



# ARV Market Report:

*The State of the Antiretroviral Drug Market in Low- and Middle-Income Countries, 2015-2020*

Issue 7, October 2016

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## Foreword

Sixteen years ago, the 13<sup>th</sup> International AIDS Society Conference (IAS) convened in Durban, South Africa, to “break the silence” on the millions of preventable AIDS-related deaths occurring around the world. The summit was notable as it laid out the clear case that HIV causes AIDS, allowed people living with HIV/AIDS (PLWHA)’s voices to be heard, and paved the way for the dedication of global resources to end the epidemic. In 2016, IAS returned to Durban and to a world that has made significant strides in fighting the HIV/AIDS epidemic.

Since 2000, HIV infections have fallen by 35 percent, AIDS-related deaths have decreased by 28 percent, and over 7.8 million lives have been saved globally. In a remarkable sign of progress, a few low- and middle-income countries (LMICs) such as Botswana and Malaysia have pediatric coverage rates exceeding 95 percent, while nations including Cambodia and Rwanda have adult coverage rates beyond 70 percent. Globally, however, further work remains before all LMICs successfully reach the UNAIDS Fast-Track targets to end the AIDS epidemic by 2030.

As of 2015, 46 percent of the nearly 37 million people globally living with HIV were accessing antiretroviral therapy (ART), an increase of two million from the year before. As the number of patients on ART expanded, so did the antiretroviral (ARV) market. Regimens were not only more affordable in 2015, but more patients continued to access clinically-recommended formulations. More than 70 percent of adults on first-line treatment were on WHO preferred TDF + (3TC or FTC) + EFV, while 70 percent of children who were on pediatric formulations were on IATT optimal formulations.

The WHO guidelines continue to be a critical influence. Major changes were announced in 2015, including the “Test and Treat” recommendation, which some LMICs such as Botswana, Cambodia, Kenya, Lesotho, South Africa, and Tanzania have already adopted. Differentiated models of care like multi-month scripting and community ART groups are promising opportunities for countries to reduce the burden of treatment on their patients. Additionally, LMICs continue to adopt combination prevention strategies, like TDF-containing oral pre-exposure prophylaxis (PrEP), as a means to lower HIV transmission rates in high-risk populations.

Countries also continue to be eager to adopt new drugs in their national treatment guidelines. The first generic dolutegravir (DTG), a clinically-superior alternative to efavirenz (EFV), has been tentatively approved by the FDA, and fixed-dose combinations of the same are eagerly awaited. Botswana became one of the first countries to adopt the drug in its national guidelines, and several others are following suit. Low-dose efavirenz (TLE400) should be available in 2017, and tenofovir alafenamide fumarate (TAF) is likely to also disrupt the ARV market in the next two to three years. Focusing on children, cold-chain independent LPV/r oral pellets have been launched in a number of countries and several countries are planning to soon procure the pill-burden-reducing ABC/3TC 120/60 mg dispersible tablets.

CHAI is excited and optimistic about the future opportunities in the ARV market. Working together with ministries of health, suppliers and partners, CHAI will continue efforts to ensure patients have rapid access to the best products at affordable and sustainable prices.

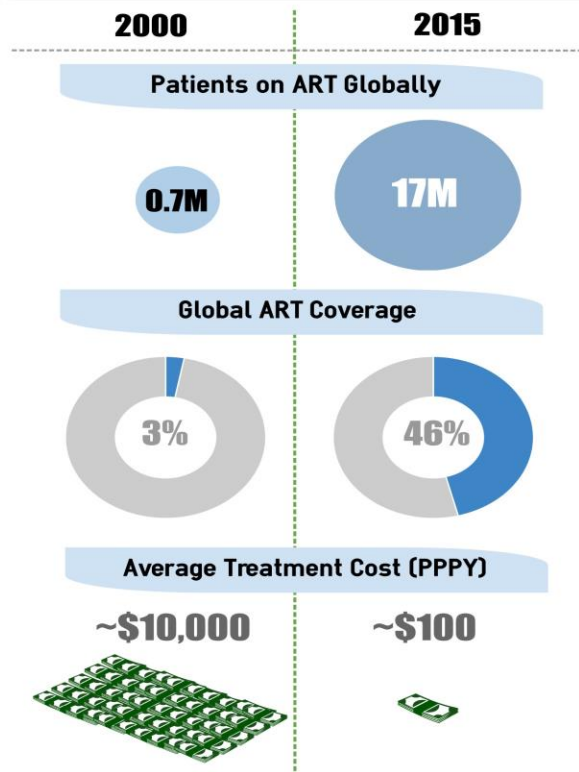


## Summary At A Glance

# State of HIV/AIDS

The HIV community reflects as IAS returns to Durban, South Africa for the first time since 2000

WHO guidelines continue to impact ART decisions in LMICs in 2015



### Test & Treat

ART initiation regardless of CD4 count or age; adoption seen in Botswana, Cambodia, Kenya, Lesotho, South Africa, and Tanzania

### Option B+

The only standard for prevention of mother to child transmission of HIV; adoption seen in 21/22 Global Plan priority countries by the end of 2015

### New Drugs

1L DTG, 1L EFV400, and 2L DRV were included in 2015 guidelines as alternates

### PrEP

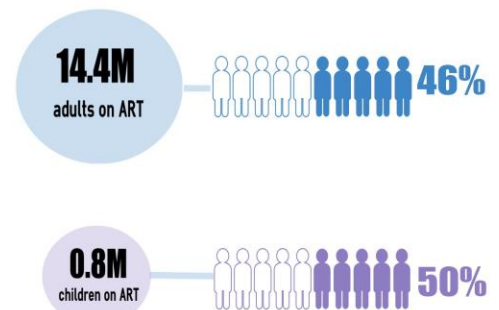
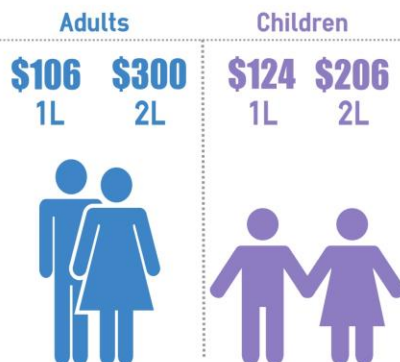
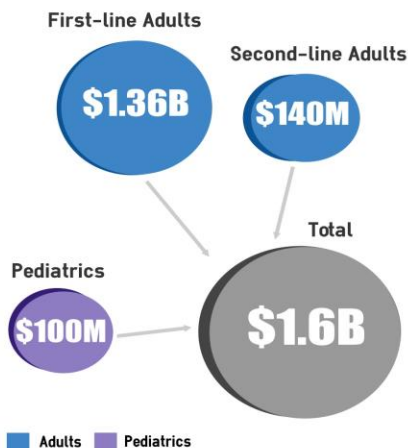
Oral pre-exposure prophylaxis (PrEP) recommended for high-risk populations; South Africa first country in Africa to roll out oral PrEP through the national system

## ARV Market Overview

Market size growth in GA LMICs primarily driven by first-line adults in 2015

Cost of treatment (PPPY) decreased by 6-10% in 2015 from 2014 for adults and second-line children in GA LMICs

Nearly half of all patients living with HIV/AIDS in LMICs were on treatment in 2015, up 41% from 2014

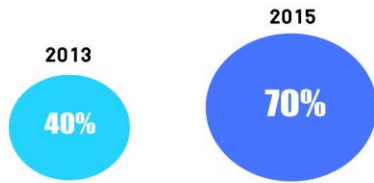




# Adult Market Trends

LMICs consolidate to WHO-recommended regimens using optimal formulations

1L Patients on TDF+ (3TC or FTC) + EFV Regimens



Top 3 Formulations

**TDF/3TC/EFV**  
300/300/600mg

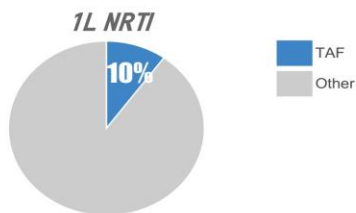
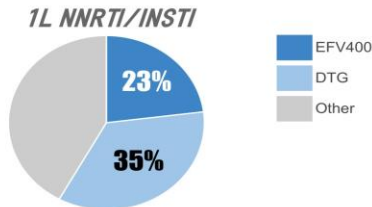


**TDF/FTC/EFV**  
300/200/600mg

**AZT/3TC/NVP**  
300/150/200mg

New products expected to be introduced in LMICs by 2019, providing clinical and cost advantages

Projected Market Share by 2020



LMICs continue to adopt ATV/r for second-line treatment



New Transitions to ATV/r

Kenya  
Swaziland  
Vietnam

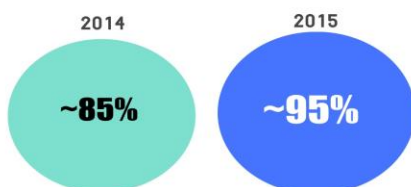
High ATV/r Uptake

India  
Malawi  
Zimbabwe

# Pediatric Market Trends

More children are using optimal formulations in LMICs

Children on Optimal Formulations in GA LMICs (ex-RSA)\*



\*amongst children exclusively on pediatric formulations, without use of any adult formulations



<1% on d4T in 2015

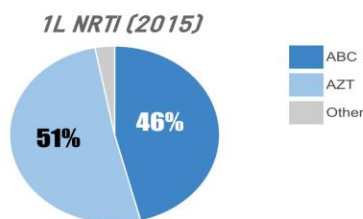
2016 Changes to the IATT Optimal Formulary List



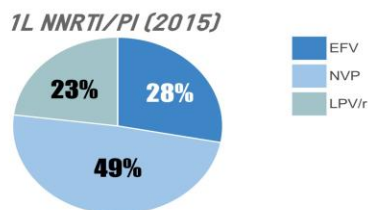
- ✓ LPV/r 40/10mg oral pellets
- ✓ RAL 100mg scored tablets

High-volume LMICs continue to adopt WHO-recommended drugs in national guidelines

High-volume LMICs almost evenly split on AZT vs. ABC



NVP use remains high due to convenience of the AZT/3TC/NVP triple FDC, but expected to decline



Various initiatives and partnerships continue to support the pediatric ARV market

Paediatric ARV Procurement Working Group

PAEDIATRIC HIV TREATMENT INITIATIVE  
CLOSING THE TREATMENT GAP



www.teampata.org



The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

THE DOUBLE DIVIDEND

A Synthesis of Evidence for Action to improve survival of HIV-exposed children in the era of eMTCT and renewed child survival campaigns

PEPFAR/PHTI  
Commitment-to-Action



# The State Of HIV/AIDS Today

## *The HIV community reflects as IAS returns to Durban*

In 2000, 12,000 scientists, clinicians, public health experts, community leaders, and people living with HIV/AIDS (PLWHA) gathered in Durban, South Africa for the 13th International AIDS Society (IAS) Conference. The theme of that summit was to “break the silence” on the millions of preventable AIDS-related deaths occurring around the world, particularly in low- and middle-income countries (LMICs).<sup>i</sup> By the end of 1999, 15 million adults and nearly four million children had died since the start of the epidemic.<sup>ii</sup> And with just 3 percent of the 34 million people living with HIV globally on treatment, more losses of life were expected to continue without significant interventions.<sup>iii</sup>

The Durban IAS conference in 2000 was notable, because it:

- **Laid out the clear case that HIV causes AIDS.** In response to many powerful skeptics, 5,000 clinicians and scientists published “The Durban Declaration” as a means to clearly lay out the scientific evidence that HIV does in fact cause AIDS.
- **Allowed PLWHA’s voices to be heard.** Thousands of patients diagnosed with HIV marched together to shed light on the epidemic.<sup>iv</sup>
- **Paved the way for the dedication of global resources and commitment to end the epidemic.** The conference laid the foundation for the 2001 United Nations General Assembly Special Session on HIV/AIDS (UNGASS 2001) Declaration of Commitment.<sup>i</sup> The Global Fund to Fight AIDS, Tuberculosis and Malaria was soon established.<sup>v</sup>

Sixteen years later, IAS returned to Durban. HIV infections since then have fallen by 35 percent, AIDS-related deaths have fallen by 28 percent and it is estimated that over 7.8 million lives have been saved.<sup>vi</sup> With the theme of “access equity rights now,” the 2016 conference set out to remind the world that significant work remains to be done to “reach the people who still lack access to comprehensive treatment, prevention, care, and support services.”<sup>vii</sup>

## *The world continues toward UNAIDS Fast-Track targets*

By the end of 2015, 17 million patients across the globe were on ART. The growth of two million new patients from 2014 marks one of the largest annual increases in PLWHA ever.<sup>viii</sup> While the number of patients on ART continues to increase, the number of new HIV infections has remained unchanged since 2013, with roughly two million new infections annually. As a result, prevention is becoming an ever-increasing area of focus as a way to end the AIDS epidemic.

Focusing on LMICs, over 30 million people were living with HIV/AIDS in 2015, representing more than 80 percent of the global HIV population. Adult ART coverage rates increased from 41 percent in 2014 to 46 percent in 2015. Further, 50 percent of children living with HIV/AIDS in LMICs are now on ART. Several countries are well on their way toward the UNAIDS/WHO Fast Track 90-90-90 treatment targets.<sup>1</sup> In an encouraging sign of progress, countries like Botswana, Malaysia, Namibia, Thailand,

and Vietnam already have pediatric ART coverage rates greater than 95 percent. Further, adult coverage rates are approaching the goal of 90 percent in Rwanda, Botswana, and Cambodia, with 79 percent, 78 percent, and 73 percent coverage at the end of 2015, respectively.<sup>ix</sup> Nevertheless, with average global ART coverage still only at 46 percent, much work remains to be done.

## *2015 WHO Guidelines bring about significant changes*

Two years after IAS 2000, the WHO published its first set of antiretroviral treatment guidelines. Seen as the gold standard for the medical treatment and prevention of HIV, the WHO Guidelines have been pivotal in shaping the treatment of adults, adolescents, and children in LMICs. The 2015 guideline changes and subsequent country highlights include:

- **Treatment for all, regardless of age or CD4 count.** The WHO now recommends the initiation of ART for all adults and children living with HIV regardless of WHO clinical stage and at any CD4 cell count. Lesotho became the first country in sub-Saharan Africa to implement test and treat guidelines in April of 2016, followed shortly after by South Africa and Tanzania.<sup>x,xi,xii</sup>
- **Option B+ as the only standard for prevention of mother-to-child transmission of HIV.** Option B+, where lifelong ARV treatment is provided to all pregnant and breastfeeding women (regardless of CD4 count or clinical stage), has been included in the WHO treatment guidelines since 2013. Twenty-one of the 22 Global Plan priority countries have either fully implemented Option B+ or in the process of scaling up treatment nationally.<sup>xiii</sup> Strikingly, in 2015, Cuba was declared the first country by the WHO as having eliminated mother-to-child transmission of HIV. By June 2016, the list expanded to Armenia, Belarus, and Thailand.
- **Innovative drugs and formulations are adopted.** Dolutegravir (DTG) and low-dose efavirenz (EFV400) were included as alternate options in first-line, and darunavir (DRV) as an alternate second-line (2L) option. These products are discussed in more detail in the [“Adult Market”](#) section.
- **TDF-containing oral pre-exposure prophylaxis (PrEP) recommended for high-risk populations.** Initially, only Gilead’s Truvada had the PrEP indication on label. Depending on various country regulations, label revisions for TDF/FTC from generic manufacturers may be required before use for PrEP, even if the product is otherwise currently being procured for treatment. South Africa was the first country to introduce oral PrEP through the national program in mid-2016, and its national drug regulator has already approved some generics for PrEP labeling. Several other countries are expected to follow suit in 2017. Since this is a newer area of focus for country programs, and as policies and roll-out plans are still being developed, overall PrEP volumes in the near future are expected to be small, especially relative to the treatment market.

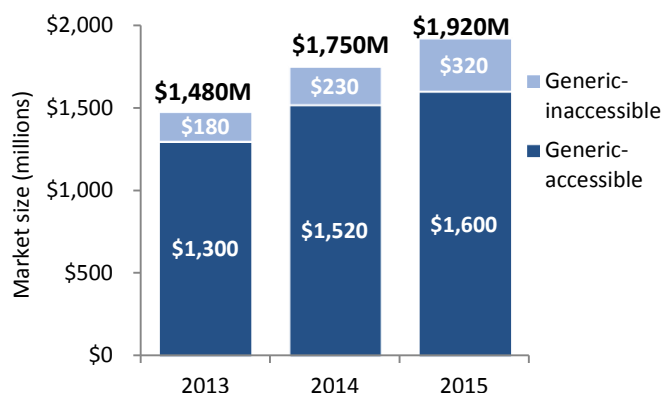
<sup>1</sup> The UNAIDS/WHO fast-track 90-90-90 treatment targets aim for 90 percent of people infected with HIV know their status, 90 percent of those diagnosed with HIV to receive effective treatment, and 90 percent of those treated to be virally suppressed by 2020.

# ARV Market Overview

## ARV market in LMICs expanded to ~US\$1.92 billion in 2015 with continued scale-up of ART

The LMIC market for ARVs expanded by ~9 percent from US\$1.75 billion in 2014 to US\$1.92 billion in 2015. The market grew as countries scaled up patients on treatment, despite declining prices for key formulations for preferred regimens.

**Exhibit 2.1: ARV MARKET SIZE (USD) IN GENERIC-ACCESSIBLE VS. GENERIC-INACCESSIBLE COUNTRIES**



The generic-accessible (GA)<sup>2</sup> ARV market, which represents 93 percent of patients in LMICs, grew by ~5 percent to US\$1.6 billion in 2015, primarily driven by growth in the adult first-line market. The adult first-line segment represented the majority of patients on ART and as a result the total GA market dollar value in 2015 (91 and 85 percent respectively).

As shown in exhibit 2.2, the overall adult market value growth in 2015 was slower than that observed from 2013 to 2014, as growth from patient scale-up was partially offset by decreasing prices for ARVs used in preferred regimens. However, prices for key ARVs are presumed to have reached their lowest point at which they could be sustainably produced (see inset). As a result, price erosion among key adult products is expected to decline, allowing patient scale-up to drive adult market size growth going forward.

The initiation of more children onto ART, coupled with greater regimen and formulation optimization, drove the pediatric market to expand by ~17 percent to US\$100 million in 2015. The hitherto widely used and low-cost pediatric AZT/3TC/NVP has now been deemed "limited-use" by the Inter-Agency Task Team (IATT). Going forward, its use is expected to decline, so that the pediatric market value is expected to continue to grow as more HIV-positive children are put on ART with optimized but more expensive formulations.

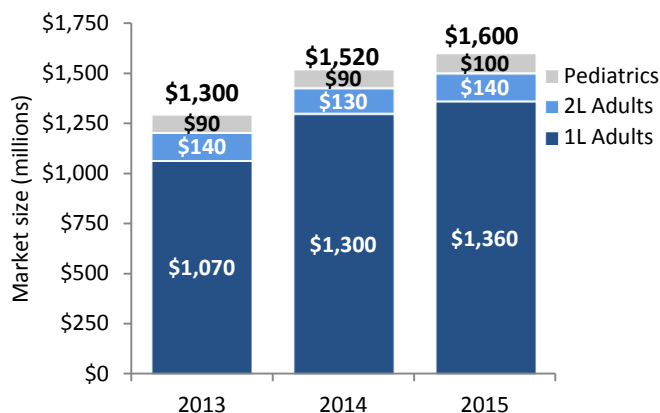
The potential impact of viral load testing on second-line patients is discussed in later sections. Conservatively, no major change in the proportion of second-line patients is assumed for market sizing purposes, albeit the number of second-line patients will undoubtedly grow.

Public data on ARV pricing in generic-inaccessible (GI) markets, such as Brazil and China, continues to be limited, beyond standardized cost of

<sup>2</sup> 'Generic-accessible' denotes countries where global generic manufacturers can register and supply a large proportion of that country's ARV volume needs. Largest 'generic-inaccessible' countries: Argentina, Brazil, China, Mexico

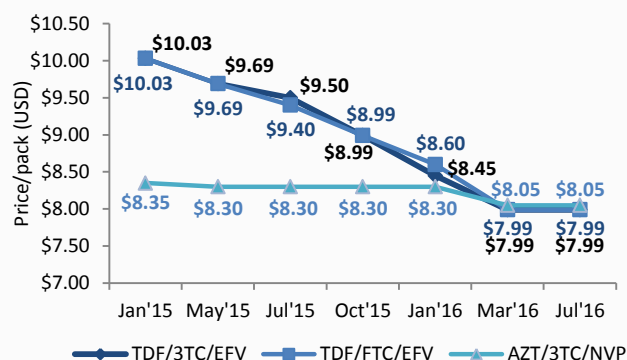
treatment provided in a 2013 report published by the Pan American Health Organization (PAHO).<sup>xiv</sup> Using those figures, CHAI estimates the GI market in 2015 was US\$316 million. Although more recent estimates for the cost per patient per line of treatment are not available, the WHO has also reported middle-income countries (mainly Brazil, China, and Eastern European countries) paying higher prices relative to lower-income countries because of the lack of access to cheaper generic ARVs.<sup>xv</sup>

**Exhibit 2.2: ARV MARKET SIZE (USD) IN GA COUNTRIES**



### ARV Prices Levelling Off

Reduced prices of key ARVs over time have lowered the overall cost of treatment. However, as indicated by Global Fund's Pooled Procurement Mechanism (PPM) reference prices for key first-line adult products, prices for certain products appear to be reaching their lowest commercially sustainable levels. Effectively, it now costs less than US\$100 per year to treat an adult first-line patient.



### Cost of treatment generally fell while quality of treatment improved in GA LMICs

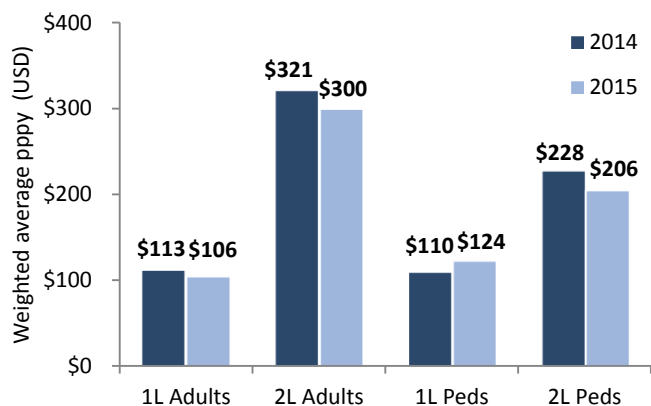
Increased volumes from more countries transitioning to preferred regimens and optimal formulations has enabled manufacturers to achieve efficiencies and stimulated further price competition.

As shown in exhibit 2.3, the weighted average prices for first-line and second-line adult regimens in 2015 have each fallen by ~6 percent from 2014. As countries continued to align with the WHO 2013 Treatment Guidelines, demand for a consolidated set of products drove prices down across first- and second-line treatment. Specifically, for first-line, the per

patient per year (pppy) costs (GA LMIC weighted averages) of the gold-standard triple FDCs of TDF/3TC/EFV and TDF/FTC/EFV have fallen by ~13 percent. For second-line products, the prices of lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r) have continued to decrease due to price competition between the two products as countries increase ATV/r uptake.

For pediatric treatment, the weighted average price in 2015 was US\$124 pppy for first-line and US\$206 pppy for second-line, representing a 13 percent increase and 10 percent decrease respectively from 2014. The increase in first-line per patient per year costs was attributed to more patients being on optimal formulations, which tend to be more expensive. Excluding South Africa, the proportion of children on optimal pediatric formulations increased from 83 percent in 2014 to 94 percent in 2015.

**Exhibit 2.3 WEIGHTED AVERAGE MARKET PRICE (USD) FOR REGIMENS IN GENERIC-ACCESSIBLE COUNTRIES<sup>3</sup>**



Several new products are likely to be introduced in GA LMICs by 2019, resulting in a range of clinical and cost advantages to current products. Contingent on uptake, these ARVs, including tenofovir alafenamide fumarate (TAF), low-dose EFV (EFV400), and dolutegravir (DTG), are expected to lower the cost of treatment significantly. While these products will enable programs to put more patients on treatment with lower per capita spend, cheaper production costs will enable manufacturers to remain profitable in a growing ARV market. CHAI's forecast for these products is discussed in the following sections.

### Indian generic manufacturers continue to dominate the ARV market

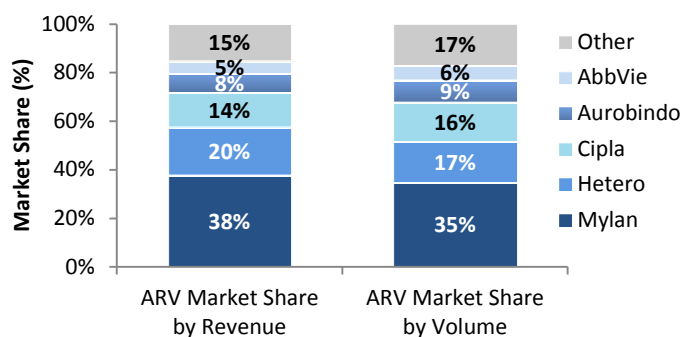
In 2015, three Indian generic manufacturers, Mylan<sup>4</sup>, Cipla, and Hetero supplied ~70 percent of the GA LMIC ARV market by revenue and volume.<sup>xvi</sup> Other Indian manufacturers like Aurobindo accounted for a further ~15 percent of revenue and ~19 percent of volume. Non-Indian generic manufacturers, innovators, and distributors captured ~13 percent of revenue and volume, primarily driven by Aspen, Sonke (Sun Pharmaceuticals), and AbbVie. Among innovators, AbbVie continues to hold the largest market share in terms of volume and revenue, primarily driven by South Africa's LPV/r 200/50mg procurements. This analysis

<sup>3</sup> Pediatric pppy calculations exclude adult formulations that may be used in older children

<sup>4</sup> Albeit Mylan itself is not India-based, its ARV business was built off its acquisition of Matrix Labs in 2007, and ARV manufacturing continues to be primarily in India

should be interpreted with caution due to varying levels of reporting of procurement data from year to year, and because where distributors are involved, most procurement data does not identify from which manufacturers they ultimately source product.

**Exhibit 2.4: ARV MARKET SHARE IN GA LMICs BY TOP MANUFACTURERS<sup>5</sup>**



Mylan continued to be among the top three manufacturers for each of the three most used formulations in LMICs – TDF/3TC/EFV, TDF/FTC/EFV, and AZT/3TC/NVP (all triple FDCs). Sales for the TDF/3TC/EFV triple FDC market, used by nearly 5.5 million patients in GA LMICs in 2015, were dominated by Mylan and Hetero with more than 70 percent of its sales. However, that picture is likely to change with the USFDA's delisting of Hetero's TDF/3TC/EFV in 2016, which makes the product ineligible for new orders funded through PEPFAR or the Global Fund.<sup>xvii, xviii</sup> Supplier shares for the TDF/FTC/EFV triple FDC, mostly used in South Africa, were more distributed, primarily due to South Africa's practice of splitting key products across suppliers, as seen in its most recent tender.

<sup>5</sup> Analysis excludes procurements where manufacturer was not specified (about five percent of overall procurement value and volume). Additionally, "Other" category also includes distributors who in turn procure from manufacturers that are not identified. Figures should therefore be interpreted with caution.

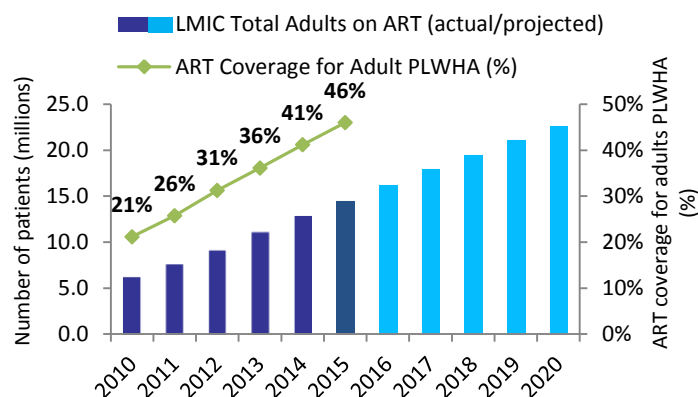


## Adult Market Trends

### Continued growth of adult patients on ART in 2015

Approximately 14.4 million adults received ART in LMICs as of 2015, reflecting a 13 percent growth from 2014.<sup>ix</sup> Treatment coverage for adults living with HIV/AIDS in LMICs also increased from 41 percent at the end of 2014 to 46 percent at the end of 2015. Exhibit 3.1 shows the number of adults on ART in LMICs through 2015, CHAI's patient projections, and the evolution of adult ART coverage in LMICs since 2010. CHAI's patient projections are relatively conservative, particularly compared to ambitious targets like the UNAIDS Fast-Track Targets.<sup>xix</sup>

**Exhibit 3.1 NUMBER OF ADULTS ON ART AND ADULT ART COVERAGE IN LMICs<sup>6</sup>**

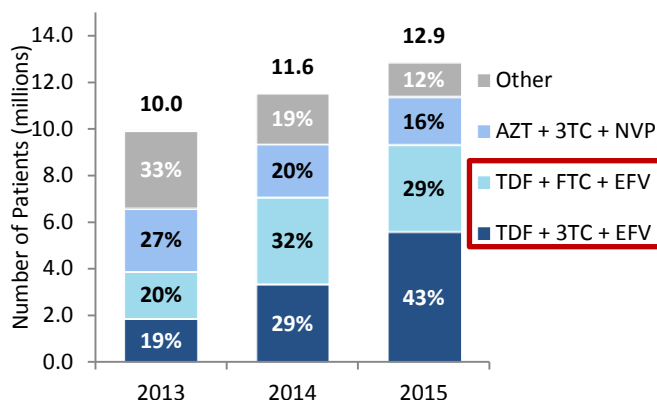


Within GA LMICs, there were 13.3 million adult patients on ART, a growth of 1.5 million patients from 2014.<sup>Error! Bookmark not defined.</sup> This incremental growth was similar to the 1.6 million patient increase seen between 2013 and 2014, and was driven, in part, by further adoption of treatment initiation at CD4 < 500 cells/mm<sup>3</sup> with some countries moving toward Test and Treat and the use of Option B+ for pregnant women with HIV. As of September 2016, 21 of 22 Global Plan priority countries had adopted Option B+.<sup>xiii</sup>

### WHO's guidance on HIV treatment has increasingly consolidated regimens in LMICs from 2013 to 2015

In an effort to simplify antiretroviral therapy, the WHO's 2013 Guidelines reduced the preferred regimens to a single option, TDF + 3TC (or FTC) + EFV, which could be used across a range of populations as a single-pill once-daily regimen. In turn, LMICs have made great strides towards simplifying their national treatment programs, phasing out non-recommended drugs such as stavudine (d4T) in favor of tenofovir-based regimens. This progress is reflected in the consolidation of adult first-line regimens from 2013 to 2015 around the preferred first-line regimen, TDF + 3TC/FTC + EFV, which represented ~70 percent of the adult first-line patients in GA LMICs in 2015, up ~30 percentage points from 2013.

**Exhibit 3.2 PATIENT GROWTH AND SHARE OF FIRST-LINE ADULT REGIMENS IN GA LMICs**



### EFV400 and DTG expected to significantly change current adult first-line NNRTI market

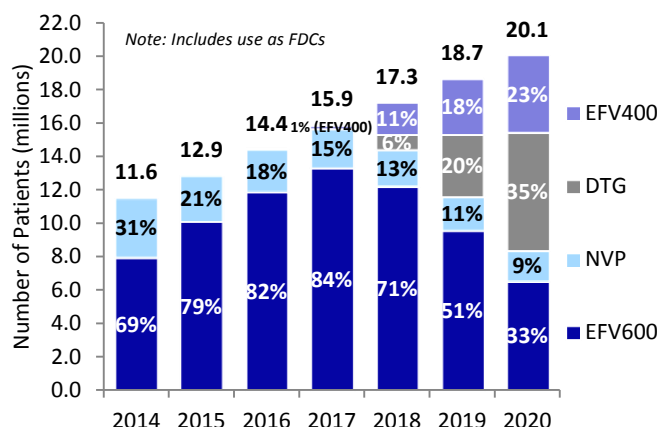
With countries ramping up TDF use in first-line treatment, EFV uptake also continues to increase, representing 79 percent of all first-line GA adult patients (10.1 million patients) by the end of 2015. With EFV being the preferred NNRTI since the 2013 WHO Guidelines, NVP use is expected to continue to decline, making up only 9 percent of the NNRTI market in 2020. As such, EFV600 is expected to be used among the majority of first-line patients in 2017, after which the NNRTI market may shift towards new products, such as lower-dose EFV (EFV400) and DTG. Both drugs are expected to be more tolerable and more affordable than EFV600.

In 2015, continued momentum around accelerating the development and market availability of EFV400 saw CHAI and the FDA collaborate to develop a novel regulatory pathway for filing EFV400 as a FDC based on the results of the Kirby Institute's ENCORE1 study, which demonstrated EFV's non-inferiority at 400 mg (reduced dose) versus 600 mg (approved dose). Following the FDA's advice, CHAI's Product Development Team (PDT) worked with the Kirby Institute in filing ENCORE1 data as an Investigational New Drug (IND) application on December 16, 2015. This IND allows generic suppliers interested in developing the product access to the clinical data via reference. Additionally, CHAI also worked with a generic supplier on the first NDA filing for the FDC product, TDF/3TC/EFV400 (TLE400), which was submitted in mid-2016 and is currently under FDA review. Several other suppliers have also expressed interest in filing an NDA. Availability of a SRA-approved TLE400 is expected in mid- to late-2017.

Furthermore, the 2015 WHO Guidelines included EFV400 as an alternative option in first-line. Pharmacokinetic (PK) studies in pregnant women and TB co-infected patients for EFV400 are also underway. If the results show an insignificant change in EFV levels in these patients, the WHO should be able to suggest this option as a preferred regimen without restrictions in its next guidelines release.

<sup>6</sup> ART coverage for adults calculated based on data available in UNAIDS AIDSinfo database as of July, 2016 (only includes countries with both ART and PLWHA numbers reported)

### Exhibit 3.3 PATIENT GROWTH AND SHARE OF FIRST-LINE NNRTI/INSTI MARKET IN GA LMICs<sup>7</sup>



Dolutegravir (DTG) is an integrase inhibitor (INSTI) that was approved by the US FDA in 2013. It has shown non-inferiority or superiority, and better tolerability than EFV and Pls.<sup>xx</sup> Some advantages of the drug include a shorter time to viral suppression, a higher genetic resistance barrier, long half-life, low-cost, and low dosing requirements. DTG is recommended as an alternate for first-line adults in the 2015 WHO Guidelines.

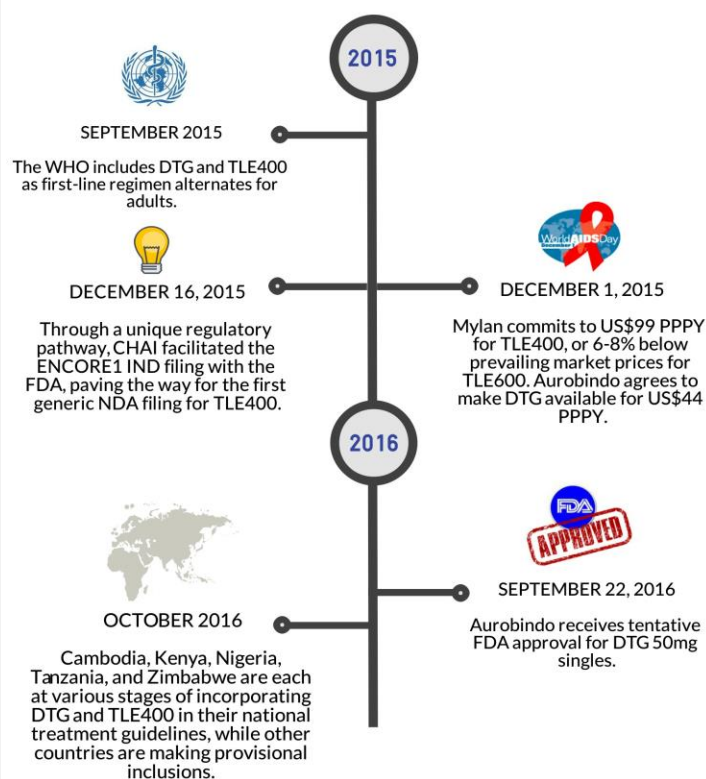
DTG was developed by ViiV as a single tablet (Tivicay) or as a FDC with ABC and 3TC (Triumeq). Botswana recently signed an agreement with ViiV to purchase DTG singles in the largest tender secured by the company in sub-Saharan Africa.<sup>xxi</sup> Botswana also included DTG in its official ART guidelines.<sup>xxii</sup> According to the US ambassador to Botswana, adoption of DTG could prevent 120,000 new HIV infections and save 55,000 lives over the next 15 years.<sup>xxiii</sup> Several other countries like Cambodia, Kenya, Nigeria, Tanzania, and Zimbabwe have included or plan to soon include DTG in their national treatment guidelines.

Aurobindo Pharma received tentative FDA approval for the DTG singles on September 22, 2016 and intends to launch the product in sub-Saharan Africa in late 2016.<sup>xxiv</sup> Initial adoption is likely to be as a replacement for single NVP or EFV use amongst first-line among patients who already take two pills a day (e.g., those on AZT/3TC + EFV or TDF/3TC + NVP). CHAI estimates that there were ~1.2 million such patients in GA LMICs at the end of 2015. Generic manufacturers are also working towards filing for a one-pill, once-per-day FDC of TDF/3TC/DTG (TLD) with the FDA, with availability expected as early as H2 2017.

As shown in Exhibit 3.3, DTG is expected to start surpassing EFV400 uptake in 2019, representing 35 percent of the adult first-line NNRTI/INSTI market in 2020 (i.e. ~7 million patients). After 2020, it is expected that DTG will be the third position drug of choice, and most remaining efavirenz use will be in the form of TLE400. It should be noted that DTG uptake will be contingent on the price of TLD relative to TLE400, and CHAI's forecast assumes TLD's price will be at least 10 percent lower than TLE400.

#### Introducing TLE400 and DTG in LMICs: Highlights

There were several notable milestones towards increasing access to these clinically superior and/or cost-effective regimens in LMICs:



#### Tenofovir-based ARVs expected to be the backbone of choice for first-line regimens

TDF comprised 77 percent of the first-line NRTI market in GA LMICs, with ~9.9 million first-line adult patients on TDF-based regimens at the end of 2015. Continued use of AZT in first-line is attributed to stable patients who were already initiated on AZT. However, with the increasing use of TDF in first-line, AZT share is expected to decline.

Tenofovir alafenamide fumarate (TAF), a potential alternative to TDF, is a tenofovir prodrug that offers high antiviral efficacy and an improved renal and bone safety profile at much lower doses than TDF.<sup>xxv</sup> As of August 2016, Gilead has received FDA approval on three TAF-containing FDCs, i.e. the "Quad"<sup>8</sup> in November 2015<sup>xxvi</sup>, TAF/FTC/RPV in March 2016<sup>xxvii</sup>, and TAF/FTC in April 2016.<sup>xxviii</sup> Additionally, Gilead filed an NDA for the TAF 25mg singles with the FDA, but only for the adult hepatitis B indication.<sup>xxix</sup>

The first generically-available TAF FDC is expected to launch in early- to mid-2018. Assuming certain API production steps can be optimized by generic companies, it is expected that TAF will be significantly less expensive than TDF since the required dose is about 10-fold lower. Additionally, the University of the Witwatersrand is about to embark on the ADVANCE study to generate clinical data on the TAF/FTC/DTG combination. Sub-studies will address issues such as the use of the new drugs in rifampicin-containing TB regimens, pregnancy, and adolescents. The trial should start enrolment by year end with results expected in mid-2018, which will hopefully support inclusion of TAF/XTC/DTG as the preferred regimen in the subsequent WHO Guidelines in 2019.

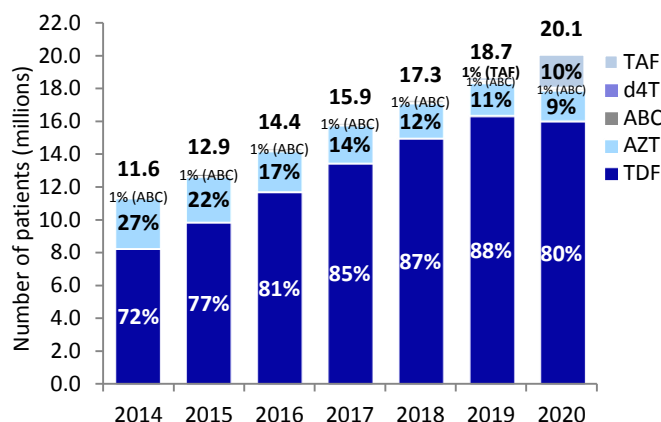
There will likely be some uptake in the latter half of 2019 when TAF may first be included in the WHO Guidelines, and by the end of 2020 it is

<sup>7</sup> Shares may not sum exactly to 100 percent due to rounding

<sup>8</sup> The TAF "Quad" is an FDC of elvitegravir, cobicistat, FTC, and TAF (E/C/F/TAF)

projected to garner up to 10 percent of the first-line NRTI market in GA LMICs, or two million patients. TDF is expected to remain the dominant drug that year, maintaining 80 percent of the first-line market. However, in subsequent years, TAF is expected to almost completely replace TDF due to its price and clinical advantages.

**Exhibit 3.4 PATIENT GROWTH AND SHARE OF FIRST-LINE NRTI MARKET IN GA LMICs<sup>9</sup>**



### Use of FTC limited outside South Africa

As of 2015, use of FTC is almost entirely concentrated in South Africa. Although both 3TC and FTC were advertised in South Africa's current tender valid through March 2018, FTC was favored for the lucrative first-line TDF/XTC/EFV segment.<sup>xxx</sup> South Africa represented the largest proportion of adult patients on FTC in GA LMICs. Botswana is the next largest user of FTC, with its treatment guidelines now recommending use of DTG with TDF/FTC in first-line. Tanzania is the third largest user of FTC, albeit with less than 10 percent of its adult first-line patients on FTC. Zambia, which had the largest number of patients on FTC outside of South Africa in 2014, and Nigeria, fully transitioned to 3TC in 2015. Although FTC production costs have hitherto been higher than for 3TC, the net price to procurers appears to have evened out for the triple FDCs (e.g. Global Fund's PPM price for TEE and TLE are both US\$7.99/pack as of Q3 2016).

It is also important to note that Gilead's filings with the FDA for the HIV indication are for TAF FDCs rather than the single, all including FTC and not 3TC. The filing for stand-alone TAF was only for the Hepatitis B indication. Whether or not TAF/3TC formulations are developed and approved, will significantly impact FTC usage after 2018, when TAF is expected to be generically available and used widely.

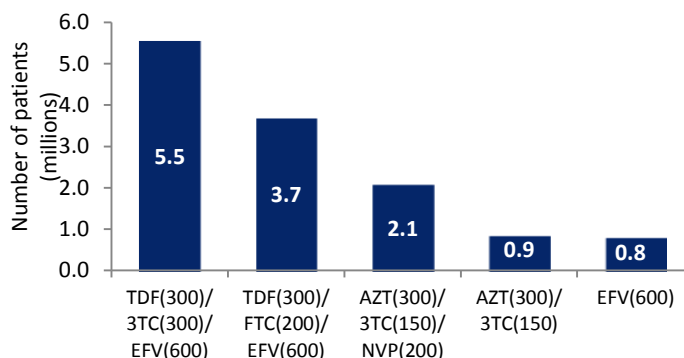
### Use of triple FDCs in first-line continues to grow

In 2015, the top five adult formulations by volume were the triple FDCs of TDF/3TC/EFV, TDF/FTC/EFV, and AZT/3TC/NVP, the AZT/3TC dual FDC, and EFV 600mg singles. Based on CHAI estimates, over 90 percent of all adults in GA LMICs were on at least one of these formulations at the end of 2015.

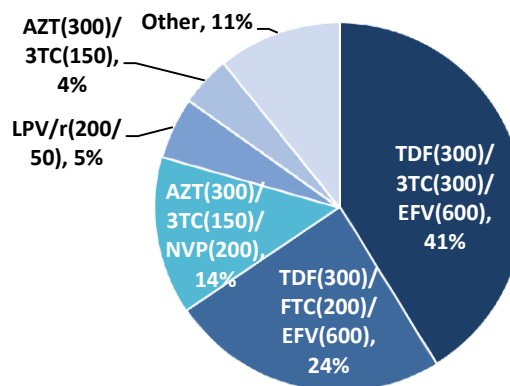
As shown in Exhibit 3.6, the TDF/3TC/EFV and TDF/FTC/EFV triple FDCs represented the largest share of the market by revenue, representing nearly two-thirds of the overall adult GA LMIC market value. Corresponding to the sparse use of FTC outside of South Africa, it is the TDF/3TC/EFV

triple FDC that has the lion's share. The LPV/r dual FDC does not appear in the top five formulations by volume but does comprise 5 percent of the market by revenue due to its relatively high price of US\$219 ppy (GA LMIC weighted average).

**Exhibit 3.5 TOP FIVE ADULT FORMULATIONS BY PATIENT VOLUME IN GA LMICs, 2015**



**Exhibit 3.6 TOP ADULT FORMULATIONS BY REVENUE IN GA LMICs, 2015**



TDF+3TC+EFV, TDF+FTC+EFV, and AZT+3TC+NVP are the three main adult regimens where a triple FDC is available for use in GA LMICs. In countries where CHAI has access to aggregate patient data at the formulation level, nearly all patients on these regimens are on the triple FDC rather than dual + single or singles (triple FDCs are not available for those on TDF+3TC+NVP or AZT+3TC+EFV regimens, so they are necessarily on dual + singles). Although the data is not inclusive of all usage in LMICs, this trend suggests significant progress towards reducing the pill burden for patients.

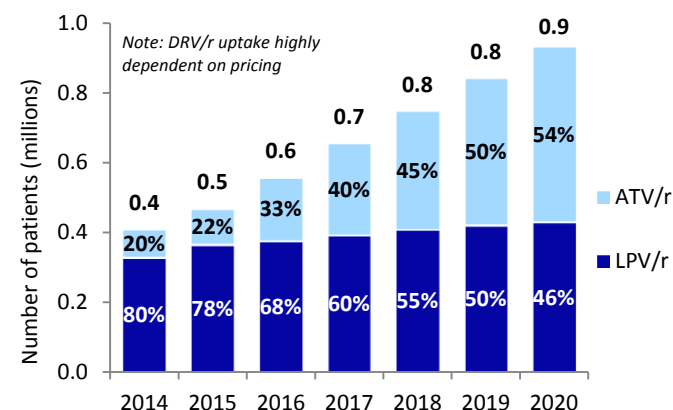
### ATV/r expected to continue growing vs. LPV/r; strong potential of DRV/r dependent on price

In 2015, 22 percent of adult second-line patients were estimated to be on ATV/r. India, Malawi, and Zimbabwe continued to have the highest individual market shares for ATV/r with more than 80 percent of their second-line adult patients at the end of 2015. Additionally, Kenya began initiating new second-line patients on ATV/r in 2015. Despite these positive developments, ATV/r uptake grew at a slower rate between 2014 and 2015 relative to the 10 percent jump observed from 2013 to 2014. Albeit previous supply issues were resolved in late 2014, and no supply issue was reported in 2015, it is possible that there are holdover concerns that slowed uptake of ATV/r during the course of 2015.

<sup>9</sup> Shares may not sum exactly to 100 percent due to rounding

ATV/r use for second-line patients is expected to grow and ultimately surpass LPV/r use by 2020, reaching 54 percent market share by 2020, especially as countries continue to adopt ATV/r as the preferred PI and overcome uptake barriers. Swaziland and Vietnam have begun transitions to ATV/r in 2016. South Africa may also potentially adopt ATV/r through its next tender in 2018, in part due its experience with LPV/r supply constraints in 2015 with reliance on a sole supplier. Other high-volume countries that currently include only LPV/r as the preferred option in their adult treatment guidelines include Zambia, Mozambique, and Botswana.

**Exhibit 3.7 PATIENT GROWTH AND SHARE OF SECOND-LINE PI MARKET IN GA LMICs<sup>10</sup>**

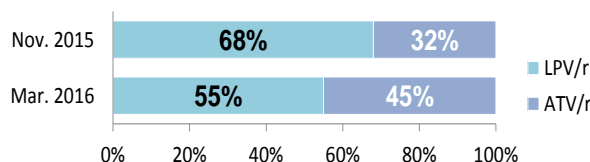


### Country Spotlight: Ethiopia Tackles ATV/r Uptake Barriers



To overcome lack of awareness among healthcare providers, Ethiopia's Ministry of Health issued a circular in July 2015 to encourage treating new and existing second-line patients with ATV/r as the preferred PI. There has already been significant progress through this initiative in less than six months per the figures reported by a Pharmaceuticals Fund and Supply Agency (PFSA) survey.

### Second-line PI Market Share in Ethiopia



Darunavir (DRV) is a PI that can be used in place of LPV or ATV. The combination of darunavir and ritonavir (DRV/r) was formally recommended in the 2015 WHO Guidelines as an alternative second-line regimen (it was a footnote mention in 2013). However, it is currently not available as a heat-stable FDC. In terms of safety and efficacy, DRV/r has shown superiority or non-inferiority over other PIs in multiple clinical trials and has a favorable resistance profile.<sup>xxxii</sup> Contingent on availability of a FDC at a competitive price, DRV/r has the potential to play an important role in

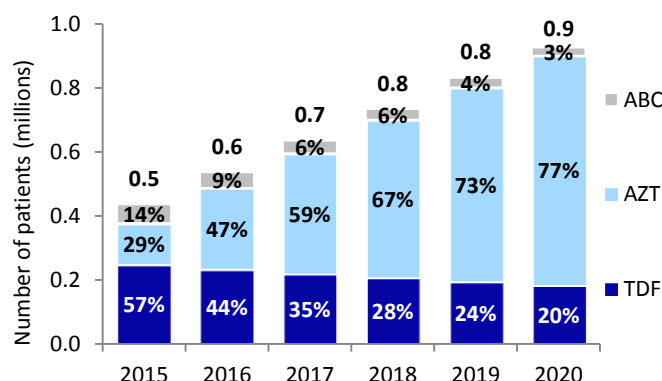
<sup>10</sup> Shares may not sum exactly to 100 percent due to rounding

second-line treatment. In particular, it could serve as a long-needed alternative to LPV/r for TB co-infected patients taking rifampicin (for whom ATV/r is contraindicated). A generic FDC of DRV/r is expected to be available in LMICs sometime in early 2018 as a 400/50mg formulation (two pills for once daily dosing of 800/100mg). CHAI is working with several partners in a multi-pronged approach to address the current high price of DRV/r relative to LPV/r.

### AZT expected to become the predominant NRTI in 2L as TDF use in 1L increases

In 2015, TDF comprised 57 percent of the second-line NRTI market, while AZT comprised 29 percent (Exhibit 3.8). There was a small proportion of patients on ABC, but this is expected to decline over time. As tenofovir-based backbones become predominant in first-line, their share of second-line adult treatment is expected to decline in future years, with AZT's second-line share conversely increasing. This inversion of market shares is unlikely to happen concurrently given that patients may be on first-line treatment for several years before being switched to second-line, so TDF share may appear to be high across both lines for a few more years.

**Exhibit 3.8 PATIENT GROWTH AND SHARE OF SECOND-LINE NRTI/INSTI MARKET IN GA LMICs<sup>10</sup>**



In addition to use in first-line, DTG may also compete in the second-line adult market in combination with PIs, replacing both the AZT+3TC and TDF+XTC backbones. However, second-line use of DTG was not included in the 2015 WHO Guidelines, and thus not included in CHAI's forecast.

### Several manufacturers are pursuing key new products

Many manufacturers are aggressively working toward SRA filings for key pipeline products. Exhibit 3.9 below summarizes projected timelines for each product per CHAI's supplier intelligence at the time of publication.

**Exhibit 3.9 TENTATIVE TIMELINES FOR NEW PRODUCT SRA APPROVALS<sup>11</sup>**

	2016	2017	2017	2018	2018
	H2	H1	H2	H1	H2
DTG	◆✓	◆	◆	◆	
TLD			◆◆	◆◆	
TLE400		◆		◆	
TAFx				◆	◆
DRV/r				◆◆	

◆ Expected SRA approval of distinct generic suppliers

<sup>11</sup> Assumes SRA approval received 9-12 months after filing date. Based on best available information of filing timelines as of October 2016. Subject to change



## Pediatric Market Trends

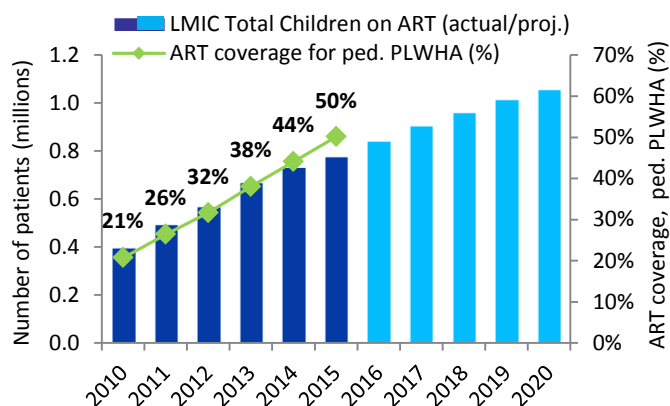
### 49 percent of children living with HIV globally were on treatment as of 2015

By the end of 2015, 1.8 million children globally were living with HIV. New infections decreased from 160,000 in 2014 to 150,000 in 2015. Overall, thanks in large part to successful prevention of mother-to-child transmission of HIV (PMTCT) efforts, the number of HIV infections has decreased significantly since 2000, when 490,000 new HIV infections were occurring annually. However, more work remains to be done to put an end to the 400 new pediatric infections occurring daily, most of which are occurring in sub-Saharan Africa.<sup>xxxi</sup>

#### UNAIDS updates its prevalence estimates

In 2016, UNAIDS revised its Spectrum epidemiology software model to account for recent study data. Changes included the addition of recent mother-to-child transmission probabilities and the use of new data from International Epidemiologic Databases to Evaluate AIDS (IeDEA) on age distribution of children initiating ART. The changes resulted in dramatically lower estimates for the number of children living with HIV across most countries. Effectively, pediatric ART coverage rates are significantly higher than previously thought.

**Exhibit 4.1 NUMBER OF PEDIATRIC PATIENTS ON ART IN LMICs, AND PEDIATRIC ART COVERAGE IN LMICs<sup>12</sup>**



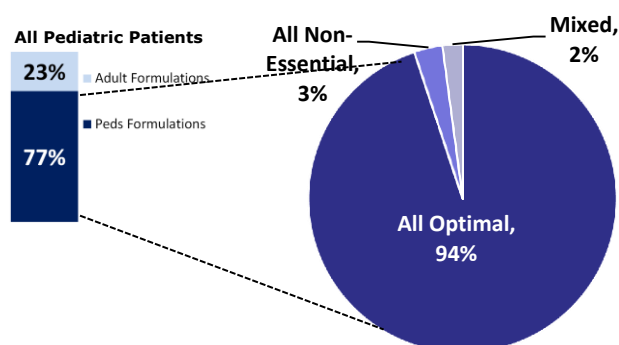
Worldwide, over 870,000 children living with HIV were on ART at the end of 2015, marking a 49 percent coverage rate. Coverage rates have steadily increased over the years; only 21 percent of children living with HIV/AIDS were on treatment in 2010.<sup>xxxi</sup> As shown in Exhibit 4.1, CHAI conservatively expects a little over one million children on treatment in all LMICs by 2020. Continued work from PEPFAR and CIFF's Accelerating Children's HIV/AIDS Treatment (ACT) Initiative and other international programs will likely shape the market growth as well. By September 2015, ACT helped double the number of children who received testing and counseling from 2.1 million in 2014 to 4.3 million in 2015. In addition, ACT provided ARV funds for 489,000 children in 2015.<sup>xxxiv</sup>

<sup>12</sup> ART coverage calculated based on UNAIDS AIDSinfo database as of August, 2016 (only includes countries with both ART and PLWHA numbers reported). Country income classification per the World Bank, July 2016

### The IATT optimal formulary was updated in 2016

The Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children (IATT) developed a list of preferred pediatric formulations in an effort to improve pediatric ARV supply security by consolidating the market around a limited number of key products that offer the highest standard of care for children of all weight bands and ages. Using the 2015 IATT classifications, CHAI estimated the proportion of pediatric patients who are on regimens comprised of all optimal or other formulations. The analysis, shown in Exhibit 4.2, only includes children who were on IATT-reviewed formulations and excludes South Africa. Of the included children, 94 percent were on all optimal formulations in 2015, up from 83 percent in 2014.

**Exhibit 4.2 FORMULATION BREAKDOWN OF PEDIATRIC REGIMENS IN GA LMICs (EXCLUDING RSA) BY IATT STANCE, 2015**



A revised list was released in 2016 with several changes including only classifying products as "optimal" if they constituted a preferred regimen per 2015 WHO Guidelines for first- and second-line treatment. Consequently, AZT/3TC/NVP 60/30/50mg dispersible and scored tablets, the most widely used pediatric formulation, were moved from the optimal list to the limited-use list. Notable additions to the optimal list include LPV/r 40/10mg oral pellets and RAL 100mg scored tablets. Products added to the limited-use list are RTV 25mg tablets, RAL 25mg tablets, and 3TC 50mg/5mL oral solution. The update also saw several formulations moved from the limited-use to the non-essential list: TDF 200mg tablets, ATV 150mg tablets, ETR 25mg tablets, and ETR 100mg tablets. The 2016 IATT optimal list is in [Appendix C](#).

### AZT and ABC will continue to dominate the pediatric NRTI market

AZT and ABC were the most common NRTIs used to treat pediatric patients in 2015. Conversely, TDF continued to be a small percentage of the market in 2015. d4T has largely been phased-out, having been used to treat less than 0.5 percent of pediatric patients in 2015, down from 19 percent in 2013 and 4 percent in 2014.

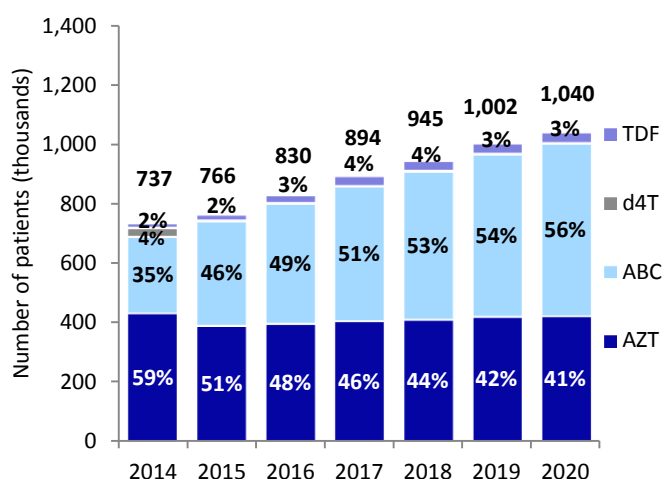
Per 2015 WHO Guidelines, AZT is only a preferred first-line option for patients under the age of 3, and is an alternate recommendation for other age groups, whereas ABC is preferred for all children 10 years and younger. CHAI estimates that 51 percent of pediatric patients were on AZT in 2015, down from 59 percent in 2014. The decrease in market share of AZT is expected to continue in the coming years, with 41 percent of patients forecasted to be on an AZT regimen by 2020. Countries like Nigeria, Malawi, Vietnam, and Zimbabwe had more than 90 percent of their patients on AZT regimens in 2015. By 2020, Lesotho, Swaziland,

Tanzania, Uganda, and Vietnam are expected to see the largest AZT regimen market share drops of more than 30 percentage points each. Nigeria and Zimbabwe are forecasted to see smaller changes, still retaining over 75 percent of their patients on AZT by 2020.

The market share of ABC increased to 46 percent in 2015, with countries like Kenya, South Africa, and Zambia having more than 60 percent of their pediatric population on ABC-based regimens in 2015. ABC is projected to represent a little more than half of the NRTI market by 2017.

TDF still retains a small percentage of the overall pediatric NRTI market in GA LMICs, representing ~2 percent in 2015. TDF's market share is expected to hover at that level over the coming years. While TDF is recommended for those patients greater than the age of 10 and weighing more than 35kg, uptake is low due to a lack of appropriate generic formulations or fixed-dose combinations. Zambia, at about 27 percent, was the only country that had more than 10 percent of pediatric patients on TDF in 2015, although this is expected a decline to 18 percent by 2020.

**Exhibit 4.3 PEDIATRIC NRTI MARKET IN GA LMICs<sup>13</sup>**



### LPV/r expected to maintain market share as EFV slowly takes share from NVP

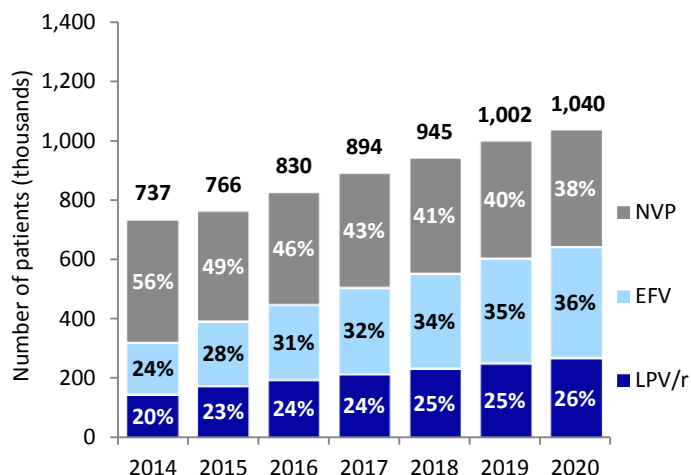
Although no longer recommended by the WHO as part of a preferred regimen, NVP use remains high due to the availability of AZT/3TC/NVP triple dispersible FDC at a relatively low price. In 2015, NVP had an estimated 49 percent share of the NNRTI/PI market. This is forecasted to decrease to 38 percent by 2020. As mentioned before, the dispersible triple FDC is no longer on the IATT's optimal formulary. As such, several high-volume countries are anticipated to see a decrease in their NVP market share by more than 30 percentage points by 2020 including India, Ethiopia, and Uganda. Further guideline changes from countries could mean even greater shifts away from NVP toward EFV, which the WHO currently recommends as the preferred 1L NNRTI for patients above the age of 3 years old. In 2015, 28 percent of patients were estimated to be on EFV and this is forecasted to increase by a further 8 percentage points by 2020. Ethiopia, India, and Uganda, the same countries forecasted to see a decrease in the NVP regimen use, are anticipated to scale-up EFV.

The PI LPV/r, which is a recommended first-line drug for children younger than 3, was estimated to have a market share of 23 percent in 2015, up

<sup>13</sup> Shares may not sum exactly to 100 percent due to rounding

from 20 percent in 2014. CHAI forecasts LPV/r share to slowly increase over the coming five years. Until recently, adoption of LPV/r had been hampered by the cold-chain limitations for the oral solution formulation. As more countries adopt heat-stable LPV/r oral pellets, however, there could be an even greater increase in LPV/r's share of the market. At the same time, a decreasing overall population of patients aged 3 or less (due to successful Option B+ roll-out) will likely cap the patient number growth.

**Exhibit 4.4 PEDIATRIC NNRTI/PI MARKET IN GA LMICs<sup>14</sup>**



### Adoption of New Pediatric ARV Formulations



#### 1 LPV/r Oral Pellets

The long-awaited alternative to cold-chain-dependent LPV/r oral solution, the LPV/r oral pellets received tentative US FDA approval in mid-2015. Since then, LPV/r oral pellets were added to the IATT's optimal formulary list in 2016 and countries like Cameroon and Zimbabwe have already placed orders. Several countries are implementing studies or pilots to introduce the product.

#### 2 ABC/3TC 120/60mg

By reducing the pill burden relative to the 60/30mg formulation, this product represents a highly optimized way to administer the preferred first-line regimen for patients under 10 years of age.

<sup>14</sup> Shares may not sum exactly to 100 percent due to rounding

## Market shaping initiatives and partnerships continue to support the pediatric market

Unlike the large scale of the adult ARV market, which is 94 percent of the overall ARV market, the pediatric market is small and requires additional support to ensure supply security and development of better products. International collaborations directed at strengthening the pediatric market include:

- **The APWG, which evolved from the Pediatric ARV Procurement Working Group (PAPWG) in 2016.** Since 2011, PAPWG, with the support of UNITAID and CHAI, has played an important role in coordinating the majority of pediatric ARV volumes and bringing together many global partners together. Due to the success of the group, the focus has been expanded to include low-volume adult ARVs, and the name has been changed to the ARV Procurement Working Group (APWG). More details can be found [here](#).
- **PHTI, which continues to pursue the development of optimal ARVs.** The Paediatric HIV Treatment Initiative (PHTI) is a joint collaboration of CHAI, the Drugs for Neglected Diseases Initiative (DNDi), the Medicines Patent Pool (MPP), and UNITAID. PHTI seeks to accelerate availability of optimal pediatric formulations by addressing technical, patent, market, and other challenges. Current products of focus include ABC/3TC/EFV triple FDC, ABC/3TC/LPV/r (“4in1”), DRV/r, and DTG/XTC/TAF.<sup>xxxv</sup>

## New WHO guidelines for EID testing will significantly increase testing coverage, case finding, and linkage to treatment

Despite a substantial increase in access to early infant diagnosis (EID) testing in recent years, it is estimated that only 66 percent of the tests needed for HIV-exposed infants born in developing countries were met in 2015. Even for those infants who receive EID testing, turnaround time (TAT) for results can take up to several months. During this time, only 22-38 percent of HIV-positive infants are initiated on treatment.<sup>xxxvi</sup> Evidence suggests that in some settings, loss-to-follow up (LTFU) of infants can be as high as 34 percent at 3 months and 78 percent by the first year in a population whose mortality for in-utero infections peaks at 2-3 months of age.<sup>xxxvii</sup>

While continued system strengthening is required to improve EID coverage, the 2016 *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* make four key new recommendations for EID testing, which when implemented will increase testing coverage, case finding, and linkage to treatment. The new recommendations are:

- Addition of nucleic acid testing (NAT) at birth to existing EID testing approaches can be considered to identify HIV infection in HIV-exposed infants (conditional recommendation, low-quality evidence).
- NAT technologies that are developed and validated for use at or near to the point of care can be used for early infant HIV testing (conditional recommendation, low-quality evidence).
- In generalized epidemic settings, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV (strong recommendation, low-quality evidence).

- In generalized epidemic settings, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics (conditional recommendation, low quality evidence).

The first recommendation for testing at or near birth addresses two issues that result in increased LTFU: 1) testing at birth or near birth will capture mothers who might not otherwise return for a 6-week visit thereby increasing coverage and 2) earlier testing, particularly given long TATs for test results, will provide more time for infants to receive test results and be initiated on treatment before the peak mortality at 2-3 months of age.<sup>xxxviii</sup> Implementing universal testing at or near birth could double the need for EID tests.

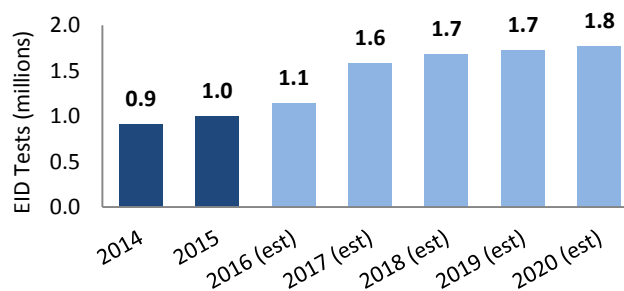
The second recommendation for point-of-care (POC) EID testing represents the biggest opportunity to reduce TATs and increase linkage to treatment. Pilot studies conducted in Malawi and Mozambique demonstrate that POC, compared with the current standard of care using conventional EID technology, reduces TATs and increase patient initiation.<sup>xxxix, xl</sup> Implementing POC would not directly affect total testing volumes, although it could have an indirect effect by facilitating testing at additional entry points. However, POC has been shown to significantly improve linkage to treatment, which could increase pediatric ART coverage.

The third recommendation for generalized screening at entry points outside of the PMTCT cascade of infants whose exposure status is unknown, represents an opportunity to test infants who would not otherwise be identified and potentially reduce the cost per infant identified. Studies have shown that the proportion of positive infants presenting at inpatient wards and nutrition centers is four to six times more than the proportion of positive infants in routine PMTCT screening.<sup>xli, xlii</sup> These results suggest that with modest increases in EID testing volumes a large number of positive infants could be identified and linked to treatment.

The fourth recommendation for screening children with unknown HIV status at outpatient and immunization clinics represents an opportunity to reach children earlier at very high volume entry points, however with a lower proportion of positive infants. These strategies could somewhat increase the EID volumes, but might actually have a larger impact on adult screening with RDT if the infants accompanying parent is screened to identify exposure prior to providing an EID test to the infant.

UNAIDS estimates show that between 2015 and 2020, the number of HIV-exposed infants will remain relatively constant, but due to the potential expansion of EID testing at birth beginning in 2017 to improve case finding in infants, total EID testing can be expected to increase to 1.8 million tests by 2020, potentially driving a modest uptake in pediatric ART patients.

### Exhibit 4.5 PROJECTED ANNUAL EID TESTING VOLUMES



# The Future of HIV/AIDS

## Viral load implementation may increase second-line patients; more data is needed

In the 2016 *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, the WHO made a recommendation to use routine HIV viral load (VL) testing to monitor the effectiveness of ART treatment in patients. Viral load testing measures the quantity of virus in a patient's blood, the results of which can be used by clinicians to evaluate the effectiveness of treatment in conjunction with the patient's adherence. The guidelines also recommend dried blood spot (DBS) using capillary whole blood to determine HIV VL at a threshold of 1,000 copies/μl. Additionally, the WHO now recommends that CD4 monitoring can be stopped in individuals who are stable on ART and virally suppressed. In September 2014, Roche, South Africa, the Global Fund, PEPFAR, and CHAI announced a US\$9.40 Global Access Price for viral load reagents and proprietary consumables, which supported efforts to accelerate scale-up.<sup>xliii</sup> In mid-2015, the Global Fund published the results of its viral load tender, which quoted pricing from diverse suppliers such as Abbott, BioMérieux, Cepheid, Hologic, Roche, and Qiagen, yielding further price reductions and transparency around scale-up costs that can be accessed by countries.

Several countries in sub-Saharan Africa, including Botswana, Kenya, Malawi, Namibia, Rwanda, South Africa, and Uganda, already have public sector viral load programs with high patient coverage. More recently, Swaziland, Zambia, and Zimbabwe have made progress scaling up national viral load testing programs. Other countries, including Ethiopia, Nigeria, and Tanzania have launched HIV VL programs and are testing specimens, but are still working to generate the higher volumes, including strengthening sample transportation, supply chain, and demand generation activities. Outside of sub-Saharan Africa, India is expected to launch a major tender to support national scale-up this year, and Brazil already has a well-established viral load testing program.

Routine viral load monitoring should provide a means of detecting cases of treatment failure earlier and more accurately than clinical or immunological monitoring alone, while providing opportunities to strengthen adherence to first-line regimens.<sup>xliv</sup> Still, there are very few studies on the impact of viral load testing on the number of patients on second-line ART, particularly at a national program level. However, it is expected that as access to HIV VL increases more patients will be moved to second-line regimens.

## Increasing investments in HIV diagnosis is a cost-efficient way to achieve universal access to effective treatment

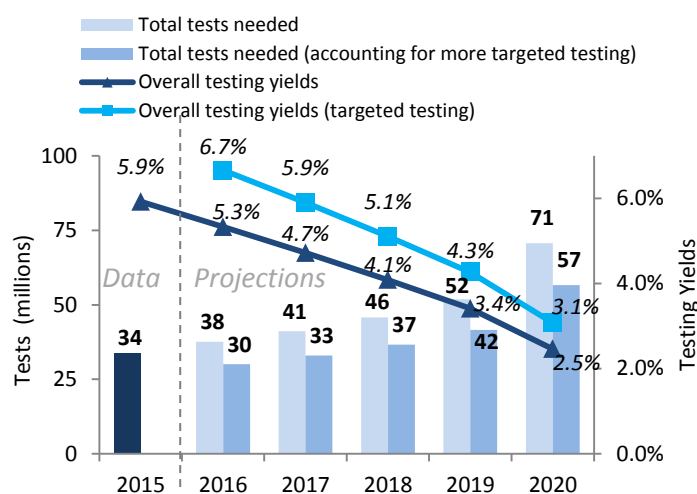
In July 2016, UNAIDS reported that less than 60 percent of people infected with HIV currently know their status.<sup>xlv</sup> This highlights a significant gap with the Fast-Track 90-90-90 targets and the need for renewed efforts to identify 90 percent of PLHIV and link to treatment at least 90 percent of those diagnosed by 2020. While HIV testing services have expanded exponentially over the last decade, mainly at the facility level, a large portion of PLHIV don't have access to these services as they live in remote or rural areas or don't want to attend health care facilities.<sup>xlvi</sup> In addition, as more people are initiated on treatment and ART coverage rates increase, it will become more difficult to find the remaining PLHIV, especially if they are not seeking health services. This will require more targeted testing

approaches to maximize testing yields and minimize increases to testing volumes.

A few countries have started revising their HIV testing services (HTS) strategies to define testing targets across entry points both at health facilities and in the community. This modeling shows that prioritizing higher yielding testing strategies and targeting interventions may not prevent a decline in testing yields as we reach 2020 targets, as more and more PLHIV are initiated on ART. Therefore increased investments may be necessary to fund the additional commodities needed to initiate at least 81 percent of clients on ART as well as to fund the testing strategies required to expand the reach of HTS. These strategies, such as index testing or other forms of targeted community based testing where support services to ensure linkage to care will be important, are likely to be more expensive than facility based testing on a cost-per-test basis.

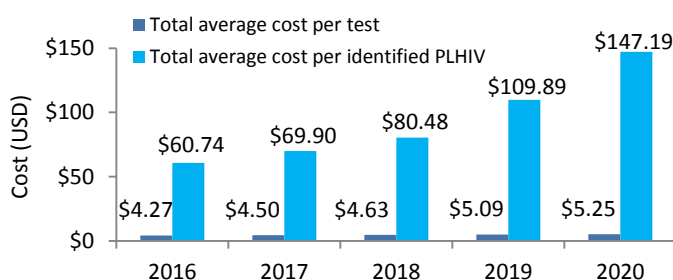
A preliminary forecast across six countries in sub-Saharan Africa predicts that testing volumes will have to double by 2020 if countries maintain current levels of testing efficiency or increase by 68 percent with more targeted testing strategies ensuring higher yields.<sup>xlvii</sup>

**Exhibit 5.1 HIV RDT FORECAST FOR SIX SUB-SAHARAN AFRICA COUNTRIES**



Despite a need to increase resources allocated to HIV testing, it is important to put HTS costs in perspective with overall HIV programming costs. Preliminary evidence from select countries which have costed revised HTS strategies suggest that all-inclusive costs per test vary between US\$4.20 and US\$5.25 over 2016-2020, and all-inclusive costs per identified PLHIV range between US\$60 and US\$148 over the same period.

**Exhibit 5.2 AVERAGE COSTS OF TESTING ACROSS TWO SUB-SAHARAN AFRICA COUNTRIES**



\*Costs included relate to commodities, HR, supply chain, IEC materials and counseling, transport for community based testing strategies, support to linkage to care



The uptake of HIV self-testing (HIVST) might also impact the testing landscape for professional-use tests, but uncertainty around the choice of distribution channels, public or private, makes it difficult to forecast testing volumes. Although HIVST is still not widely used in developing countries, there is increasing evidence of its benefits to expand testing beyond the reach of healthcare workers, and empower clients by addressing many of the stigma concerns that prevent some people from being tested in health facilities. Preliminary evidence suggests that acceptability and testing uptake are high, social harms are rare, testing accuracy and linkage to care are satisfactory with appropriate support materials and support services available.<sup>xviii, xlix, l, li, lii</sup> The WHO is also planning to release normative guidance on HIVST by the end of 2016. In the meantime, some countries have started showing interest to move towards implementation pilots to inform operational requirements for scale-up. On the product side, although more HIV RDTs are becoming available for self-testing, lack of in country product registration might continue slowing down uptake. However, the WHO has initiated a new prequalification assessment process for HIV rapid diagnostic assays that are intended for self-testing, which should lead to new WHO-PQ accreditations over the next year and support product approvals in countries.

### **Funding outlook for 90-90-90**

International funding has come a long way since the days of Durban 2000, when only US\$4.8 billion was allocated for global HIV support. Current investments for the HIV response are estimated at US\$19 billion for 2015 for LMICs. However, this belies the fact that since 2012, the level of funding for HIV in LMICs has been plateauing after years of steady growth.<sup>xxxii</sup> Funding from donor governments decreased by more than US\$1 billion (13 percent) to US\$7.53 billion, compared with 2014 figures of US\$8.62 billion, although some of this is due to timing and exchange rate fluctuations, and the trend may look different for 2016.<sup>iii</sup> During the same period, funding from domestic public and private sources increased, accounting for 57 percent of total funding at US\$10.9 billion. Private sector contributions made up the remaining investments of US\$618 million (3 percent).

At current ARV costs, 90-90-90 targets in LMICs will require an estimated US\$3.2 billion in funding in 2020. ARVs typically represent 40-50 percent of facility-level treatment costs in LMICs, implying resource needs of US\$6.5-8 billion in 2020. Making up only 34-42 percent of the available funding for the response, these estimates indicate that scale-up should be affordable within current funding levels with efficient resource allocations.

An important recent development was the 5th Global Fund Replenishment Conference, which took place in Montreal in September and successfully met its goal of raising nearly US\$13 billion for the next three years.<sup>lv</sup>

### **Differentiated models of care seek to reduce health system burden while improving patient convenience**

As programs expand treatment to all HIV patients, careful thought needs to be given to how health system resources will be utilized, particularly as international donor funding plateaus. Virally suppressed and stable patients do not require the same level of health care support as sicker patients with lower CD4 counts, or those newly-initiated on ART. Differentiated models of care strive to deliver the most cost-effective and time-efficient care, while still meeting different patients' needs with clinically successful outcomes. Many differentiated models of care are being piloted and implemented in countries, including:

- **Multi-month scripts as a way to decrease patients' time spent at health facilities.** At some health clinics in LMICs, virally suppressed patients are given the option to refill their ARVs in bi-monthly or quarterly, or even semi-annual intervals as opposed to the traditional monthly intervals. Not only do multi-month scripts save patients and health workers time, they have also been shown to decrease costs. One study in Uganda found that the average cost of a patient refill appointment in 2012 was US\$38.86, meaning a high potential net savings is possible for health care facilities that adopt multi-month scripting.<sup>lv</sup> Larger pill bottles (e.g. 100 count), which some suppliers already have SRA approval for, could be useful in multi-month scripting to reduce the number of bottles patients have to carry every time. Additionally, even if rolled out in a staggered manner, programs will need to carefully consider the initial bolus of drug volumes they will need to order as buffer stock
- **Community groups as a way to boost retention on ART.** For HIV patients who live in rural villages or mountainous regions, a trip to the health clinic can be laborious and time consuming. One solution, community action groups (CAGs), enables healthy patients to take turns at picking up medications for the group. One CAG study based out of Mozambique found that patients in a community group were more than four times less at risk to die or to be loss to follow-up than those not in the groups.<sup>lvi</sup> A Lesotho CAG study also showed that community members not only spent less time and money collecting ARVs, but virologic suppression rates were 79 percent after one year.<sup>lvii</sup>

### **Treatment and prevention modalities will evolve**

- **Novel drug deliveries methods that will put an end to daily dosing.** Trials are currently underway to look at the effectiveness of long-acting injectables (LAIs) as an alternate to daily oral pills. A phase II study of LAI cabotegravir, has found that the drug is well tolerated and 74 percent of patients prefer the injectables over pills.<sup>lviii</sup> Other research is looking into subdermal implants as a way for drugs to be administered several months at a time. Lastly, two studies, ASPIRE and The Ring Study, done in South Africa, Uganda, Malawi, and Zimbabwe, tested the effects of vaginal rings loaded with dapivirine as a way of prevention. While a significant protective effect was seen overall, unfortunately there was little to no effect seen amongst the important target of young women ages 18-21. This was thought to be due to poor adherence and potentially biological factors; follow-up studies and analyses are exploring how to ensure maximum efficacy.<sup>lix</sup>
- **A HIV vaccine that will completely change the prevention landscape.** The 2009 RV144 trial out of Thailand found that while the tested vaccine lowered the rate of HIV infection by 31 percent relative to the placebo group, it did not meet the criteria for public use.<sup>lx</sup> A new study, HVTN 702, is set to begin in November of 2016 and will test the safety and efficacy of a new HIV vaccine that is based off of the RV144 vaccine. The trial will be held in South Africa.<sup>lxi</sup> Given that the study is expected to span multiple years, it is unlikely that a marketable vaccine will be available before 2020.
- **A deeper understanding on the impact of an increasingly large, ageing, and virally suppressed HIV population.** As more patients are identified as HIV positive, put on ART, and become virally suppressed, they are able to live much longer lives. More research and work is needed to understand the needs of these patients as the

community adapts from an emergency response to one that focusses on helping patients live full and productive lives. Some of the newer

drugs discussed in this report will undoubtedly be part of the armamentarium to treat the disease while preserving quality of life.



## Appendix A: Projected 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 used to calculate yearly API demand. Patient years calculated by assuming newly-initiated patients are on treatment for 6 months on average in the year of initiation; 15 percent attrition rate assumed to estimate yearly new initiations. Note that all figures are based on demand for adults only.

Exhibit A.1: TDF

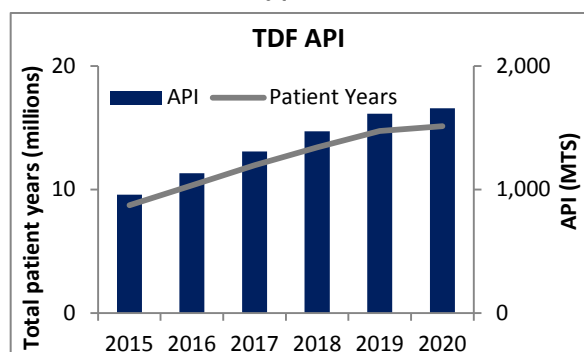


Exhibit A.5: NVP

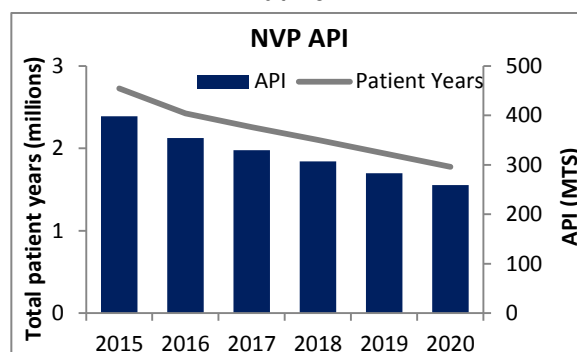


Exhibit A.2: AZT

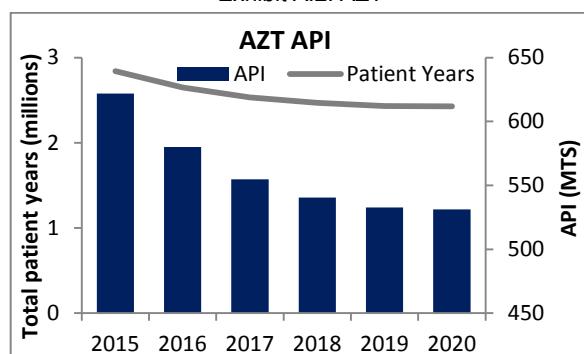


Exhibit A.6: LPV

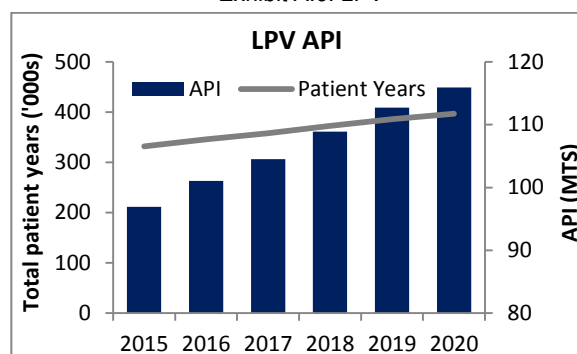


Exhibit A.3: 3TC

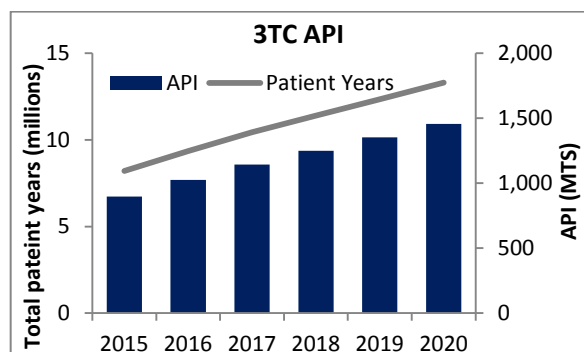


Exhibit A.7: ATV

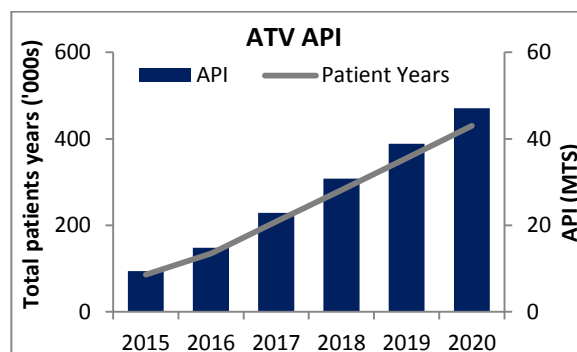


Exhibit A.4: EFV

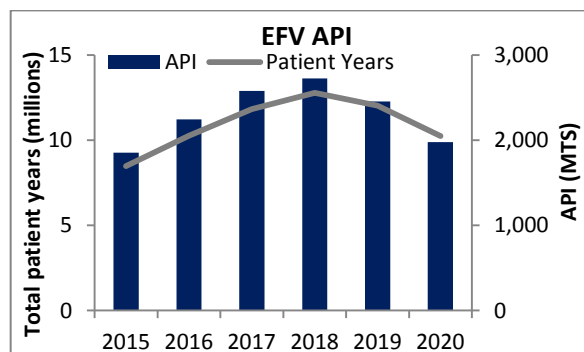
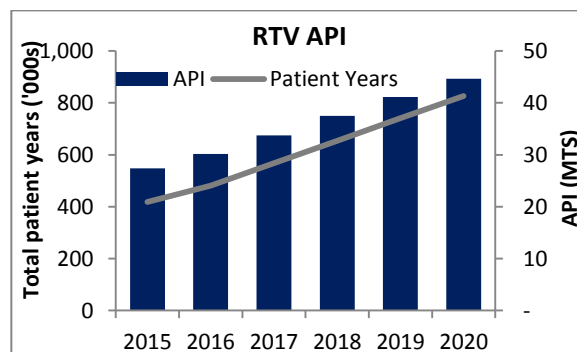


Exhibit A.8: RTV



## Appendix B: Reference Price List

The reference price list below provides per pack or bottle prices for key adults and pediatric ARVs included in CHAI's most recent Reference Price List. Prices are EXW unless otherwise noted.

Product	Packaging	CHAI Reference Price, 2016 (USD)	SCMS E-Catalog Price (USD) <sup>lxii</sup>	MSF Price, July 2016 (USD) <sup>lxiii</sup>	GF Pricing, July 2016 (USD) <sup>lxiv</sup>	2015-2018 RSA Tender Weighted Average Price (USD) <sup>xxx</sup>	Kenya Tender Prices, awarded 2014 (USD) <sup>lxv</sup>
<b>Adult Products*</b>							
3TC (150mg)	HDPE bottle 60 tablets <sup>1</sup>	\$2.25	\$2.25	\$1.86	\$2.25	\$1.66	\$2.12
ABC (300mg)	HDPE bottle 60 tablets <sup>1</sup>	\$11.50	\$9.80	n/a	\$11.00	\$10.20	\$11.14
ATV/r (300/100mg)	HDPE bottle 30 tablets	\$16.00**	\$20.00	\$17.49	\$16.50	n/a	\$18.50
AZT (300mg)	HDPE bottle 60 tablets <sup>1</sup>	\$6.25	\$5.21	\$4.08	\$5.60	\$5.63	n/a
AZT/3TC (300/150mg)	HDPE bottle 60 tablets <sup>1</sup>	\$6.60	\$5.97	\$6.00	\$6.40	\$7.04	\$6.65
AZT/3TC/NVP (300/150/200mg)	HDPE bottle 60 tablets	\$8.20	\$6.96	\$7.74	\$8.05	n/a	\$8.24
DTG (50mg)	HDPE bottle 30 tablets	n/a	n/a	n/a	\$4.00***	n/a	n/a
EFV (600mg)	HDPE bottle 30 tablets <sup>1</sup>	\$3.40	\$2.94	\$1.65	\$3.20	\$3.37	\$3.25
LPV/r (200/50mg)	HDPE bottle 120 tablets <sup>1</sup>	\$20.00	\$19.10	\$18.96	\$18.41	\$12.70	\$18.73
NVP (200mg)	HDPE bottle 60 tablets <sup>1</sup>	\$2.50	\$2.02	\$1.98	\$2.20	\$2.35	\$2.21
RTV (100mg) heat-stable	HDPE bottle 30 tablets	\$7.50	n/a	\$3.42	n/a	n/a	n/a
TDF (300mg)	HDPE bottle 30 tablets <sup>1</sup>	\$3.00	\$3.77	\$3.21	\$3.50	\$2.45	n/a
TDF/3TC (300/300mg)	HDPE bottle 30 tablets	\$4.50	\$3.43	\$3.75	\$4.25	n/a	\$4.49
TDF/FTC (300/200mg)	HDPE bottle 30 tablets <sup>1</sup>	\$5.00	\$5.74	\$5.25	\$5.25	\$5.32	n/a
TDF/3TC/EFV (300/300/600mg)	HDPE bottle 30 tablets	\$8.20	\$7.96	\$8.76	\$7.99	n/a	\$10.50
TDF/FTC/EFV (300/200/600mg)	HDPE bottle 30 tablets <sup>1</sup>	\$8.50	\$8.99	\$8.19	\$7.99	\$8.91	n/a
<b>Pediatric Products</b>							
ABC (60mg) disp.	HDPE bottle 60 tablets <sup>1</sup>	n/a	\$6.20	\$4.02	\$3.80	\$5.13	n/a
ABC/3TC (60/30mg) disp. scored	HDPE bottle 60 tablets	\$3.50	\$3.51	\$4.50	\$4.25	n/a	\$3.16
ABC/3TC (120/60mg) disp. scored	HDPE bottle 30 tablets	\$3.50	n/a	n/a	\$3.50	n/a	n/a
AZT/3TC (60/30mg) disp. scored	HDPE bottle 60 tablets	\$2.00	\$1.86	\$1.92	\$1.90	n/a	\$2.03 <sup>2</sup>
AZT/3TC/NVP (60/30/50mg) disp. scored	HDPE bottle 60 tablets	\$3.50	\$3.25	\$3.30	\$3.36	n/a	\$3.60
EFV (200mg) scored	HDPE bottle 90 tablets	n/a	\$9.30	\$9.27	\$9.30	n/a	n/a
LPV/r (40/10mg) oral pellets	HDPE bottle 120 capsules	\$19.20	n/a	\$19.20	\$19.20	n/a	n/a
LPV/r (80+20mg/ml)	HDPE bottle 5 x 60ml (300ml) <sup>3</sup>	n/a	\$30.82	\$30.90	\$30.82	\$19.70	\$32.15
LPV/r (100/25mg)	HDPE bottle 120 tablets	n/a	\$9.94	\$11.88	\$10.00	n/a	n/a
RAL (100mg) chewable scored	HDPE bottle 60 tablets	n/a	n/a	\$36.00	n/a	n/a	n/a

\*Please refer to the following [link](#) for pricing on DTG and TLE400

\*\*Lower prices may be offered for higher volume orders. Please contact Carolyn Amole at [camole@clintonhealthaccess.org](mailto:camole@clintonhealthaccess.org) for more details

\*\*\*The Global Fund's DTG pricing served as an indicative reference before any generic manufacturer received SRA approval; more refinement to the price is likely given Aurobindo's tentative US FDA approval

<sup>1</sup> RSA is 28 tablet bottle (vs. 30), 56 tablet bottle (vs. 60); 112 tablet bottle (vs. 120)

<sup>2</sup> Assumes dispersible was procured based on indicated supplier, though not explicitly stated in tender document

<sup>3</sup> RSA price provided for 60ml bottle. Multiplied by 5 to get 300ml estimate for comparability purposes



## Appendix C: IATT List of Optimal Pediatric Products (2016)<sup>18</sup>

Product	Dosage	Formulation	Stance
ABC + 3TC	60/30mg	Tablet (dispersible, scored)	Optimal
ABC + 3TC	120/60mg	Tablet (dispersible, scored)	Optimal
AZT + 3TC	60/30mg	Tablet (dispersible, scored)	Optimal
EFV	200mg	Tablet (scored)	Optimal
LPV/r	100 mg/25mg	Tablet (heat stable)	Optimal
LPV/r	80/20mg/ml	Oral liquid	Optimal
LPV/r*	40mg/10mg	Oral pellets	Optimal
NVP	50mg	Tablet (dispersible, scored)	Optimal
NVP**	50/5mg/ml (100ml)	Oral liquid	Optimal
RAL*	100mg	Chewable tablet	Optimal
<p>*Additions to the 2016 IATT list</p> <p>** For infant prophylaxis as part of PMTCT.</p>			

<sup>18</sup> Per IATT presentation at WHO/UNAIDS Annual Meeting with Pharmaceutical Companies and Stakeholders, March 9, 2016, Geneva. Presentation available at [link](#)

## 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 five-year forecast for the total number of patients on ART in LMICs. CHAI compiles historic data on the number of patients on ART in 21 high ART patient burden countries (Botswana, Brazil, Cameroon, China, Côte d'Ivoire, Ethiopia, India, Kenya, Lesotho, Malawi, Mozambique, Myanmar, Nigeria, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe) from progress reports issued and annual data published by the WHO, UNICEF and UNAIDS. For each country, CHAI assumes that the number of people receiving treatment will increase linearly at the same rate as the linear trend observed in the last four years and will plateau as universal access is approached, and then extrapolates to the rest of the world. Universal access (for the growth plateau) is defined by PLWHA to reflect WHO Guideline changes and subsequent anticipated ART scale-up.
- *ARV demand forecast:* CHAI collects aggregate country data on patient regimens, formulations used, national guidelines, and anticipated future trends from CHAI's country teams and published literature each year. CHAI uses the data, an internally developed forecasting model, and the ART patient forecast (above) to project ARV demand in LMICs over the next five years. This year, CHAI received information for 13 countries (i.e. Ethiopia, India, Kenya, Lesotho, Malawi, Nigeria, South Africa, Swaziland, Uganda, Tanzania, Vietnam, Zambia, and Zimbabwe). The countries included represent 75 percent of the patients on ART in GA LMICs in 2015.
- *ARV procurement database:* CHAI aggregates procurement data from several sources, including Supply Chain Management System (SCMS), The Global Fund, UNITAID, IDA, and national governments. The data is evaluated on an annual basis to understand pricing and volume trends by country, region, and globally.
- *Market sizing analysis:* Each year, CHAI combines the ARV demand forecast with pricing data from the ARV procurement database to calculate the current size of the ARV market in dollar terms, to estimate the market size over the next five years, and to calculate the average cost of treatment for first- and second-line adult and pediatric patients.
- *Pipeline drug forecast:* CHAI updated its global pipeline drug forecast model, which estimated uptake at the molecule level, to a more nuanced approach that accounts for country-specific uptake at the regimen level. The global forecast was divided into two segments, i.e. eleven high-volume countries and the generic-accessible (GA) rest of world (RoW), which were both used to estimate global uptake for adult pipeline products. New product uptake assumptions were based on three main factors: 1) anticipated price differential between new and current products, 2) relative clinical improvement of new product relative to current, and 3) anticipated launch year (i.e. likely first availability of product in country post-SRA and NDRA approval, inclusion in national guidelines and procurement plans), with the expectation that WHO guideline inclusion would have already occurred. Based on these three variables, uptake curves were then selected for each of the twelve focal countries based on CHAI's country intelligence, and one set of global uptake assumptions for GA RoW, separately for existing and newly initiating patients. These uptake curve choices for new products relative to current products estimated the total number of patients in a given year in GA LMICs.

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