix C). The Optimal Formulary helps countries, procurement agents, and funding agencies choose the minimum set of pediatric formulations needed to deliver WHO-recommended regimens for all lines of pediatric treatment.[xxxviii] Major updates to the formulary can be found below:

Figure 30: Major Updates to WHO Optimal Formulary and Limited-Use List for Pediatric ARVs, 2018[xxxviii]

2016 Optimal Products Demoted in 2018 Update

2018 Limited-Use

LPV/r (80/20 mg/ml) Oral Solution

EFV (200 mg) Scored Tablets

Rationale

Focus on pediatric DTG, high levels of NNRTI resistance, move towards LPV/r solid oral dosage forms

2018 Non-Essential

ABC/3TC (60/30) Tablets (Disp.)

Consolidate market around ABC/3TC (120/60 mg) dispersible tablets while reducing pill burden

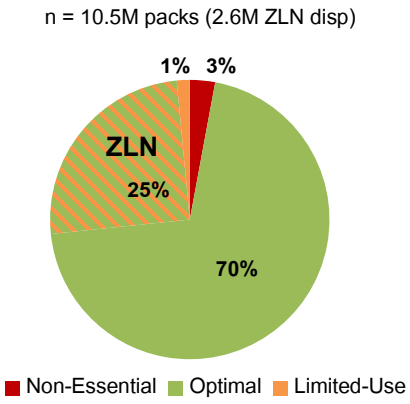
It is expected that the Optimal Formulary and Limited-Use List for Pediatric ARVs will be updated to reflect new pediatric forms of DTG as they are made available.

Pediatric regimen splits in 2017 reflect continued transition toward previously recommended regimens

Until the latest WHO guidelines were released this year, previous recommendations for pediatric ART supported consolidation of treatment around ABC/3TC-based regimens (away from AZT), and toward EFV and LPV/r (away from NVP).

As monitored by the APWG, nearly three-quarters of pediatric formulations procured in 2017 were "optimal" under the previous (2016) IATT Pediatric ARV Formulary and Limited-Use List (Figure 31). The overwhelming majority of non-optimal procurement was for AZT/3TC/NVP (60/30/50 mg) dispersible tablets (ZLN), often still procured due to low prices and ease of administration.[xxxix]

Figure 31: Product Status of 2017 Pediatric Procurements Monitored by the APWG (Under 2016 IATT Optimal Formulary)[xxxix]

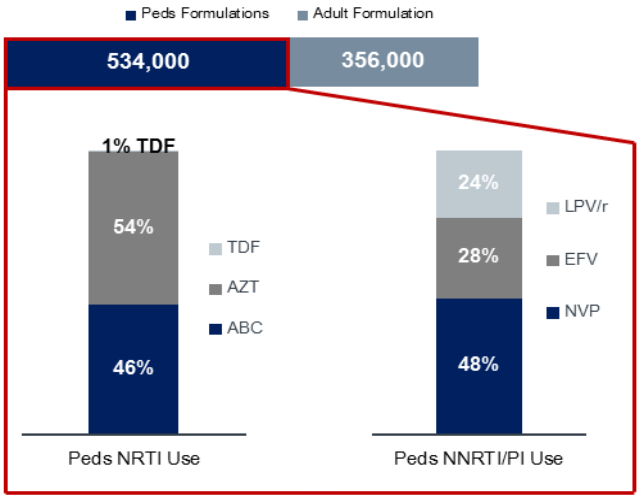


There is often a lag between procurement and use. Based on data received from country programs, CHAI estimates that approximately 40 percent of CLHIV on ART in 2017 were on adult formulations (e.g., ABC/3TC 600/300 mg). Of children on pediatric formulations, the percent on ABC-based regimens is nearing 50 percent as countries move toward WHO-recommended ABC/3TC-based products. Despite strong guidance, nearly 50 percent of CLHIV on pediatric formulations were still on NVP-based products (primarily AZT/3TC/NVP (60/30/50 mg) dispersible), illustrating the challenges of moving to optimal products that are less convenient in terms of administration, pill burden, and price (Figure 32). However, with the new WHO guidelines, the market should eventually move toward DTG-based regimens.

Supply situation improving for solid oral formulations of LPV/r for young children, but constraints remain

Until August 2018, the only heat-stable formulation of LPV/r for young children unable to swallow tablets was Cipla's LPV/r (40/10 mg) oral pellets. Since late 2016, global demand for the pellets has outpaced supply (around 20,000 packs per month), which has limited uptake in LMICs. However, recent information from Cipla suggests that production output will increase to 50,000-60,000 packs per month by early 2019.[xl]

Figure 32: 2017 Pediatric Regimen and Formulation Splits for GA LMICs (Pediatric Formulations Only)[xviii]



Mylan received tentative-FDA approval on August 16, 2018 for their LPV/r (40/10 mg) oral granules.[xli] Although serving the same population as Cipla's pellets, and both being listed as "optimal" per the 2018 WHO Optimal Formulary, there are relevant differences between the two products in terms of packaging and administration. The APWG recommends national programs consider adopting only one product to avoid confusion at facilities and for caregivers.[xlii]

While these new developments are likely to ease some of the global supply constraints on LPV/r solid oral dosage, further capacity increases will likely be required to support the entire market need (children less than 10 kg or unable to swallow tablets). The APWG is monitoring the supply situation on an ongoing basis, and will issue recommendations on procurement as new intelligence emerges.

Imminent new pediatric FDCs may have a more limited role than initially anticipated given new WHO guidance

Two fixed-dose combinations (FDCs) of generic pediatric ARVs are in the development pipeline and relatively close to market, but due to the latest WHO guideline changes, these ARVs are now only recommended for use as alternates or in special circumstances.

The 4-in-1 LPV/r product will be important for a short window of time until generic pediatric DTG formulations and dosing recommendations for young infants are available, whereas the ABC/3TC/EFV product will likely have a limited role from the very outset of availability, due to high-levels of resistance resulting in a need for a shift away from NNRTI-based regimens for children. See the sequencing chart in Figure 33 for more information on where the below products fit in.

Figure 33: Pediatric ARVs in Development Pipeline[xl]

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

For use as an alternative regimen in children where a DTG-based option is not available/tolerated and for those who can't swallow tablets

First generic SRA approval expected **mid-2019**

ABC/3TC/EFV "ALE"

Due to decreased focus on NNRTIs due to resistance, ABC+3TC+EFV recommended for use in children when ***no other alternatives are available***

First generic SRA approval expected ***late 2019***

Development of transition plans needed to ensure seamless shift to new pediatric ARVs

As countries begin considering the new WHO pediatric guidance and adopting their own updated guidelines, national programs in LMICs will need to develop transition plans to help with the adoption of new pediatric products, and to ensure that treatment sequencing can flow uninterrupted as children grow older.

Figure 34 below shows potential pediatric ART sequencing as countries move toward adoption of optimal ARVs. The "Short-Term Future" column reflects treatments under the latest WHO guidelines (discussed above) with available formulations. The "Medium-Term Future" column reflects the ideal treatments with the development of generic pediatric DTG formulations. As the chart shows, the desired ultimate future state greatly simplifies pediatric treatment to just three discrete regimens.

Figure 34: Potential Sequencing of Pediatric ARVs[xxx,xix]

Weight (kg)	2016 WHO Recommendations	Short-Term Future	Medium-Term Future
0 – 2.9 (neonates)	AZT OS + 3TC OS + NVP OS	AZT OS + 3TC OS + **RAL granules**	AZT OS + 3TC OS + RAL granules
3.0 – 5.9	ABC (or AZT)/3TC (disp & scored) + LPV/r OS	ABC/3TC **(120/60 mg)** (disp & scored) + LPV/r OS	ABC/3TC (120/60mg) (disp & scored) + **DTG (10mg) tab (disp & scored)** *(Eventually an FDC)*
6.0 – 9.9	ABC (or AZT)/3TC (disp & scored) + LPV/r pellets/granules	ABC/3TC **(120/60 mg)** (disp & scored) + LPV/r pellets/granules *("4-in-1" FDC expected)*	
10.0 – 13.9	ABC/3TC (disp & scored) + EFV scored tab	ABC/3TC **(120/60 mg)** (disp & scored) + LPV/r tab *(or DTG depending on dosing recommendations)*	
14.0 – 19.9			
20.0 – 24.9			
25.0 – 29.9	ABC/3TC (adult) + EFV	ABC/3TC (adult) + **DTG (50 mg)**	ABC/3TC (adult) + **DTG (50 mg)**
30.0 – 34.9			

In addition to the WHO Optimal Formulary described in the previous section, a number of resources from partners and normative bodies exist to assist countries with their transition plans, including phasing out "non-essential" products (Figure 35).

Figure 35: Resources to Support New Product Adoption and Transition Planning[xliii,xliv,xlv]

Transition Planning Resources

- **Transition to an Optimal Paediatric ARV Formulary: Implementation Considerations (WHO Policy Brief)**
  Assists national programs in ensuring they are well prepared to transition their pediatric ARV formularies to align with the updated Optimal Formulary and Limited-Use List.
- **CHAI HIV New Product Introduction Toolkit**
  Provides Ministries of Health (MoHs) and implementing partners with the tools necessary to evaluate the adoption and introduction of new products in their local context.
- **AIDSFree LPV/r Pellet Toolkit**
  Provides information on how to implement rollout of LPV/r pellets into the national health care system, as well as clinical information.

The APWG serves as an excellent resource to stay abreast of global demand and supply side updates. Earlier this year, the APWG released a new website (http://www.arvprocurementworkinggroup.org/en/home) to host useful documents such as the quarterly demand forecast, bi-annual newsletters, and product-specific memos on topics like TLD and LPV/r oral pellet adoption and supply security.

New generic pediatric formulations of DTG still needed to align with latest WHO treatment guidelines

Although the WHO-approved dosing of DTG (50 mg) for pediatric patients down to 25kg is a major step toward providing all PLHIV with best-in-class treatment, pediatric formulations of DTG suitable for younger children are still needed to align with the latest WHO guidelines. See below for a summary of current dosing recommendations for pediatric DTG by WHO.

Figure 36: WHO-Recommended Pediatric DTG Daily Dosing[xix,xlvi,xlvii]

WHO DTG daily dosing recommendations	0 - 4.9kg	5.0 - 24.9kg	25.0 - 39.9kg
Current FCTs & Future DTs		**DTG recommended; dosing data expected late 2019**	**1 x 50mg FCT**

FCT: film-coated tablet, DT: dispersible tablet.
Note: DTs and FCTs are not bioequivalent at the same dosage

The IMPAACT P1093 and ODYSSEY trials will inform safety and PK information for pediatric DTG, with enough data to support a WHO recommendation on dosing for children under 25kg anticipated by late 2019.[xlviii]

The prioritized formulation for pediatric DTG is a 10mg tablet that is both dispersible and scored to allow for greatest flexibility when it comes to

dosing across pediatric weight bands. Additionally, a scored 10mg dispersible tablet covers the recommendation coming out of the third Pediatric ARV Drug Optimization meeting (PADO 3) that a 5mg tablet of DTG be developed as a mid-term priority product.[xlix] To accelerate the development of this product, CHAI and Unitaid launched an RfP in late 2017 and announced awardees in Q2 2018 (Figure 37).

Figure 37: CHAI-Unitaid RfP to Accelerate Development of and Access to Pediatric DTG[l]

DTG (10 mg) Dispersible and Scored

In Nov. 2017, CHAI and Unitaid released an RfP to **accelerate development of and access to generic pediatric dolutegravir**.

The project, which also involves a **close collaboration with ViiV**, will contribute to the reduction of the generic development timeline by 2-5 years by providing financial incentive and increasing access to a significant body of technical evidence earlier and in more detail than is typical in a generic development program.

Awards to **Mylan** and **Macleods** were announced in July 2018. Both suppliers will receive a financial incentive from Unitaid and technical assistance from ViiV to accelerate development of pediatric DTG.

Unitaid ViiV Healthcare CLINTON HEALTH ACCESS INITIATIVE

Proactive capacity planning can help suppliers better understand potential market size while minimizing delays in drug access

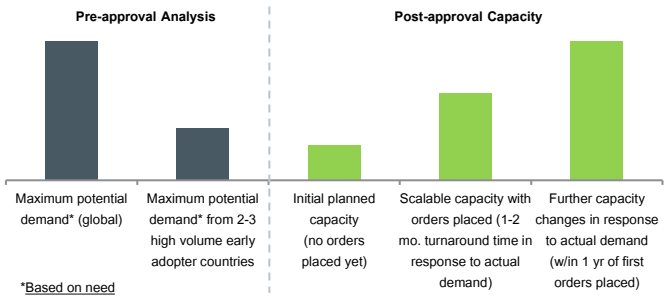
As shown previously in Figure 24, CHAI projects that the number of children put on ART will increase over the next five years to over 1 million by 2022. With treatment coverage in GA LMICs only at ~50 percent, there is plenty of room for this market to continue to grow.

However, the *total number of CLHIV* is expected to decrease over time as pediatric mortality and aging out into adult formulations occur at higher rates than new infections. CHAI modeling on 26 high-burden LMICs (representing 79 percent of global CLHIV) suggests that there may be between 380,000 and 716,000 CLHIV by 2027, depending on whether the Super Fast-Track[5] targets are met by 2020 or pediatric infections decline according to historical rates.

These large variances in the number of CLHIV makes forecasting volumes of future products (e.g., ABC/3TC/DTG, ABC/3TC/LPV/r) difficult. Variations in the total number of CLHIV will likely mask any differences in ART coverage or API-/formulation-level market share assumptions forecasters may typically make. Rather, understanding the relative scale and order of magnitude of future pediatric populations will be more useful for proactive capacity planning.

By proactively planning supplier capacity based on total potential need rather than current orders, the required volumes can be produced in response to actual demand so as to not delay access (Figure 38). For example, a lack of proactive capacity planning around potential market size during development of LPV/r oral pellets led to the supply constraints currently facing the market.[li]

Figure 38: Illustrative Proactive Production Scale-up Planning[li]



Partner organizations continue to work with suppliers to accelerate access to pediatric formulations

A number of global partners are focused on the development and optimization of pediatric ARVs, and these groups have developed resources to support suppliers with this effort.

The Pediatric ARV Working Group (PAWG) launched a research toolkit at AIDS 2018 that provides guidance to manufacturers interested in developing pediatric ARVs covering topics, such as PK studies and modeling, target product profiles, and community engagement.[lii]

Earlier this year, the US FDA issued draft recommendations on developing drugs for treating pediatric HIV, with a final version to be released pending public comments.[liii]

Finally, the Global Accelerator for Paediatric Formulations (GAP-f) is a new mechanism working to support and formalize collaboration across sectors to ensure that new optimal pediatric ARVs are available as soon as possible (Figure 39).[liii]

Figure 39: Operationalizing the GAP-f[li]

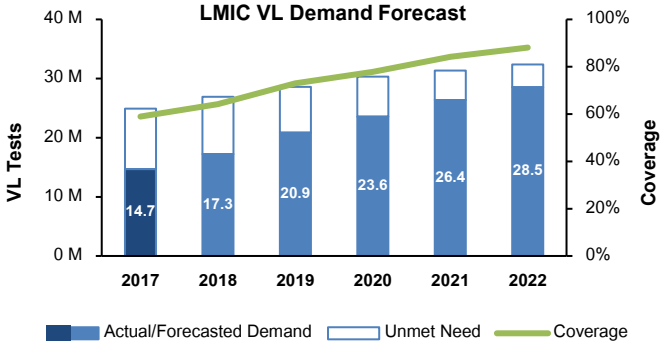
[5] Super Fast-Track target here refers to fewer than 20,000 new infections among children by 2020.

Diagnostics and Lab Services

LMICs continue to scale up their viral load testing programs as prices decrease

A majority of LMICs have adopted VL testing for *routine monitoring* per WHO guidelines. As such, VL volumes are on the rise. Over 14 million VL tests were conducted in LMICs in 2017, and CHAI projects that testing volumes may double by 2022, reaching nearly 29 million tests at a five-year CAGR of 14 percent (Figure 40).[liv]

Figure 40: Estimated/Forecasted VL Tests in LMICs Globally[liv]



Prices for virologic testing continue to decrease, freeing up resources for other country priorities

There have been a number of pricing deals over the past 12 months, affecting both conventional and point-of-care (POC)/near-POC diagnostic platforms, which are making virologic testing more affordable in LMICs in both the private and public sectors.

CHAI and other partners negotiated a landmark all-inclusive pricing agreement that has dramatically reduced the cost and simplified the costing structure of conventional viral load testing (Figure 41). Importantly, this simplified pricing structure promotes integrated testing (i.e., testing across multiple diseases/test types), which is key to maximize the efficient use of finite resources, bring about better-integrated disease management, and improve overall health outcomes. Countries will be able to invest in further scaling up viral load testing or in other priorities because of these cost savings.

Unitaid, along with CHAI and UNICEF, is piloting *all-inclusive pricing contracts* in Uganda, Malawi, Zimbabwe, and Tanzania. As discussed earlier, all-inclusive pricing dramatically simplifies the costing structure for diagnostic testing. The results from the all-inclusive testing pilots will be used to generate evidence for broader implementation in LMICs, including key information on the pathway and challenges faced when shifting to locally monitored contracts.

At AIDS 2018, Cepheid, along with Unitaid, announced the lowering of the cost of HIV, HCV, and HPV GeneXpert test cartridges to a standard public sector price of US$14.90 (EXW) for all 130 LMICs that are part of Cepheid's High-Burden Developing Country (HBDC) program.[lv] This new pricing will not only benefit HIV programs, but will also allow hepatitis and cervical cancer programs to expand testing.

Figure 41: Hologic Panther Pricing Agreement Details[lvi]

Breakthrough Laboratory Testing Pricing Agreement

ASLM MedAccess Clinton Health Access Initiative The Zambian Ministry of Health

The UK Department for International Development (DFID), Unitaid, MedAccess, CHAI, the President's Emergency Plan for AIDS Relief (PEPFAR), the African Society for Laboratory Medicine (ASLM), and the Government of Zambia announced a breakthrough pricing agreement at AIDS 2018 that will significantly reduce the cost of diagnostic testing for HIV/AIDS, hepatitis, and cervical cancer for millions of people in LMICs.

The agreement allows public sector programs in LMICs to access the Hologic Panther system at a price of US $12 per patient sample.

US $12 per patient sample

Key Pricing Agreement Details

- No additional cost for machine placement, service and maintenance, distribution, etc.
- Covers HIV, HBV, HCV, HPV

Hologic Panther Benefits

- Random access
- Multiplex capabilities
- Increased operator walkaway time
- Load primary blood tubes directly on instrument

In the private sector, a CHAI-supported consortium of private labs in India has agreed to offer HIV and HCV viral load tests on the GeneXpert platform at half of the market rate, increasing access to these vital tests across India.[lvii]

POC VL generating evidence, likely to be first used for high-risk populations

While the clinical and programmatic benefits of POC EID are established, the case for POC VL testing is currently being developed and refined. Current evidence suggests that the initial rollout of POC VL will be prioritized for monitoring ART in certain populations that are expected to clinically benefit most from a faster result turnaround time (Figure 42). However, as more evidence emerges, the benefits of POC VL may be extended to all populations on ART. Regardless, POC VL is an important tool to enable equity and access for patients at more remote sites who may otherwise never receive a VL result (or receive it too late) with a conventional network.

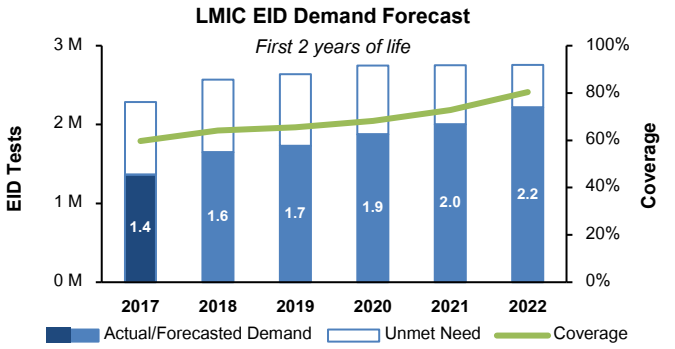
Figure 42: Likely Initial Target Populations for POC VL

Elevated Initial Viral Load	POC testing to confirm true virological failure will enable a faster transition to 2L regimens
Pediatrics and Adolescents	Pediatric patients have higher rates of unsuppressed VL due to challenges with appropriate ART dosing and formulations, as well as psychosocial factors that influence adherence, and thus are at higher risk of failure and may benefit from
Pregnant Women	POC testing will quickly identify mothers at high-risk of transmission, and allow the mother's VL to be brought down before

EID testing, with a global focus on point-of-care testing, continues to scale up to identify remaining CLHIV

As with viral load, EID testing continues to scale up, albeit at a slower rate. Approximately 1.4 million EID tests were run in 2017, with 2.2 million projected by 2022 at a five-year CAGR of ten percent (Figure 43).[lviii]

Figure 43: Estimated/Forecasted EID Tests in LMICs Globally[lviii]



POC EID testing has been established as a way to reduce result turnaround times, improve linkage to care, and ultimately improve rates of ART initiation in HIV-positive infants.[lix] Given the proven benefits of POC EID, a number of partners are working to expand access to these platforms, including multiple Unitaid-funded projects in sub-Saharan Africa implemented by CHAI/UNICEF and Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) (Figure 44).

Figure 44: Unitaid-supported Project to Improve Access to POC EID

Unitaid

Accelerating access and integration to innovative point-of-care (POC) diagnostics for HIV in national diagnostic programs

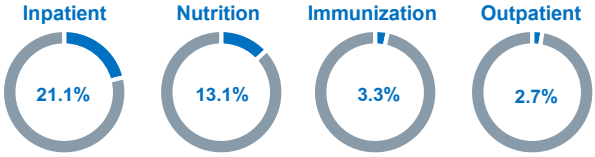
- Project to improve access to POC EID in 10 focal countries (to the left)
- Countries are piloting and rolling out POC EID platforms, conducting training and mentorship activities, and beginning demand generation activities

Despite improvements in EID coverage, new case finding approaches are needed to reach the 90-90-90 goals

In 2017, UNAIDS estimated that the global prevention of mother-to-child transmission (PMTCT) coverage rate was 80 percent. However, approximately 180,000 children were newly infected with HIV the same year.[i] Finding HIV-positive children is significantly more challenging than finding HIV-positive adults given lower pediatric HIV prevalence. With advances in PMTCT coverage and children transitioning to adult programs, pediatric prevalence continues to decline, making the job even harder. In addition, pediatric patients require the help of parents/caregivers to get tested, and children under 18 months need molecular testing instead of rapid diagnostic tests (RDTs). This harder-to-reach group of infants and children need new, and more targeted, case finding approaches to be identified.

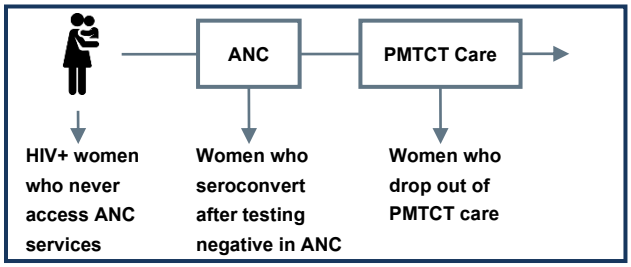
Testing at high-risk alternative entry points (non-PMTCT) with POC platforms is a key strategy to improve case finding given relatively high positivity rates (Figure 45). In fact, the WHO recommends routine testing of infants and children with unknown status in inpatient wards and malnutrition clinics, and also recommends offering testing services in outpatient or immunization clinics (in generalized epidemic settings).[xxx]

Figure 45: Estimated Positivity Rates at non-PMTCT Entry Points[lx]



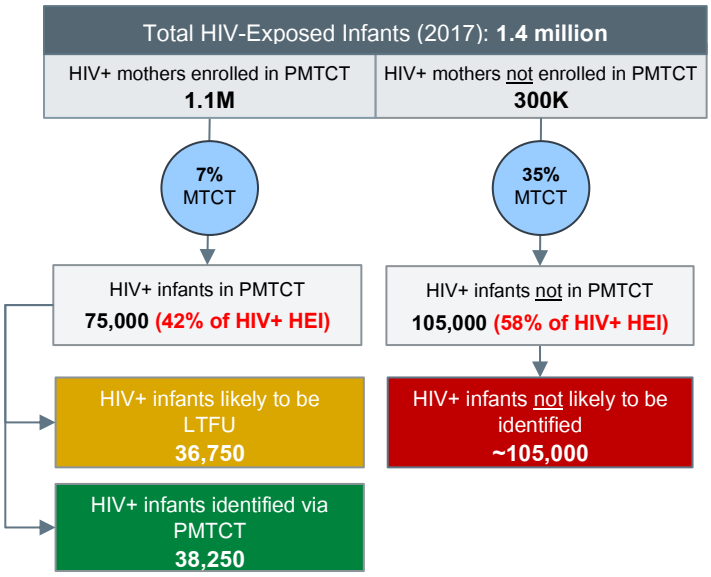
Testing at these priority alternative entry points is needed as a number of HIV-positive pregnant women never make it to PMTCT care or drop out of care before the transmission window has closed (Figure 46). Although this number is relatively small, transmission rates among women not enrolled in PMTCT programs (i.e., not accessing ART to suppress their viral load) are around 35 percent (Figure 47).[lxi]

Figure 46: Populations of HIV-Positive Pregnant Women Likely Driving Continued Vertical Transmission



Given the high mother-to-child transmission (MTCT) rates of women not enrolled in PMTCT, the majority of HIV-positive infants are likely to show up outside of the PMTCT cascade, further emphasizing the importance of looking at non-PMTCT entry points and expanding access to POC EID. There are a number of strategies to improve case finding beyond testing at high-priority alternative entry points, and the optimal mix of these strategies is country context-dependent. Through work funded by The ELMA Philanthropies, CHAI is supporting countries in developing a smart, targeted approach to pediatric case finding.

Figure 47: Estimated Size of HIV-positive Infant Population via PMTCT and Non-PMTCT Channels



Birth testing, in addition to the 4-6 week test, which the WHO conditionally recommended in their 2016 guidelines update, has yet to see significant uptake (outside of South Africa) despite inclusion in a number of country-specific HIV testing and treatment guidelines. Kenya is piloting birth testing in 2018 to generate evidence for potential nationwide rollout.

One barrier to widespread adoption of birth testing has been limited ARV formulations for neonates. The inclusion of RAL (100 mg) granules on the updated 2018 Limited-use List, as well as their recommendation in the 2018 WHO guidelines, may encourage more birth testing but implementation challenges remain.

In November 2017, global partner organizations convened a high-level meeting in the Vatican City, focused on accelerating diagnosis and treatment for children and adolescents living with HIV. The meeting was convened by His Eminence Cardinal Turkson of the Holy See, in collaboration with PEPFAR, UNAIDS, Caritas International, World Council of Churches-Ecumenical Advocacy Alliance, WHO, and EGPAF; and attended by leaders of major pharmaceutical and medical technology companies, multilateral organizations, donor agencies, and government representatives. This high-level dialogue provided an opportunity for stakeholders to commit to a concrete set of actions to accelerate the development, registration, introduction, and rollout of the most optimal pediatric formulations and diagnostics. These commitments and the corresponding specific actions taken by each stakeholder (should finding be catalyzed) are expected to significantly accelerate pediatric testing and treatment in countries with the largest unmet need for HIV-positive children and adolescents over the next 2-3 years.

New WHO recommendations aim to reduce number of children incorrectly put on lifelong ART, while also simplifying the EID algorithm

As part of the guidelines released at AIDS 2018, the WHO released a new recommendation to improve EID accuracy.[xix]

New WHO Recommendation

"An indeterminate range should be used to improve the accuracy of all nucleic acid-based early infant diagnosis assays"

(strong recommendation, moderate-certainty evidence)

The positive predictive value of early infant diagnosis assays decreases as MTCT rates decline.[xix] Development of an indeterminate range that requires retesting when a low amount of virus is detectable can help ensure that only truly HIV-positive infants receive ART. To implement an indeterminate range, manufacturers will need to update their software and send a change notification to regulatory authorities, including the WHO Prequalification (PQ) program.

In addition to the above recommendation on the establishment of an indeterminate range, the WHO released three key considerations for optimizing high-quality EID (Figure 48).

Figure 48: Key Considerations for Optimizing EID Testing[xix]

1. Repeat testing of indeterminate results in the laboratory
2. Confirmatory testing of all positive results, which can take place on POC devices
3. Testing throughout the exposure period, including through cessation of breastfeeding

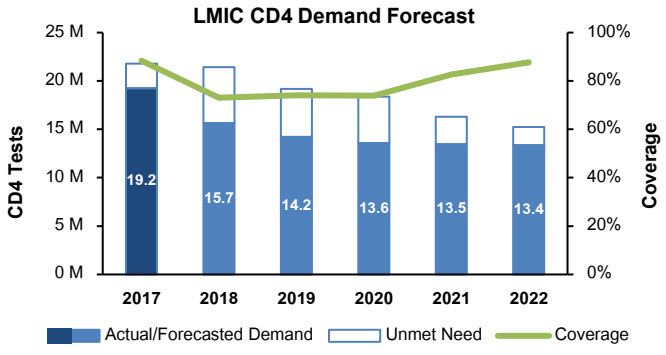
Finally, the WHO also simplified the EID testing algorithm. One of the major changes to the updated algorithm is that providers should perform a nucleic acid test (NAT) at nine months for both symptomatic and asymptomatic HIV-exposed infants who have previously had a negative NAT result. This will likely have a large impact on national EID testing volumes, as previously the WHO recommended that the nine-month test be an RDT, with a NAT used only for confirmation.[lxii]

CD4 testing still relevant, especially for advanced disease and opportunistic infections

Although CD4 testing volumes are decreasing as VL monitoring continues to scale up and CD4 count is no longer a criterion for ART eligibility, CD4 testing still very much has a place in national programs. Approximately 19 million CD4 tests were run in 2017.[lxiii] With 55 percent of patients found to start ART at a CD4 cell count below 200/μL, the WHO recommends a CD4 test at treatment initiation to identify patients who need additional services to prevent opportunistic infections and possibly death.[lxiv] See the *Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy* released by the WHO in June 2017 for further details.[lxv]

In addition to identification of patients with advanced disease, CD4 testing is still important for routine monitoring of patients who do not yet have access to viral load monitoring (Figure 49).

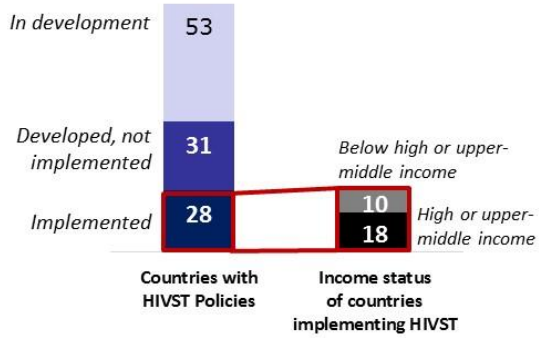
Figure 49: Estimated/Forecasted CD4 Tests in LMICs Globally[lxiii]



Self-testing can help find hard-to-reach populations, while freeing up health-care worker capacity

HIV self-testing (HIVST) continues to generate excitement in many countries as a way to both find hard-to-reach populations and increase their testing frequency. Over 100 countries have developed, or are in the process of developing policies supporting HIVST, although only 10 countries with an income status below high-or upper middle-income have implemented such policies (Figure 50).[lxvi]

Figure 50: Country Status of HIVST Policies[lxvi]



Procurement of self-tests continues to increase, with over 1 million self-tests procured globally in 2017. The public sector alone is expected to procure over 4.7 million self-tests in 2018.[lxvi]

A number of projects, such as the Unitaid-funded STAR Initiatives, have been generating evidence to support the rollout of HIVST. Emerging evidence suggests that community-based distribution, index testing of HIV-positive pregnant women, and outreach services for key populations are all testing strategies than can be enhanced through the integration of HIVST.

There is also a potential for HIVST to increase testing rates while reducing healthcare worker (HCW) burden at the same time. In a study presented at AIDS 2018, patients offered HIVST in outpatient clinics in Malawi were significantly more likely to take an HIV test than even those offered optimized provider-initiated testing and counseling.[lxvii]

In a study among men who have sex with men (MSM) in Australia, clients permitted to conduct HIV tests *without* a required HCW consultation had 24 percent fewer consultations than those required to test with an HCW present, without a reduction in overall testing volumes.[lxviii]

With well over 100M HCW-administered rapid diagnostic tests (RDTs) conducted every year, there is an opportunity to shift a significant proportion of this volume to HIVST to free up HCW resources. However, a key barrier to widespread adoption of HIVST by programs is affordability. Current HIVST prices are well over twice that of RDTs – even the Bill & Melinda Gates Foundation (BMGF)-subsidized US$2/test OraQuick HIVST price is more than double that of professional-use RDTs. At an attractive price to consumers, the private sector may also play an important role in growing the HIVST market and reaching so-far unreached populations at risk of contracting HIV.

The first-ever WHO Essential Diagnostics List will assist LMICs in disease testing prioritization and advocacy

For the first time ever, the WHO has released an Essential Diagnostics List (EDL), mirroring the Essential Medicines List published since 1977, which outlines diagnostic products that are key to a well-functioning health system (Figure 51).[lxix]

Figure 51: WHO Essential Diagnostics List, 2018[lxx]

WHO Essential Diagnostics List

Contents:

- 58 general laboratory tests for routine patient care
- 55 tests for detection, diagnosis, and monitoring of HIV, TB, malaria, HBV, HCV, HPV, and Syphilis

Covers: Includes tests for both the primary level and facilities with clinical laboratories

Benefits: Improve patient access, improve regulation and quality of IVDs, improve supply chain and infrastructure, etc.

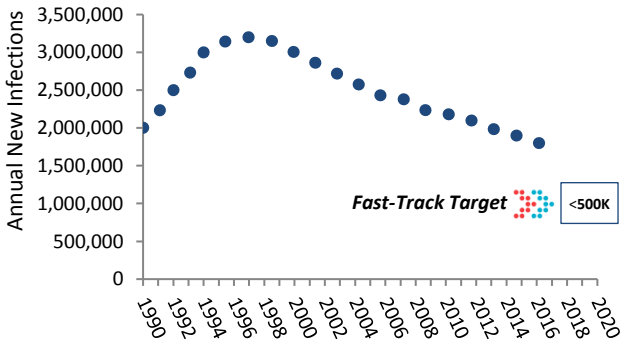
The second edition of the EDL is expected to be released in May 2019, and it is hoped that countries will develop their own EDLs based on the WHO list released in 2018.

Prevention

Annual new HIV infections are declining but not at a rate fast enough to meet 90-90-90 targets

Globally, new HIV infections have been cut by nearly half since peaking in 1996, when more than three million new individuals were being infected with HIV on an annual basis.[i] However, the global community is off-track to reach the 90-90-90 target of lowering annual new infections to <500,000 by 2020 (Figure 52).

Figure 52: Estimated Annual New HIV Infections Globally Between 1990 and 2017



While bolstered by new data, effective treatment alone will not put a stop to high infection rates

Effective treatment for PLHIV has been useful in decreasing transmissions. Building on data from heterosexual couples, new PARTNER2 data presented at AIDS 2018 showed treatment as prevention (TasP) was effective among serodiscordant gay couples. There were zero new infections across nearly 75,000 condomless sexual acts, where the seropositive individual had an undetectable VL.[lxxi]

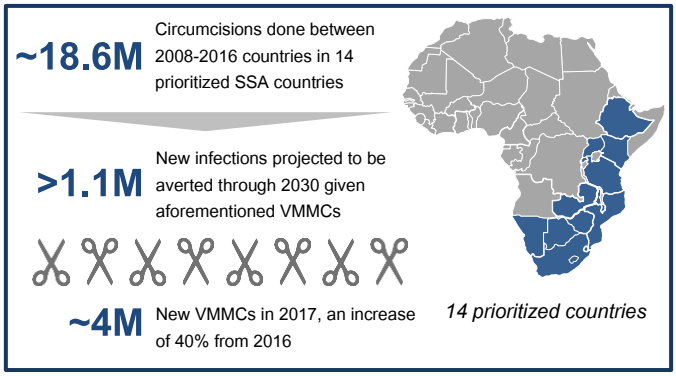
Optimal ARVs, such as DTG, will certainly help maintain viral suppression for PLHIV, but ART scale-up and effective treatment alone will not be

enough to meet the Fast-Track targets. Even in the 90-90-90 scenario, 27 percent of PLHIV will be virally unsuppressed with potential to transmit HIV to others. Thus, further work is needed to ensure access to effective prevention technologies and enable use and adherence by all populations at risk, particularly those most vulnerable.

VMMC scale-up can continue to help reduce annual new HIV infections

Studies have shown that voluntary medical male circumcision (VMMC) reduces the risk of female-to-male transmission of HIV by ~60 percent, and that it can enable savings by averting HIV treatment costs.[lxxii,lxxiii] In 2007, the WHO recommended VMMC as an additional HIV prevention intervention. Further, the WHO and UNAIDS prioritized 14 eastern and southern African countries given their high HIV prevalence, generalized heterosexual HIV epidemics, and low levels of circumcision.[lxxiv] Priority countries have scaled up their programs to reach a global annual peak of four million VMMCs in 2017, and a cumulative total of 18.6 million since 2008. (Figure 53).[lxxv]

Figure 53: VMMCs in 14 Prioritized SSA Countries[i,lxxv]



MOHs and donors have driven VMMC scale-up with evidence-based targets, intensive outreach and campaigns, and coordinated technical and programmatic support at the country level. While VMMC amongst older males 15-29 years old yields immediate preventive benefits, it also offers long-term preventive benefits for adolescents (10-14 yrs), making them a critical component of a sustainable HIV prevention strategy.

At the national level, most priority countries have a mature (post scale-up) VMMC program. However, given differential rates of subnational coverage within countries, there are three core principles that can help direct national strategy (Figure 54).

Figure 54: Three Core VMMC Principles

1. **Achieve saturation**: circumcise 80-90% of 15-29-year-olds)
2. **Maintain high coverage**: circumcise adolescents ages 10-14 as they age into the priority population
3. **Ensure sustainability:** continue offering VMMC to priority populations in years ahead

The continued scale-up and sustainability of VMMC will remain important for achieving HIV prevention goals.

Oral PrEP uptake to date primarily in high-income settings, but adoption increasing in LMICs

TDF-based oral pre-exposure prophylaxis (PrEP) is another prevention offering for individuals at high risk of infection. Over 350,000 individuals have started oral PrEP globally. A vast majority of these initiations were in the US and other high-income countries (HICs), and primarily in urban settings such as London, New York City, and San Francisco.[iii] In May 2018, the US FDA approved Truvada (the innovator TDF/FTC offering) for adolescents between the ages of 15 and 17, which should help promote access in this key population.[lxxvi] Less than two percent of oral PrEP users in the US were 17 years old or younger, with most of this use driven by adolescent girls.[lxxvii]

LMICs are also building momentum around oral PrEP. As of March 2018, over 50 countries were offering oral PrEP, including LMICs such as Botswana, Kenya, Lesotho, Nigeria South Africa, Uganda, Zambia, and Zimbabwe.[lxxviii,lxxix] A benefit of TDF-based oral PrEP is that generic formulations, such as TDF/FTC, are already in supply chains at relatively low prices (Figure 55). Further, generic TDF/FTC has been specifically approved for prevention use in many of these countries to date.[lxxx]

Figure 55: Supply and Demand of TDF-based Dual Formulations

Approved Generics: *Registration of products for prevention use varies depending on the country and supplier*

TDF/FTC (300/200mg)
Aspen, Aurobindo, Cipla, Hetero, Macleods, Micro Labs, Mylan, Strides, Sun Pharma

TDF/3TC (300/300mg)
Aurobindo, Cipla, Hetero, Macleods, Micro Labs, Mylan, Sun Pharma

15M+ **packs** of **TDF/FTC (300/200mg)** and **TDF/3TC (300/300mg)** were procured in 2016 and 2017*

***Source:** WHO GPRM (accessed Aug 2018)

Early LMIC adopters such as South Africa and Kenya have played an important role in generating lessons learned that can help countries move from demo projects to at-scale adoption. For example, a recent USAID-funded OPTIONS Consortium and a BMGF-funded Prevention Market Manager (PMM) operations research project in South Africa indicated that provider attitudes and client perceptions of side effects may be major barriers to uptake and continued use.[lxxxi]

South Africa, which introduced oral PrEP in 2016, has generated useful data on continued-use of oral PrEP, i.e. staying on PrEP beyond the first few months after initiation. Sixteen-month data on continued-use found that stoppage rates were slower in later months, and that MSM demonstrated higher levels of continued use than sex workers.[lxxxii] Given much discontinuation happens after the first few months of oral PrEP use, support services will likely be required to ensure sustainable use of oral PrEP in populations who need it most. Since oral PrEP is still relatively nascent, national programs should aim to be agile in their rollout of oral PrEP to ensure that they can incorporate the latest data from early adopters, as well as their own monitoring and evaluation.

Prevention products in development represent a varied set of offerings that could meet the individual needs of diverse populations

Beyond VMMC, oral PrEP, and condoms, there are pipeline offerings in development. The hope is that these additional offerings will meet the

needs of those individuals at the highest-risk of HIV infection by acting longer, having fewer side effects, and being less disruptive to daily life.

Two prevention offerings in development are highlighted below:

Long-acting injectables (LAIs)

Long-acting formulations such as ViiV's injectable formulation of cabotegravir (CAB LA) offer the promise of less frequent dosing and discretion for high-risk clients. Two phase III trials are under way:

- **HPTN 083**: MSM and transgender women. Expected primary completion date in late 2021
- **HPTN 084**: Sexually active women in SSA. Expected primary completion date in early 2022

While there are potential limitations to CAB LA, including the need for an oral lead-in, it could be the choice offering for certain high-risk individuals.

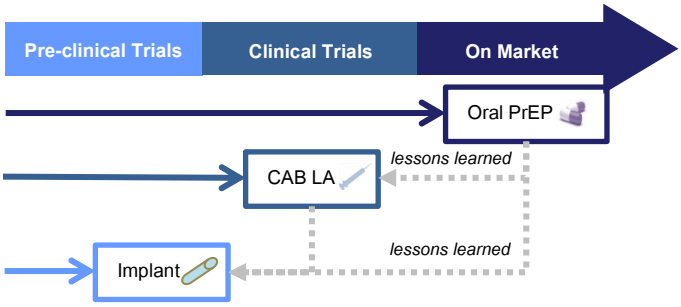
Implants

Building on the successful development of implantable contraceptives and insulin pumps for diabetes, researchers are progressing towards developing a sub-dermal implant that can deliver ARVs for extended periods of time, including for PrEP. For example, Intarcia Therapeutics, with funding from the BMGF, is developing a sub-dermal osmotic implant that will dispense PrEP over the course of 6-12 months. The minipump is the size of a matchstick and made out of titanium. Given the implant is not in clinical trials yet, it will likely take several years to reach the market.

New prevention product introduction will build off lessons learned from rollout of existing offerings

Since biomedical prevention is a relatively new space, the global prevention community must focus on transferring the early lessons learned from rollout and development of existing offerings, such as oral PrEP, to newer products like CAB LA and implants (Figure 56).

Figure 56: Illustrative Example of Sharing Lessons Learned



Further, global coordination to support the development and introduction of prevention products is critical, particularly to ensure lessons from current product introduction is used to inform research and development (R&D) around tools earlier in the pipeline (Figure 57). To this end, the BMGF-funded Prevention Market Manager (PMM), which works with partners to expand the portfolio of prevention offerings and ensure appropriate products are available, accessible, and used by those who need them most, is supporting the coordination of key global stakeholders to support the development and uptake of long-acting forms of PrEP (Figure 57).

Figure 57: Goals of Coordinating New Prevention Product Development

Ideal Scenario for Future Prevention Products

- Post-approval studies are **well-designed** to address decision-maker questions
- Data from research is **well-timed** to inform decision-making at global and country level
- **Coordinated** stakeholder landscape with roles agreed upon in advance

Funding will ultimately determine market size of existing and new prevention products

Unlike the treatment space, in which ARVs are offered to *all* HIV-positive individuals, resource and capacity constraints will require many countries to target HIV prevention services to those at the highest risk of HIV infection. However, quantifying risk and potential demand for new prevention products can be challenging (Figure 58).

Figure 58: Sample Considerations When Quantifying Potential Need for New Prevention Products

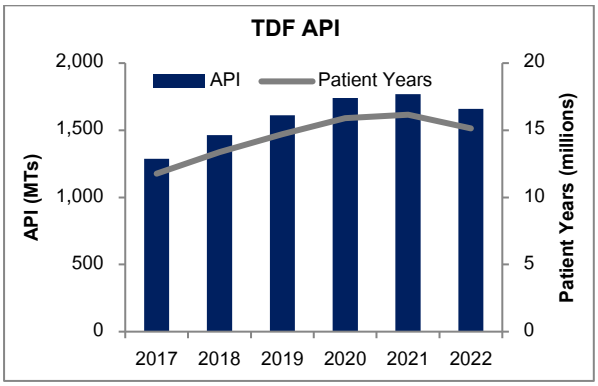
1. **Eligibility criteria for PrEP require defining and will likely vary by country; inclusions could be based on:**
   - FSW? **MSM?** **PWID?** — *Key Population*
   - *Geography*
   - *Age & Gender*
2. **The 'need' for prevention technologies is transient**
   An individual may go through periods of varying levels of risk throughout their lives
3. **Perceived risk of HIV infection may not align with actual risk**
   An individual will be more likely to start using a HIV prevention technology if s/he believe s/he is at risk

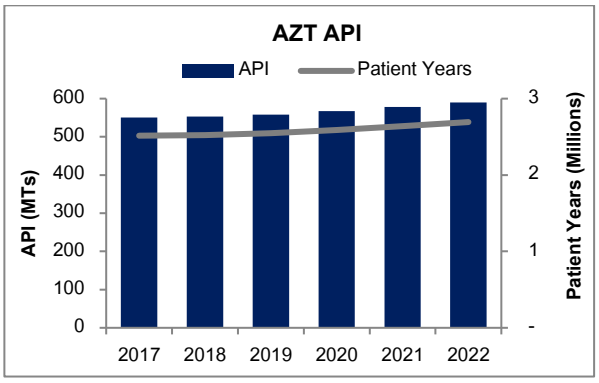
Thus, understanding the relative magnitude of the market size based on theoretical need for, and acceptability of, the product can be useful for early development strategy. Further down the line, as a product nears launch in LMICs, an actual demand forecast based on end-user research, country planning, and implementing experiences could better estimate the likely uptake trajectory at a more granular level.

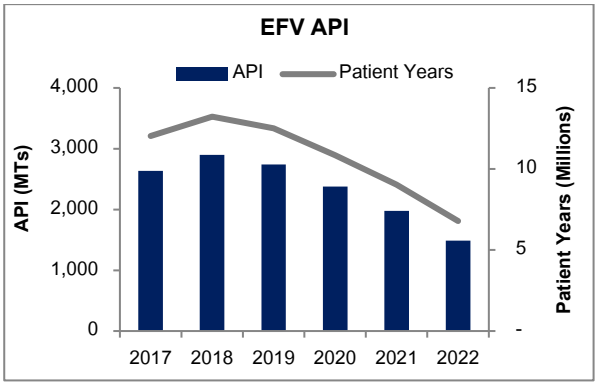
Ultimately, funding will play a major role in determining the market size for any specific prevention product. As the 'State of HIV/AIDS Today' section highlights, global funding for HIV is stagnating. UNAIDS estimates that to end the epidemic by 2030, about a quarter of total HIV funding should be directed at prevention. However, many countries spent less than 10 percent in 2016.[lxxxiii] Given global prevention funding is limited, having highly targeted strategies can help countries have the most impact with a finite set of resources.

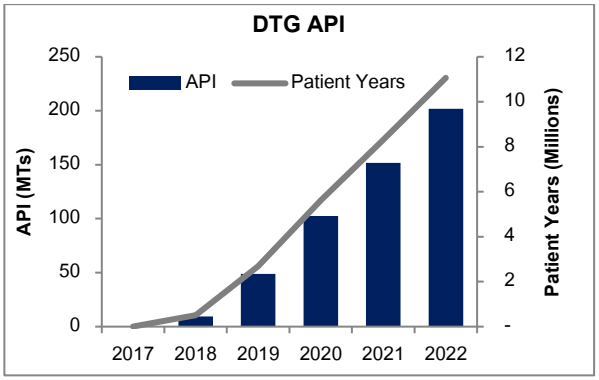
Appendix A: Forecasted API Demand in GA LMICs

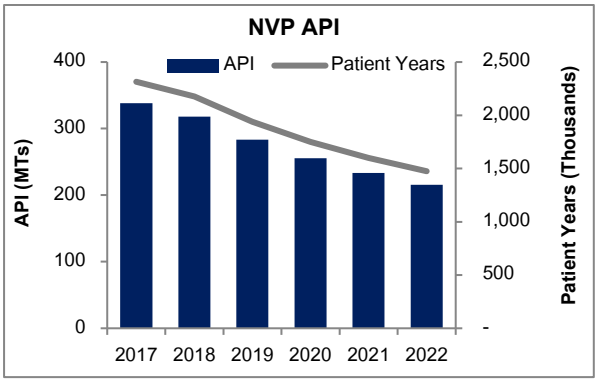
The graphs below show the estimated generic-accessible patient demand and API volume forecast for key adult ARVs. Patient years represent the effective number of patients on treatment for a full year and are used to calculate yearly API demand. Patient years are calculated by assuming newly-initiated patients are on treatment for six 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.

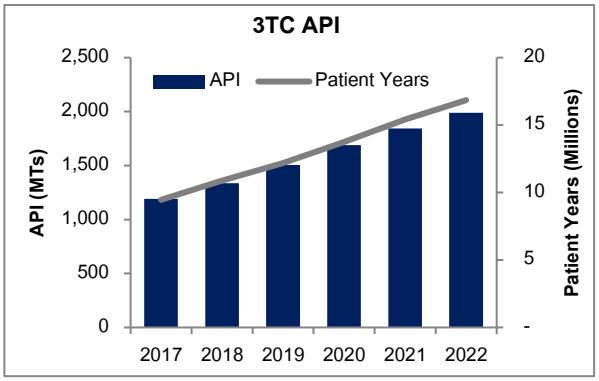












Appendix B: CHAI Benchmark Price Comparison List

The table below provides per pack or bottle prices for key adults and pediatric ARVs at the time of publication of this report. Please refer to the latest reference price lists for most up-to-date pricing. Prices are Ex-Works (EXW) unless otherwise noted.

Product	Packaging*	Global Fund PPM Reference Price, July 2018 (USD)[6]	GHSC-PSM E-Catalog, July 2018[7]	MSF Price, July 2017 (USD)[8]
Adult Products				
ABC/3TC *(600/300mg)*	HDPE bottle 30 tablets	$9.80	$9.12	$11.01
ATV/r *(300/100mg)*	HDPE bottle 30 tablets	$13.25	$13.75	$17.01
AZT/3TC *(300/150mg)*	HDPE bottle 60 tablets	$5.10	$5.11	$4.98
AZT/3TC/NVP *(300/150/200mg)*	HDPE bottle 60 tablets	$6.05	$6.00	$6.48
DTG *(50mg)***	HDPE bottle 30 tablets	$3.80	$3.60	$5.01
EFV *(600mg)*	HDPE bottle 30 tablets	$2.75	$2.75	$2.46
LPV/r *(200/50mg)*	HDPE bottle 120 tablets	$16.90	$16.93	$17.76
NVP *(200mg)*	HDPE bottle 60 tablets	$2.20	$1.79	$1.92
RTV *(100mg)* heat-stable	HDPE bottle 60 tablets	$6.85	$6.85	$6.84
TDF *(300mg)*	HDPE bottle 30 tablets	$3.25	$3.50	$2.49
TDF/3TC *(300/300mg)*	HDPE bottle 30 tablets	$3.75	$3.02	$3.21
TDF/FTC *(300/200mg)*	HDPE bottle 30 tablets	$4.75	$4.15	$3.99
TDF/3TC/DTG *(300/300/50mg)****	HDPE bottle 30 tablets	$6.00*****	$6.25	n/a
TDF/3TC/EFV *(300/300/400mg)*	HDPE bottle 30 tablets	$5.90*****	n/a	$6.90
TDF/3TC/EFV *(300/300/600mg)*	HDPE bottle 30 tablets	$6.00*****	$6.18	$6.75
TDF/FTC/EFV *(300/200/600mg)*	HDPE bottle 30 tablets	$6.25*****	$6.11	$6.75
Pediatric Products				
ABC *(60mg)* disp.	HDPE bottle 60 tablets	$3.80	$3.80	$4.02
ABC/3TC *(60/30mg)* disp. scored	HDPE bottle 60 tablets	$4.00	$4.25	$3.48
ABC/3TC *(120/60mg)* disp. scored	HDPE bottle 30 tablets	$3.10	$3.30	$3.75
ABC/3TC *(120/60mg)* disp. scored	HDPE bottle 60 tablets	$7.10	$7.50	$7.74
AZT/3TC *(60/30mg)* disp. scored	HDPE bottle 60 tablets	$2.00	$1.85	$1.74
AZT/3TC/NVP *(60/30/50mg)* disp. scored	HDPE bottle 60 tablets	$3.00	$2.90	$3.12
EFV *(200mg)* single scored	HDPE bottle 90 tablets	$6.40	n/a	n/a
EFV *(200mg)* double scored	HDPE bottle 90 tablets	$9.30	$9.30	$9.27
LPV/r *(40/10mg)* oral pellets	HDPE bottle 120 capsules	$19.20	$19.20	$19.20
LPV/r *(80+20mg/ml)*	HDPE bottle 5 x 60ml	$30.82	$30.82	$30.90
LPV/r *(100/25mg)*	HDPE bottle 60 tablets	$5.94	$5.94	n/a
RAL *(100mg)* chewable scored	HDPE bottle 60 tablets	n/a	$36.00	$36.00

**For certain products, pricing on other pack sizes might be available (e.g., multi-month prescription pack sizes). Please refer to relevant price list for more information*

***Please refer to the following link for pricing on DTG 50mg singles*

****Please refer to the following link for pricing on TLD*

*****PPM lists discounted prices for products with a "no carton" presentation, please refer to latest price list for more information*

[6] Global Fund Pooled Procurement Mechanism Reference Pricing: ARVs, Ex-Works, July 2, 2018; prices shown can be treated as ceiling prices and used for budgeting purposes; lower prices may be accessible. Link

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Appendix C: 2018 Optimal Formulary and Limited-Use List for Paediatric ARVs

Optimal Formulary		
Product	**Dosage**	**Formulation**
AZT	50/5 mg/mL	Oral Solution – 100 mL
NVP	50 mg	Tablet (Dispersible, Scored)
NVP	50/5 mg/mL	Oral Solution – 100 mL
LPV/r	100/25 mg	Tablet (Heat Stable)
LPV/r	40/10 mg	Solid Oral Dosage Form
AZT/3TC	60/30 mg	Tablet (Dispersible, Scored)
ABC/3TC	120/60 mg	Tablet (Dispersible, Scored)
RAL	25 mg	Tablet (Chewable, Scored)

Limited-Use List		
Product	**Dosage**	**Formulation**
LPV/r	80/20 mg/mL	Oral Solution
3TC	50/5 mg/mL	Oral Solution – 100 mL
ABC	60 mg	Tablet (Dispersible, Scored)
DRV	75 mg	Tablet
RTV	25 mg	Tablet
RTV	100 mg	Powder
ATV	200 mg	Capsule
AZT/3TC/NVP	60/30/50 mg	Tablet (Dispersible, Scored)
EFV	200 mg	Tablet (Scored)
RAL	100 mg	Granules for Suspension

Appendix D: 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 forecast for the total number of patients on ART in GA LMICs. 'Generic-accessible' denotes countries where global generic manufacturers can register and supply a large proportion of that country's ARV needs. For this purpose, GA countries are defined as those LMICs that are covered under voluntary licenses for generic TDF/TAF. The largest *generic-inaccessible* countries are Argentina, Brazil, China, and Mexico.

CHAI compiles historic data on the number of patients on ART from the UNAIDS AIDSInfo Database. 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, will plateau as universal access (under a "Treat All" paradigm) is approached, and, then, extrapolates to the rest of the world.

Adult ARV Demand Forecast: CHAI collects aggregate country data on patient regimens, formulations used, national guidelines, and anticipated future trends from CHAI 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. CHAI's ARV demand forecast for current drugs includes data from: Benin, Burkina Faso, Cambodia, Cameroon, DRC, Eswatini (formerly Swaziland), Ethiopia, India, Kenya, Laos, Malawi, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Togo, Uganda, Vietnam, Zambia, and Zimbabwe. The countries included represent 84 percent of adult patients on ART in GA LMICs in 2017.

Pipeline (i.e., newer or not on market) ARV uptake is modeled based on 12 high-volume countries and the GA rest of world (GA RoW). Expected launch years and uptake curves are selected for each of the 12 focal countries based on CHAI's country intelligence, as well as for GA RoW as a group, separately for existing and newly initiating patients. These uptake curve choices for new products relative to current products estimate the total number of patients on each new regimen/drug in a given year in GA LMICs.

Market Sizing Analysis: Each year, CHAI combines known regimen and formulation splits by country with pricing data to calculate the 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's regimens and formulations. For all other countries, the average Global Fund Pooled Procurement Mechanism (PPM) pricing across 2017 is used.

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