CLINTON HEALTH ACCESS INITIATIVE

2022 HIV MARKET REPORT

The state of HIV treatment, testing, and prevention in low- and middle-income countries

ISSUE 13, NOVEMBER 2022

Foreign, Commonwealth & Development Office

Unitaid
Innovation in Global Health

BILL & MELINDA GATES foundation

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ACKNOWLEDGEMENT

This report was made possible through the generous support of Unitaid, with complementary support from the UK Foreign, Commonwealth & Development Office, and the Bill & Melinda Gates Foundation.

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ACRONYMS

1HP	One month of daily RPT+INH for TPT
1L	First-line
2L	Second-line
3HP	Three months of weekly RPT+INH for TPT
3L	Third-line
3TC	Lamivudine
5FC	Flucytosine
ABC	Abacavir
AGYW	Adolescent girls and young women
AHD	Advanced HIV Disease
AIDS	Acquired immunodeficiency syndrome
AmB-d	Amphotericin B deoxycholate
API	Active pharmaceutical ingredient
APWG	ARV Procurement Working Group
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
bNABs	Broadly neutralizing antibodies
CAB	Cabotegravir
CADO	Conference on ARV Drug Optimization
CHAI	Clinton Health Access Initiative
CLHIV	Children living with HIV
CM	Cryptococcal meningitis
CROI	Conference on Retroviruses and Opportunistic Infections
DPP	Dual prevention pill
DRT	Drug resistance testing
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
DVR	Dapivirine vaginal ring
EFV	Efavirenz
EID	Early infant diagnosis
EXW	Ex-works
FDC	Fixed-dose combination
FTC	Emtricitabine
GA	Generic-accessible
HIV	Human immunodeficiency virus
HIVST	HIV self-test
INH	Isoniazid
INSTI	Integrase strand transfer inhibitor
ISL	Islatravir
LA	Long-acting
L-AmB	Liposomal amphotericin B
LEN	Lenacapavir
LMIC	Low- and middle-income country
LPV/r	Lopinavir/ritonavir
MAPs	Microarray patches
MOH	Ministry of health
MPP	Medicines Patent Pool
MPT	Multipurpose prevention technology
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
NVP	Nevirapine
OBR	Optimized background regimen
OI	Opportunistic infection
PADO	Pediatric ARV Drug Optimization
pALD	Pediatric ABC+3TC+DTG
pDTG	Pediatric DTG (10 mg) scored, dispersible
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease inhibitor
PLHIV	People living with HIV
POC	Point-of-care
PrEP	Pre-exposure prophylaxis
RFP	Request for proposal
RPT	Rifapentine
RPV	Rilpivirine
RTV	Ritonavir
SAHPRA	South African Health Products Regulatory Authority
SRH	Sexual and reproductive health
SSA	Sub-Saharan Africa
TAF	Tenofovir alafenamide fumarate
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TLD	TDF+3TC+DTG
TPT	TB preventive therapy
UNAIDS	Joint United Nations Program on HIV/AIDS
US FDA	United States Food and Drug Administration
VL	Viral load
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
XTC	Emtricitabine or lamivudine

AT-A-GLANCE

HIV DATA OVERVIEW

38.4M
People living with HIV (PLHIV)

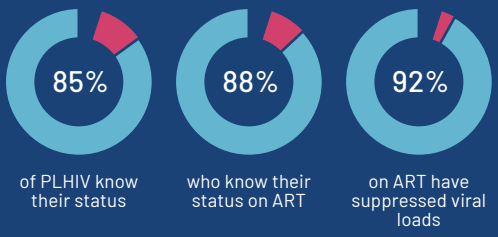
36.7M Adults | 1.7M Children

28.7M
People on treatment

27.8M Adults | 880K Children

Global progress toward UNAIDS 2025 goals

Gap to 95-95-95 targets as of Dec 2021



of PLHIV know their status | who know their status on ART | on ART have suppressed viral loads

TEST SMART

US$1 or below for an HIV self-test (HIVST) and a dual HIV/syphilis rapid diagnostic test due to pricing deals

1.9M early infant diagnosis (EID) tests run in low-and middle-income countries (LMICs) in 2021

TREAT RIGHT

BY ADDRESSING ADVANCED HIV DISEASE

214K global tuberculosis (TB) deaths among PLHIV in 2020, the first increase in over a decade

WHO recommends simplified dosing of L-AmB to treat cryptococcal meningitis (CM)

Additional suppliers of 3HP and L-AmB, key drugs for the prevention and treatment of TB and CM

WITH OPTIMAL ARVs FOR ADULTS

~80% of all adults in generic-accessible LMICs on TLD in 2021

Nigeria and Zambia introduced DRV/r (400/50 mg) for second-line use

The European Union approved **twice-yearly subcutaneous lenacapavir** for treatment of multi-drug resistant HIV

WITH OPTIMAL ARVs FOR CHILDREN

Over 100K children on pDTG, with over 60 countries procuring

Generic pALD expected to receive US FDA tentative approval in mid-2023

STAY NEGATIVE

~1.5M new HIV infections globally in 2021, **70%** of these among key populations and their partners

Long-acting cabotegravir injections for HIV prevention (CAB-LA) voluntarily licensed to allow for generic development and included in updated WHO guidelines

2.8M cumulative oral PrEP initiations in LMICs, with 50% occurring between Q3 2021 and Q3 2022

GENERAL TRENDS

In an era defined both by the COVID-19 pandemic and new innovations that have greatly improved HIV services, urgent action is required to meet global targets. While some aspects of HIV programs are beginning to rebound from COVID-19-related disruptions, others, such as pediatric HIV, are still lagging pre-COVID levels. Despite the challenges of the past few years, the HIV market is robust and continues to grow, as costs associated with HIV testing, treatment, and prevention continue to fall. On the horizon, long-acting therapies and holistic approaches to care, including mental health support, will define the next era of the HIV response.

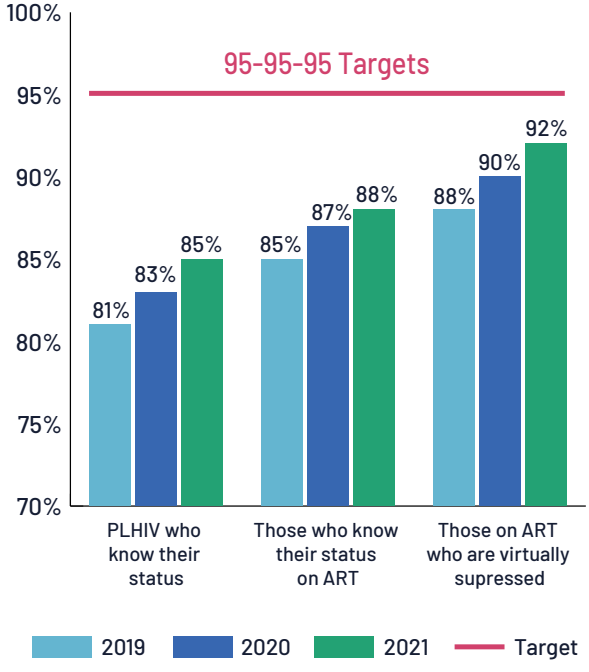
Aspects of HIV programs begin to rebound from pandemic challenges, but some populations remain disproportionately impacted

The COVID-19 pandemic impacted HIV services across the cascade as people were less able or less willing to access services, and healthcare systems grappled with increased pressure and limited resources. While some services began to rebound in 2021 as lockdowns lifted, demonstrating the resilience of HIV programs, urgent action is required to ensure continued progress.

In particular, pediatric HIV outcomes continue to unacceptably fall behind those of adults. Persistent global disparities exist between children and adults on antiretroviral therapy (ART) (52 percent compared to 76 percent respectively) and achieving viral suppression (40 percent compared to 67 percent).[i] The COVID-19 pandemic led to significant disruptions in HIV care, particularly for pediatric HIV testing, putting this population further off-track. In 2021, children living with HIV (CLHIV) accounted for 98,000 AIDS-related deaths and 160,000 new HIV infections, both unacceptably high given the availability of highly effective tools and technologies for testing, treatment, and vertical elimination.[ii]

Further, across all age groups, in 2021 new HIV infections declined only marginally, new initiations on ART increased by only six percent, and AIDS-related deaths declined by only six percent.[ii] To achieve the Fast-Track 95-95-95 targets from the Joint United Nations Program on HIV/AIDS (UNAIDS) by 2025, significant efforts are required to accelerate equitable access to HIV care [Figure 1]. Additionally, as new epidemic threats such as mpox and recent polio outbreaks point to the potential for future disease-related disruptions, the global community must remain vigilant to prevent further setbacks to HIV progress.

Figure 1: Global Fast-Track Target Progress 2019-2021[ii]

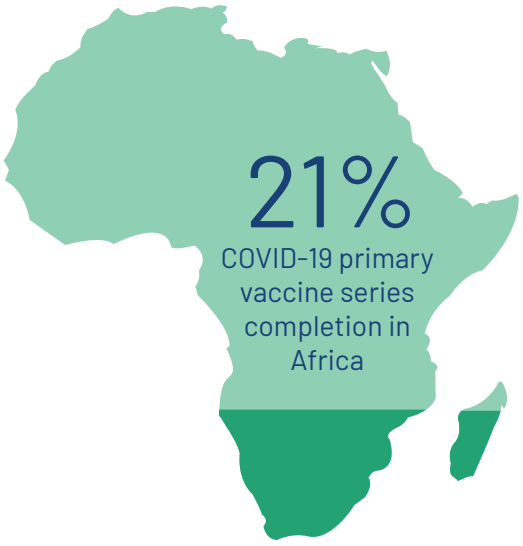


Expanding access to COVID-19 vaccines and treatment remains critical for PLHIV

In addition to the impacts of the COVID-19 pandemic on HIV services, people living with HIV (PLHIV) remain at higher risk of dying after hospitalization due to COVID-19, according to research from the World Health Organization (WHO).[iii] PLHIV have also not experienced the same decline in COVID-related mortality as HIV-negative people during the omicron wave.[iii] Further, a small US study found that unvaccinated PLHIV were four times more likely than HIV-negative people to experience 'long COVID' symptoms.[iv]

Although the WHO recommends prioritization of PLHIV for the COVID-19 vaccine, access has been unequal across the globe with only 21.1 percent of Africa's population completing their primary series of vaccines as of July 2022 [Figure 2].[v]

Figure 2: Percent of Africa's Population Completing Primary Series of COVID-19 Vaccines as of July 2022[v]



Complementing vaccination, a new COVID-19 treatment containing nirmatrelvir and ritonavir, branded as Pfizer's *Paxlovid*, received emergency use authorization from the United States Food and Drug Administration (US FDA) in Dec. 2021.[vi] In order to ensure access to this product in low- and middle-income countries (LMICs), in May 2022 CHAI and partners announced agreements with leading generic manufacturers to make generic *Paxlovid* available for less than US$25 per treatment course for high-risk patients.[vii]

Access to COVID-19 vaccination and treatment in LMICs, especially for PLHIV, continues to be critical to reduce deaths and ensure continued progress toward HIV program targets.

New PEPFAR leadership sets the stage for continued progress despite ongoing pandemic challenges

In May 2022, the US Senate confirmed Dr. John Nkengasong as the US global AIDS coordinator, which will include leadership of the US President's Emergency Plan for AIDS Relief (PEPFAR).[viii] Dr. Nkengasong is a Cameroonian virologist and the first person born on the African continent to take on this critical leadership role. He has more than thirty years of experience in global health and previously served as the director of the Africa Centres for Disease Control and Prevention.[ix]

> *"We need to capitalize on the capacity and experience of those in the countries where we work, coming to the table with a deep respect for their perspectives and needs, taking account of their insights, their knowledge of local contexts, and their reservoirs of expertise."*
>
> *Dr. Nkengasong's opening testimony before the Senate Foreign Relations Committee*[x]

Long-acting products dominating the pipeline offer increased user choice and potential to improve adherence

Looking forward, several exciting developments in the HIV pipeline have the potential to transform HIV services. Across both prevention and treatment, several new and pipeline products offer novel delivery modalities and longer-acting options. For the first time, this could allow PLHIV or those at risk of HIV the ability to choose between daily oral tablets and longer-acting injectables, although enabling true client choice will require an overhaul of current HIV service delivery systems. The updated adult and pediatric Conferences on Antriretroviral Drug Optimization (CADO-

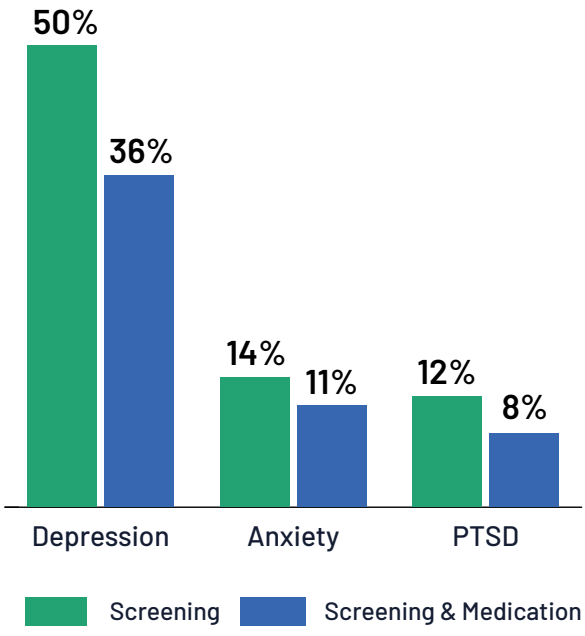
4 and PADO-5) priority and watch lists, highlighted later in the Adult and Pediatric Treatment sections of this report [Pages 21 and 26 respectively], further reflect this shift and highlight the role that choice will play moving forward.

Holistic approaches to HIV care seek to incorporate mental health support

As HIV programs continue to put people at the center of care and decision-making, there has also been a shift to increase emphasis on other aspects of health, including mental health. There is a strong bidirectional relationship between HIV and common mental disorders. People with common mental disorders are more vulnerable to acquiring HIV and PLHIV experience significantly higher rates of common mental disorders compared to the general population.[xi]

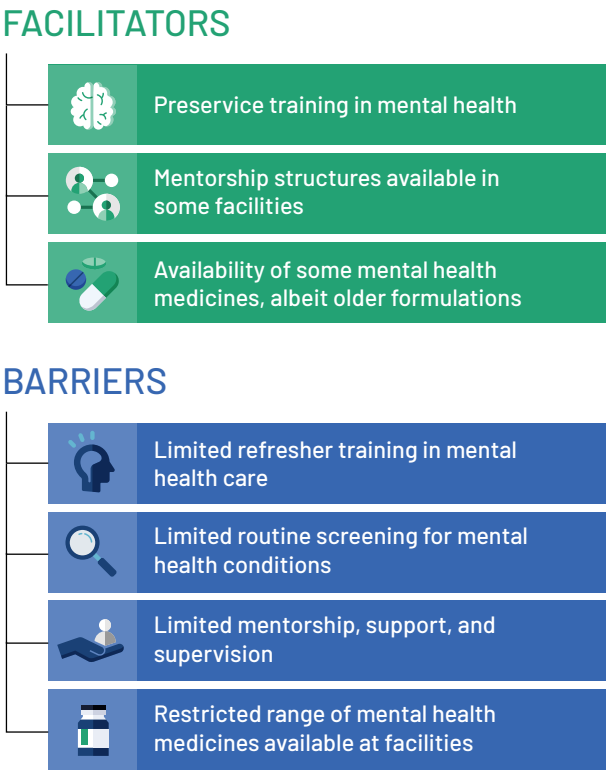
However, access to screening or treatment for mental health is limited in most LMICs. For example, a recent study presented at AIDS 2022 based on data from the International Epidemiology Databases to Evaluate AIDS consortium reported serious gaps in the availability of screening and treatment for depression, anxiety, and post-traumatic stress disorder in HIV clinics across 41 countries in Asia, the Caribbean, Latin America, sub-Saharan Africa (SSA), North America, and Australia [Figure 3].[xii]

Figure 3: Proportion of HIV Clinics with Screening or Medication for Common Mental Disorders[xii]



There is a significant body of evidence showing that LMICs can implement low-cost, effective treatments for common mental disorders, but current implementation is geographically limited, disjointed, and smaller-scale. A key part of improving mental healthcare for PLHIV includes understanding existing country level enablers, gaps, and needs in order to scale implementation of these cost-effective interventions nationally. To this end, in 2021 the Zimbabwe Ministry of Health and Child Care, in collaboration with the Clinton Health Access Initiative (CHAI), conducted the largest and first of its kind mental health needs assessment across facilities providing services for PLHIV. The assessment identified key facilitators of success as well as critical barriers to the implementation of mental health services [Figure 4].[xiii]

Figure 4: Facilitators and Barriers to Mental Healthcare for PLHIV in Zimbabwe[xiii]



Underscoring the importance of mental healthcare among PLHIV, UNAIDS, and the WHO released a joint publication emphasizing integration of HIV prevention, testing, treatment, and mental health services for PLHIV. This document provides policy makers and program implementers with a compilation of tools, best practices, recommendations, and guidelines that facilitate the integration of interventions and services to address the interlinked issues of mental health and HIV.[xiv]

Significant price reductions seen across the cascade, but continued investment and focus are needed to sustain program gains

There have been many reductions in the costs of products across the HIV cascade in recent years. The cost of HIV treatment and prevention therapies in generic-accessible[1] (GA) LMICs continues to decrease and a recent CHAI-led pricing agreement for US$1 HIV self-tests (HIVSTs) brings them closer to parity with professional-use rapid diagnostic tests [Figure 5].

Figure 5: Major HIV Pricing Updates as of October 2022[xv, xvi]

TREATMENT

- Treatment with TLD now **below US$50 PPPY** (using cartonless 180-count packs)
- FDC of DRV/r, the best-in-class protease inhibitor, available at a price of **US$17.50 per pack**, lower than LPV/r
- pDTG available at **US$4.50/ 90-count pack**, significantly cheaper than LPV/r-based regimens

TESTING

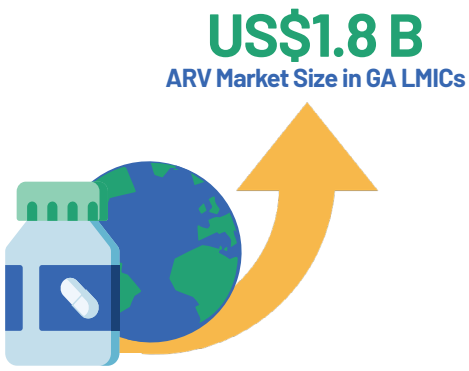
- A HIVST is now available at **US$1 per test**, expanding opportunities for use

PREVENTION

- TDF/FTC, a key product for oral PrEP, now costs **less than US$4 per month**

The antiretroviral (ARV) market in GA LMICs is robust and the number of people on ART continues to grow. Overall, CHAI estimates that the approximate ARV market size in GA LMICs was US$1.8 billion in 2021 (based on annual costs of regimens in-use in 2021) [Figure 6].[xvii]

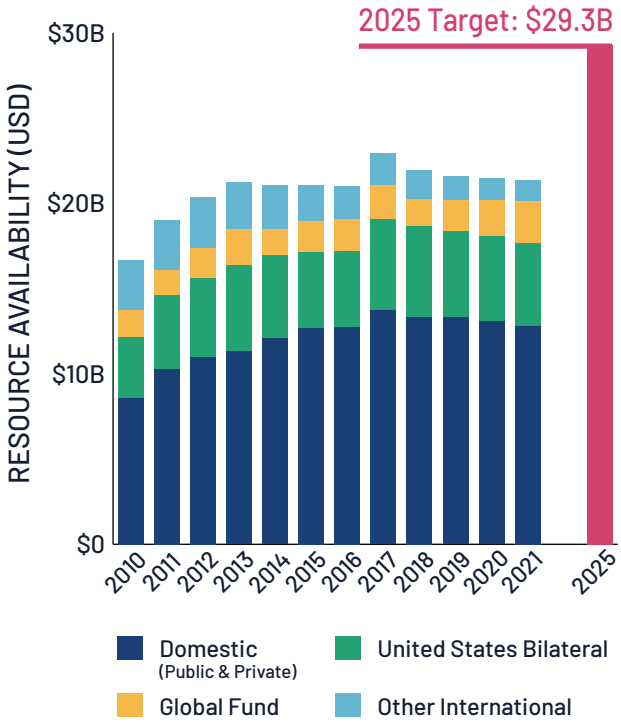
Figure 6: ARV Market Size in GA LMICs



While we reflect on these transformational successes in commodity cost reductions, it is also important to look to the future and plan what is required to achieve global targets. Global HIV funding continues to stagnate despite the critical role of donor funding in achieving targets and expanding access to innovations.

In 2021, total HIV resources in LMICs totaled US$21.4 billion, a small decrease from the previous year, and continuing a four-year declining trend in resources [Figure 7].[xviii] Additionally, although the Global Fund's seventh replenishment conference in 2022 raised a record amount (US$14.25 billion), it was still lower than the goal of US$18 billion for the next three years.[xix]

Figure 7: Resource Availability for HIV in LMICs, 2010-2021 and 2025 Target[xviii]



Over the past ten years, overseas development assistance for HIV from bilateral donors outside of the US fell 57 percent. UNAIDS estimates that approximately US$8 billion in *additional* total funds will be required by 2025 to meet HIV elimnation goals.[xx] Across the HIV landscape, additional and continued resourcing will play a critical role in sustaining and expanding access to HIV services.

[1] See Appendix D (p. 42) for a definition of generic-accessible.

TEST SMART

Declines in testing volumes threaten progress toward global targets, but recent price reductions and innovations for testing commodities could restore and expand access to testing. For HIV-exposed infants, scale up of point-of-care technologies continues, but timely linkage to care and clinical action remain critical to realize impact and save lives.

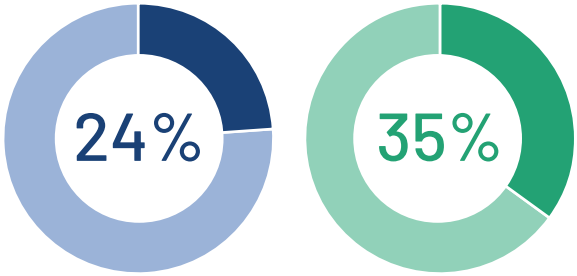
Targeted HIV testing strategies lead to decline in testing volumes and diagnoses

Diagnosis remains the largest gap among the UNAIDS 95-95-95 targets. Only 85 percent of PLHIV globally knew their status in 2021, with even larger gaps in diagnosis among key populations. Despite these gaps, there have been significant declines in HIV testing volumes over the past few years, with fewer HIV tests conducted in eastern and southern Africa in both 2020 and 2021 compared to 2019.[xx] These declines are in part due to the COVID-19 pandemic, which acutely affected HIV testing services. Compounding this, PEPFAR's HIV testing guidance since 2019 has emphasized more targeted testing for those at the highest risk of acquiring HIV.[xxi]

As a result, total HIV tests in 41 PEPFAR countries decreased from 20 million in 2018 to 15 million in 2021. While the proportion of positive test results has remained stable at around four percent, decreased testing volumes overall have resulted in fewer PLHIV accessing testing and aware of their status. Of those with a positive diagnosis, there was a 90 percent linkage to care rate within the data set, although the study did not follow individuals after the first ARV dispensation. This high linkage rate was likely due to several factors: WHO guidance on same day ART initiation, improved counseling, and increased capacity of countries for linkage.[xxii]

As countries continue to consider new testing approaches, they should also recognize the non-linear pathways that individuals may take when accessing care. For example, an analysis from Zambia showed 24 percent of newly identified HIV-positive clients had suppressed viral loads, which suggests many are already or were recently on ART.[xxiii] Similarly, a survey among individuals enrolled at one ART center in Uganda revealed that 35 percent of clients sought repeat testing for various reasons, including having a new sexual partner or due to experiences with traditional healers [Figure 8].[xxiv]

Figure 8: Study Findings from Zambia and Uganda on Repeat HIV Testing[xxiii, xxiv]



of newly identified HIV-positive clients had suppressed viral loads in Zambia

of individuals sought repeat testing for various reasons in Uganda

Despite more PLHIV accessing treatment than ever before, persistent challenges with early retention in treatment and the nature of lifelong care mean that without intervention, many PLHIV will continue to cycle in and out of care through the so-called "revolving door of care".[xxv] Even as retention and reengagement strategies improve, HIV testing will likely remain a critical reengagement pathway for many clients.

Recent trends toward reducing testing volumes in pursuit of efficiency have restricted access to testing and slowed progress toward treatment goals. This focus on increasing yield has also discouraged the use of testing for demand generation for prevention interventions and monitoring, two touchpoints where yield is expected to be low. A more holistic and status-neutral approach to testing is emerging that, combined with recent price reductions for testing commodities, could restore and further expand access to testing. Linkage from testing to prevention and treatment services will be critical, as will the integration of testing across other health service delivery channels, including within the private sector.

Historic pricing agreement brings the cost of an HIV self-test to just one dollar

In July 2022, CHAI and MedAccess, in partnership with Wondfo Biotech Co., announced a historic pricing agreement for Wondfo's new HIVST. This WHO-prequalified, blood-based HIVST is available to public sector purchasers in 140 LMICs for US$1 (EXW) per test, half the cost of the current leading HIVST.[xxvi] This one-dollar price brings HIV self-testing closer to parity with conventional HIV rapid diagnostic tests, enabling testing programs to leverage existing funding for testing commodities without sacrificing overall testing volumes.

In April 2022, the WHO also granted prequalification to Abbott's third-generation CheckNOW HIV Self-Test. This blood-based self-test is available for US$1.50 (EXW) per test for public sector purchasers.[xxvii]

With the addition of these two tests, there are now six HIVSTs with WHO prequalification, with several tests available at a cost below US$2 [Figure 9]. A new oral-fluid self-test is expected to be approved in early 2023, with additional blood-based HIVSTs expected in the next 12 to 18 months. These products are expected to cost US$2 or less.

Figure 9: Cost of HIVSTs with WHO PQ[xxviii, xxvi, xxix, xxx]

Research on HIV self-testing demonstrates high linkage to care and highlights additional areas for use

The introduction of low-cost HIVSTs can enable countries to scale up self-testing to meet currently unmet testing demand. Given that self-testing may occur outside of a facility, ensuring linkage to care is particularly important and has been the focus of many studies. Four of five STAR program studies conducted in Malawi, Zambia, and Zimbabwe found that community-based HIVST distribution led to an overall increase in ART initiations.[xxxi] Similarly, two systematic reviews and meta-analyses demonstrated that HIV self-testing not only increases uptake of testing among general and key populations, but also achieves linkage rates similar to standard HIV testing.[xxxii, xxxiii]

New evidence and guidance also suggests that HIV self-testing can play an important role in prevention services. A Kenyan implementation study found that utilizing interim HIV self-testing reduced the overall number of clinic visits without compromising testing, retention, or adherence.[xxxiv] In response to this and additional evidence, a new WHO technical brief on oral pre-exposure prophylaxis (PrEP) delivery highlights the potential applications of HIV self-testing for prevention services.[xxxv]

This expanded use of HIV self-testing could reduce the burden on oral PrEP users as well as healthcare facilities, while also serving as a key entry point and demand creation tool for new oral PrEP enrollees.

"HIVST provides an additional testing choice to PrEP users when starting, restarting or continuing PrEP."

WHO Technical Brief on Oral PrEP Delivery [xxxv]

Early infant diagnosis shows signs of rebound from COVID-19 challenges, but further scale-up remains critical

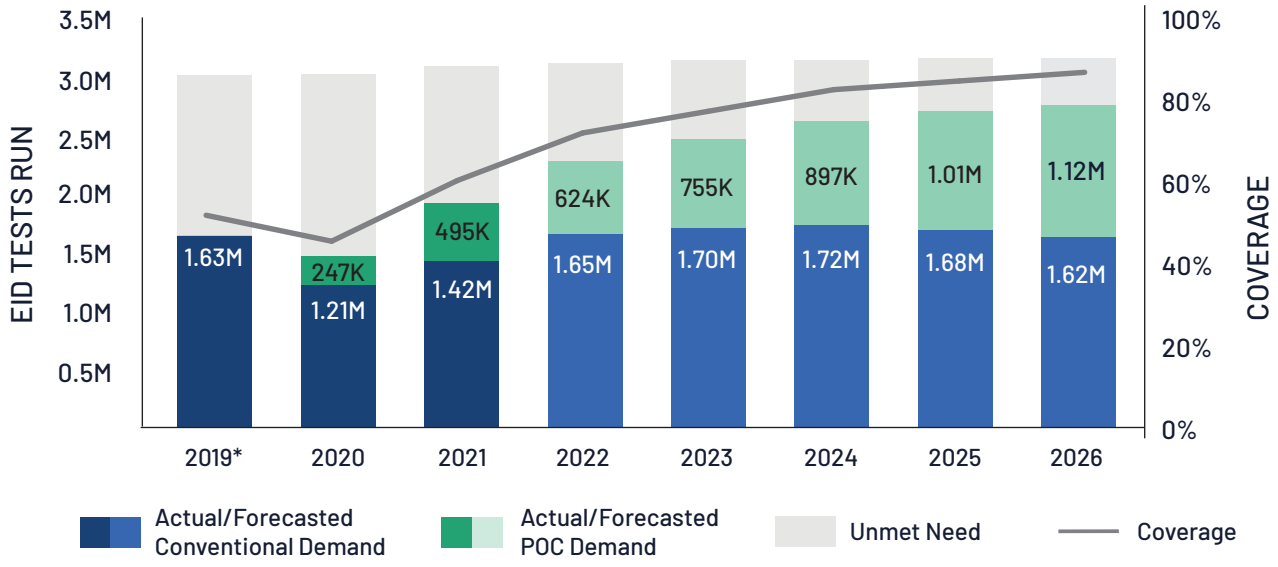
Following a concerning decrease in early infant diagnosis (EID) testing volumes in 2020 due to the COVID-19 pandemic, volumes now appear to be rebounding. In 2021, CHAI estimates that there were approximately 1.9 million EID tests run, an increase of over 30 percent compared to 2020 [Figure 10]. While encouraging, progress is still too slow, and CHAI estimates that overall EID testing coverage[2] in LMICs is only 62 percent.[xxxvi] Reflecting this poor coverage, only 59 percent of CLHIV globally are aware of their status.[xx]

Looking forward, point-of-care (POC) EID testing will be a key tool to increase testing coverage, but ensuring rapid linkage to care and long-term retention are still critical. In 2021, the number of POC EID tests run increased to 495,000 tests and CHAI estimates this share will continue to grow given the benefits of POC testing to ensure timely diagnosis and ART initiation [Figure 10].[xxxvi]

Early identification of infants born HIV-positive remains critical to ensure linkage to lifesaving care. New research also suggests a potential benefit of immediate diagnosis and treatment at birth. The IMPAACT P1115 study found that nearly 30 percent of children born with HIV who began taking ART within 48 hours of birth had undetectable HIV RNA, no detectable proviral DNA, and had not produced antibodies to HIV two years later. This suggests that for some infants born HIV-positive, very early treatment initiation may result in complete clearing of the HIV infection.[xxxvii] While this early data is encouraging, this would require both birth testing and access to neonatal formulations of ARVs, neither of which are currently commonly implemented nor available in LMICs.

Following diagnosis, increased attention to result utilization and improved management remains critical. For example, a study in Zambia showed that strengthening result return in an existing dried blood spot-based system had similar long-term outcomes to infants diagnosed via POC testing. However, in both arms, only 19-30 percent of HIV-positive infants were alive, in care, and suppressed at 12 months, underscoring the importance of linkage to appropriate care after diagnosis.[xxxviii]

Figure 10: LMIC EID Demand Forecast[xxxvi]



**POC tests were not recorded separately in 2019*

[2] Calculated as total EID tests run divided by estimated total number of tests needed as defined by country testing algorithms.

Dual HIV and syphilis test now available for less than one US dollar

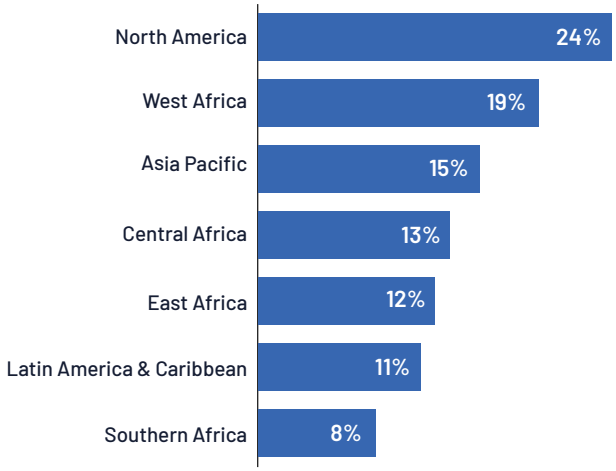
Due to the expansion of vertical HIV elimination programs, up to 95 percent of pregnant women receive HIV testing during antenatal care in many countries.[ii] However, less than half of pregnant women receive testing for syphilis, which causes 200,000 annual stillbirths or newborn deaths globally.[xxxix] Congenital syphilis is the second leading cause of stillbirths worldwide, which are preventable if the mother is tested and treated in time.[xxxix]

To address this gap, MedAccess, CHAI, and SD Biosensor announced a partnership and volume guarantee to expand access to a dual HIV/syphilis test. Through this agreement, the WHO-prequalified SD Biosensor STANDARD Q HIV/Syphilis Combo test is now available at US$0.95 (EXW) per test for public sector procurers in over 100 LMICs.[xxxix] This combination of HIV and syphilis testing at an affordable price could greatly expand access to syphilis testing and further reduce infant deaths.

New data suggests aging populations should be a focus for testing initiatives

Recent surveys suggest that a substantial proportion of new HIV diagnoses are among people over 50 years old. According to data from the International Epidemiology Databases to Evaluate AIDS consortium, the proportion of people diagnosed with HIV over 50 years old ranged from eight percent to 24 percent depending on the region [Figure 11].[xl]

Figure 11: Proportion of Adults 50 Years or Older at Initial Presentation for Care, 2000 to 2019[xl]



Further, according to the survey, late HIV diagnosis, defined as a CD4 count below 350 cells/uL, occurred at a higher rate among older people compared with younger people in almost all global regions studied.[xl] This suggests that older populations are being left behind when it comes to HIV diagnosis. Moving forward, new testing strategies for specific populations, such as older people, will be critical to reach and identify the remaining PLHIV.

TREAT RIGHT

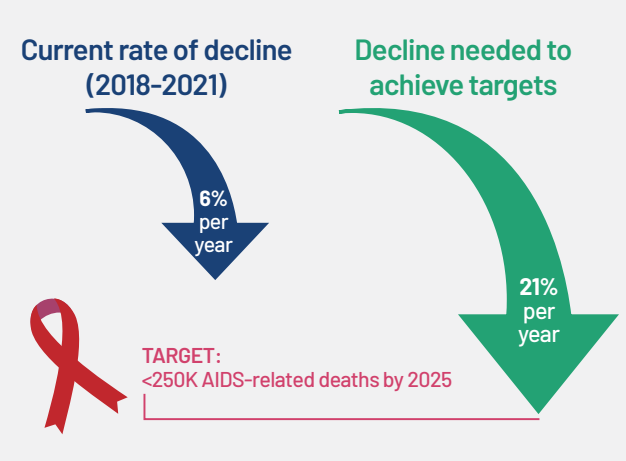
Continued introduction of TLD, pDTG, and the nascent rollout of DRV/r represent exciting milestones in HIV treatment optimization, with advances in optimizing advanced HIV disease (AHD) care set to save lives from tuberculosis and cryptococcal meningitis. Additionally, a development pipeline of long-acting products will change the way ART is delivered and usher in a new era of user choice. However, the global community must rise to the challenge to ensure affordable and equitable access to next-generation treatment products for their lifesaving potential to be realized.

TREAT RIGHT BY ADDRESSING ADVANCED HIV DISEASE

AIDS-related deaths remain high despite improvements in HIV treatment coverage and AHD care

In 2021, there were still 650,000 AIDS-related deaths globally, only a six percent decrease from 2020.[xx] At this rate, and in the absence of major investments in scaling up access to the WHO AHD package of care, UNAIDS estimates there will still be 460,000 AIDS-related deaths in 2025, significantly off course from global targets of less than 250,000 deaths annually [Figure 12].

Figure 12: Decline in AIDS-Related Deaths[xx]



These deaths occurred despite major improvements in treatment quality and coverage, with over 80 percent of adult clients in GA LMICs now on a DTG-based regimen.[xli] There have also been improvements in AHD care for opportunistic infections (OIs) with increased supply and higher levels of procurement and rollout of a number of diagnostic, preventative, and treatment commodities.

For CLHIV, treatment coverage remains low, with only 52 percent of CLHIV globally on ART compared to 76 percent of adults.[ii] As a result, AHD continues to affect this population disproportionately, with children accounting for 15 percent of AIDS-related deaths despite representing only four percent of PLHIV.[xx] To address these remaining gaps in AHD care and eliminate deaths, it is necessary for national programs to identify children, link and retain them in care, and continue to scale up the lifesaving interventions included in the WHO AHD package of care, including STOP guidance for children with HIV.[xlii]

Rollout of same-day CD4 testing picks up speed with early adopters catalyzing interest and generating evidence

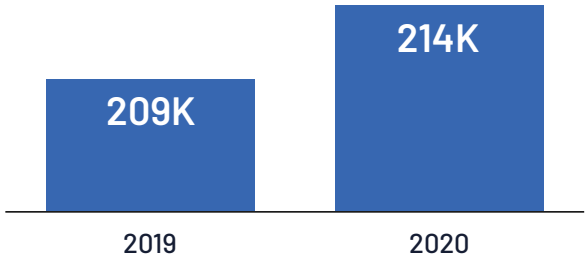
The gateway to the full AHD package of care is CD4 testing, which indicates if a client has AHD. To this end, the VISITECT® CD4 Advanced Disease test ("VISITECT®")

provides same-day CD4 results at a cost of US$3.98 (EXW).[xliii] In 2020, CHAI and Unitaid initiated the Early Market Access Vehicle to expand access to VISITECT® and catalyze early interest. Through this work, 44 countries have introduced VISITECT® and over 480,000 tests have been ordered as of October 2022.[xxx] Adoption is ongoing and further rollout could help ensure prompt access to AHD diagnosis and rapid initiation in AHD care where necessary.

Early diagnosis and treatment of opportunistic infections remains critical as deaths from TB among PLHIV rise for the first time in a decade

Prevention, diagnosis, and treatment of OIs is critical to eliminating AIDS-related deaths. Tuberculosis (TB) is the most common OI among PLHIV, accounting for roughly one in three AIDS-related deaths despite largely accessible treatment options and expanding availability of short-course preventative therapy.[xliv] For the first time in over a decade, TB deaths among PLHIV increased in 2020 [Figure 13]. Similarly, ART coverage among PLHIV with incident TB decreased to 42 percent in 2020 compared to 49 percent in 2019, the first decline since 2004, likely due to COVID-related disruptions.[xx]

Figure 13: Global TB Deaths among PLHIV[xx]



In light of these worrying trends, early TB diagnosis and treatment are even more essential to preventing further deaths. Underscoring this, a study from Thailand found that one in three people in their first year on ART had incident TB. However, following this first year, incidence decreased significantly until reaching levels comparable to the general population after ten years.[xlv] Given this increased rate of TB among PLHIV newly linked to care, timely TB diagnosis for clients (re-)initiating care should remain a focus.

Supply and price improvements aim to increase availability of rifapentine-based products used in TB preventative therapy

Implementation of rifapentine (RPT)-based TB preventative therapy (TPT) continues to scale up following the easing of supply challenges experienced over the past few years. In May 2022, the Global Fund's Expert Review Panel recommended Lupin's Isoniazid/Rifapentine (300/300 mg) tablets, a complete 3HP regimen, adding a second supplier to the market (alongside Macleods). Lupin's RPT (300 mg) single tablets, used for both 1HP and 3HP, also received Global Fund's Expert Review Panel approval, which is valid until May 2023.[xlvi] In addition to this new supplier, Macleods continues to increase production capacity for their INH/RPT (300/300 mg) tablets.[xlvii]

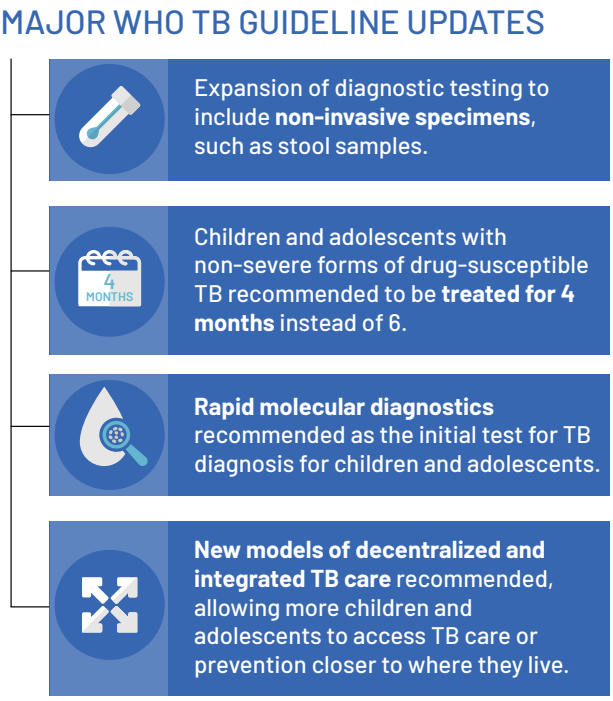
To improve access further, Unitaid, the Aurum Institute, CHAI, and MedAccess announced two new agreements in Aug. 2022 to lower the price of these RPT-based formulations in 138 LMICs.[xlviii] Through the agreements, RPT/INH (300/300 mg) tablets will now be available at a ceiling price of US$14.25 (EXW) from both Macleods and Lupin, and RPT (300 mg) single tablets will be available from Lupin for US$33.90 (EXW) per 100 tablets.[xlviii] These agreements, as well as the improved supply capacity, represent important steps in increasing access to these critical therapies. However, in addition to these supply improvements, further work is still needed to ensure that the medicines reach PLHIV as part of the AHD package of care.

New WHO recommendations aim to improve TB diagnosis and management, particularly among children

In 2021, the WHO released updated consolidated guidelines on TB, which include a number of new recommendations. Among these, the WHO now strongly recommends rapid molecular testing, such as the GeneXpert, for TB in all HIV-positive inpatients in settings where TB prevalence is higher than 10 percent.[xlix] The WHO based their recommendation on results from a recently released meta-analysis demonstrating that the existing four symptom screening tests for TB have suboptimal accuracy in HIV-positive inpatients.[l]

The WHO also released updated guidelines on the management of TB specifically in children and adolescents [Figure 14]. Children remain a focal population for TB control, with children under 15 years of age representing about 11 percent of all people with TB globally.[li]

Figure 14: Major Highlights from Updated WHO Consolidated Guidelines on the Management of TB in Children and Adolescents[li]



See full guidelines for more information

Several recent advances have significantly shortened the time needed to treat TB infection, which is now possible in as little as one or three months for drug-susceptible TB, or four to six months for most forms of drug-resistant TB. Reflecting this, in May 2022, the WHO issued rapid guidance recommending a shorter six-month, all-oral treatment regimen for multi-drug resistant tuberculosis as the new standard of care.[lii]

In July 2022, results from the TB-PRACTECAL clinical trial presented at the AIDS 2022 conference confirmed that this short-course regimen is effective and safe in PLHIV.[liii] In the study, only 28 percent of HIV-positive TB patients experienced unfavorable outcomes in the experimental arm compared with 40 percent in the standard-of-care arm. While PLHIV did have a higher rate of unfavorable outcomes compared to HIV-negative participants, the small sample size of 153 HIV-positive participants makes comparison between the groups difficult.

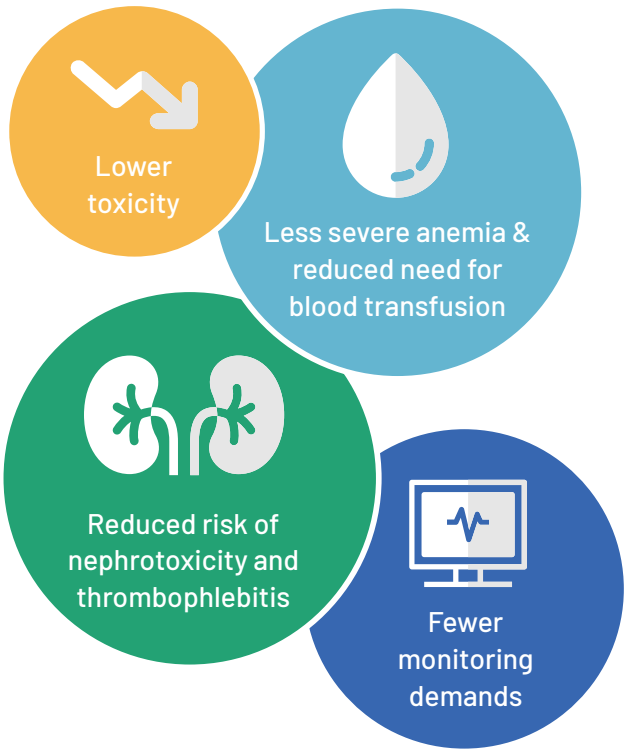
Access to these shorter treatment regimens remains limited in many LMICs, with multiple steps before widespread introduction can occur, including the development of affordable fixed-dose combinations (FDCs) and rapid national-level registration for new products.

Updated WHO guidelines drastically simplify cryptococcal meningitis treatment for PLHIV

Cryptococcal meningitis (CM), another common OI among PLHIV, is responsible for an estimated 19 percent of all AIDS-related deaths.[liv] With the aim of improving CM care, in July 2022 the WHO released updated guidelines for diagnosing, preventing, and managing cryptococcal disease among adults, adolescents, and CLHIV.[lv]

Among other updates, these new guidelines strongly recommend a single high dose of liposomal amphotericin B (L-AmB) as part of the preferred induction regimen for the treatment of CM in PLHIV. Results from the AMBITION trial showed that this simplified regimen of a single high dose of L-AmB paired with other standard medicines (flucytosine and fluconazole) is as effective as the previous WHO standard of care with amphotericin B deoxycholate (AmB-d). Further, this new regimen offers a number of client and provider benefits [Figure 15]. However, multiple steps, including healthcare worker training and updating monitoring and evaluation systems, are required to ensure successful guideline adoption and behavior change.

Figure 15: Key Benefits of L-AmB



In addition to these benefits, a modelling analysis presented at the Conference on Retroviruses and Opportunistic Infetion (CROI) 2022 found that despite increased treatment costs, L-AmB is cost-effective compared to AmB-d due to the decreased mortality risk and potential for less hospitalization time. The study found that there was an incremental cost effectiveness ratio of US$128 per life year gained. Further, these results were similar across five country settings in east and southern Africa, and fell to US$80 per life year gained in a potential real-world implementation scenario, indicating increasing cost-effectiveness.[lvi]

However, there are pricing disparities across countries despite a public access agreement from Gilead. For example, while the cost of Gilead's L-AmB in many LMICs is US$16.25 (EXW) per vial, in some countries, such as Brazil, costs can exceed US$300 (EXW), which negatively affects access.[lvii, lviii]

Despite these challenges, adoption of L-AmB, as well as flucytosine (5FC), another key drug used in induction treatment, is ongoing as countries begin to roll out the WHO AHD package of care [Figure 16].

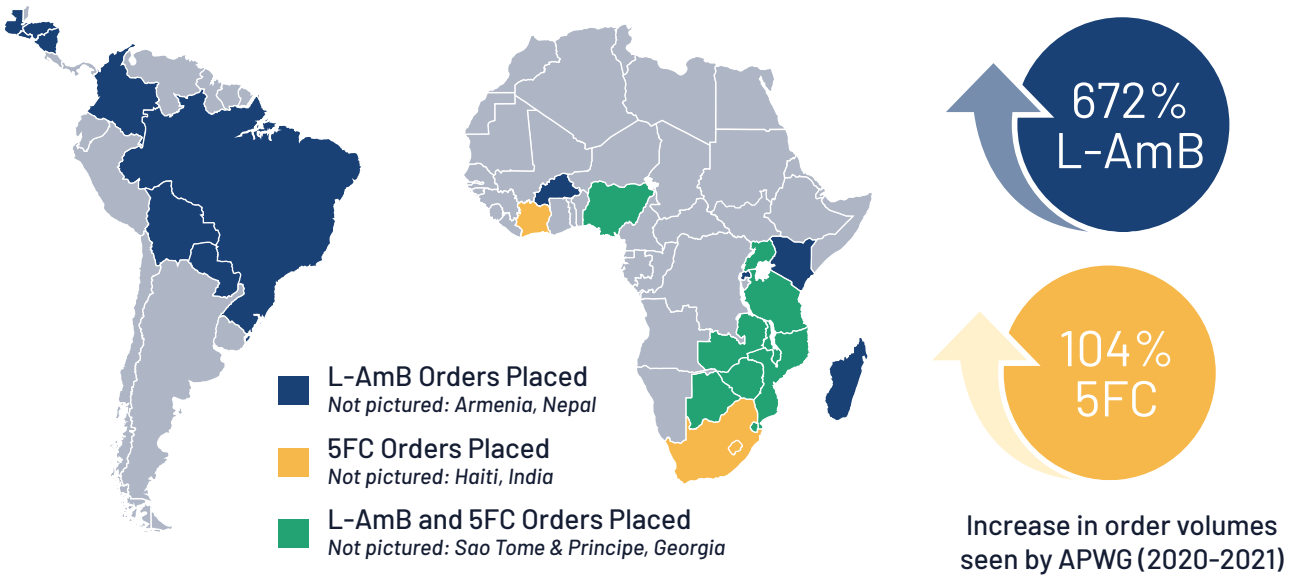
In parallel, improvements in supply of both 5FC and L-AmB continues to ramp up. Sun Pharma received US FDA approval for L-AmB in Dec. 2021, making them the first generic supplier and the second stringent regulatory authority-approved supplier of L-AmB.[lix] They are currently working to develop an LMIC pricing and access strategy.

Viatris received approval for a new 5FC active pharmaceutical ingredient (API) source in July 2022, allowing them to reinitiate supply. The WHO also approved an extension of the shelf life of the Viatris 5FC product, which could reduce wastage, enable more sustainable access, and alleviate supply issues.[lxi] Strides has also now commercialized 5FC for LMICs. These improvements in supply capacity will support continued introduction of these critical products to save lives.

Continued efforts needed to achieve global targets and eliminate AIDS-related deaths

Increasing ART coverage has led to huge reductions in AIDS-related deaths since their peak in 2005, and recent improvements in the supply of AHD commodities have further set the stage for continued reductions in mortality. However, to achieve the global target of under 250,000 AIDS-related deaths by 2025 and an end to the epidemic by 2030, efforts cannot let up.[lxii] Through the continued rollout of the AHD package of care, as well as ongoing efforts to improve linkage and retention in care, countries can ensure that people with AHD are rapidly identified and linked to testing, treatment, or preventative therapies for OIs, ending these preventable deaths.

Figure 16: 5FC and L-AmB Adoption Map[lx]

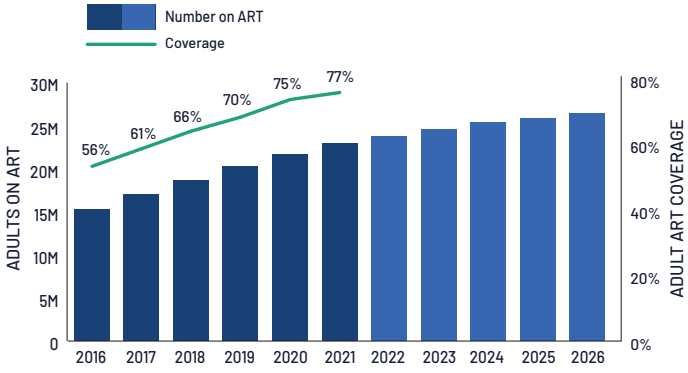


TREAT RIGHT WITH OPTIMAL ARVs FOR ADULTS

Nearly 28 million adults on ART globally in 2021, with almost 23 million in GA LMICs

Annual treatment (re-)initiations continue to rise with an additional 1.5 million adults on ART globally in 2021 compared to 2020 [Figure 17]. However, the rate of increase is slowing, with only a 5.7 percent increase between 2020 and 2021 compared to a 7.3 percent and 8.9 percent increase between 2019-2020 and 2018-2019, respectively.[ii] While a slowing growth rate is expected given expanded ART coverage and increasing difficultly identifying the remaining undiagnosed PLHIV, ensuring all PLHIV have access to treatment remains a priority. In addition to this slowing globally, national programs, partners, and donors must address regional and population-specific gaps in access to ART.

Figure 17: Adults on ART and Coverage in GA LMICs[xli]



Long-running paradigm of well-defined lines of therapy beginning to shift with DTG used in all lines and DRV now used in second- and third-line

Following a public health approach, HIV treatment in LMICs has long been classified into lines of therapy. Each line of therapy has historically been defined by the drug classes used, with clients progressing through first-, second-, and third-line after experiencing treatment failure. These traditional lines of therapy are beginning to change with the introduction of DTG in first- and second-line (in addition to its previous use only in third-line) and DRV/r now used in second-line in addition to third-line. This shift necessitates a change in how national programs and partners manage and track cohorts of PLHIV on ART.

As programs continue to roll out DTG and DRV/r, and with new classes of ARVs on the horizon, the global community needs to revisit this traditional structure to ensure it is fit for purpose. Classifying clients based on prior exposure, such as integrase strand transfer inhibitor- (INSTI) or protease inhibitor (PI)-exposed, may be a more relevant way to understand cohorts of PLHIV on ART moving forward (aligning more with the orthogonal approach articulated in the recent CADO-4 report). However, given the newness of this shift, this report will still primarily reference the traditional lines of therapy, but some data will be presented as combined across lines when data inconsistencies or unavailability do not allow for separation into lines of therapy.

Over 80 percent of all PLHIV on ART in GA LMICs take DTG-based regimens, but further optimization away from sub-optimal PIs still needed

Over 80 percent of first- and second-line regimens in GA LMICs now include DTG [Figure 18].[xli] CHAI expects this to increase and begin to stabilize around 88 percent in 2023, with a slight rise in the use of PIs as some clients begin to experience treatment failure on DTG. However, the introduction of pipeline products, such as lenacapavir, is possible toward the tail end of the forecast and may significantly change the treatment landscape (more on page 23).

The paradigm shift in the conceptualization of lines of therapy has implications for client sequencing and for reporting and monitoring and evaluation. However, data systems in many countries cannot currently differentiate between DTG use in first- and second-line, with many second-line clients now incorrectly reclassified as first-line following a transition from PIs to DTG. As such, monitoring second-line optimization with DTG is challenging. A CHAI analysis based on historic second-line (2L) trends found that there were ~130,000 fewer 2L clients reported in 2021 in GA LMICs than expected, suggesting that these clients were likely reclassified when transitioned to DTG. After accounting for this, CHAI estimates that there may be approximately 500,000 clients on DTG in 2L [Figure 19].[xvii]

Further supporting the WHO's recommendations to optimize away from PIs and use DTG in 2L, a recent systematic review and meta-analysis found that PI use during pregnancy was associated with higher rates of small and very small for gestational age outcomes, although not for pre-term birth or other perinatal outcomes.[lxiii]

Figure 18: Adult INSTI/NNRTI/PI Use in GA LMICs[xli]

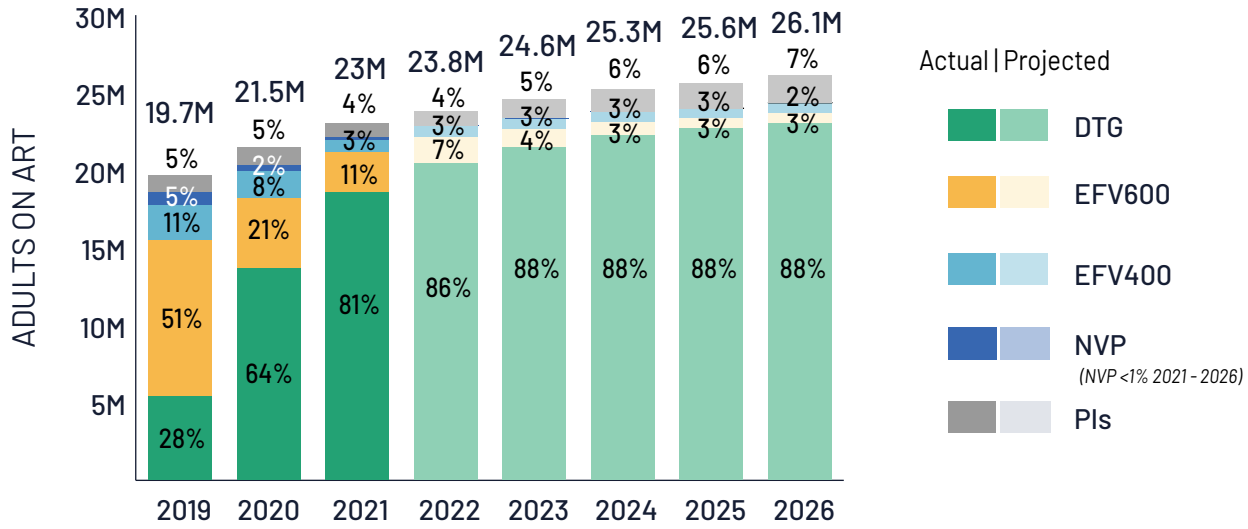


Figure 19: Adult Second-line Regimens Over Time[3]

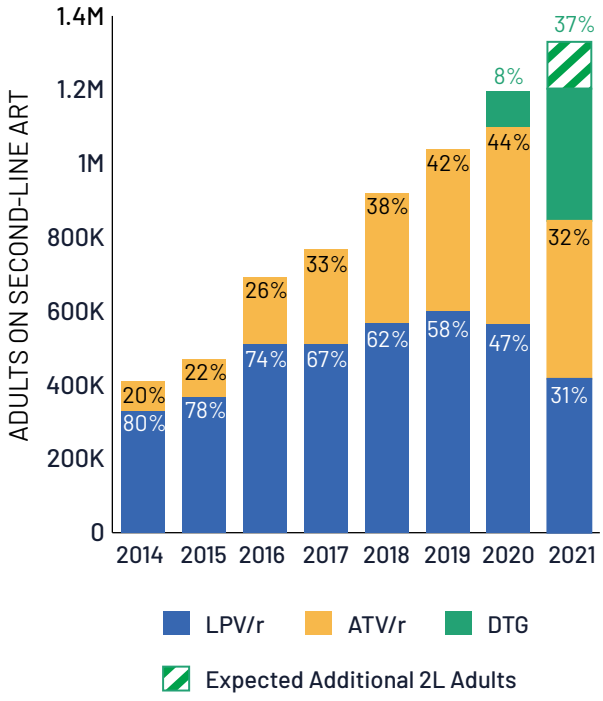
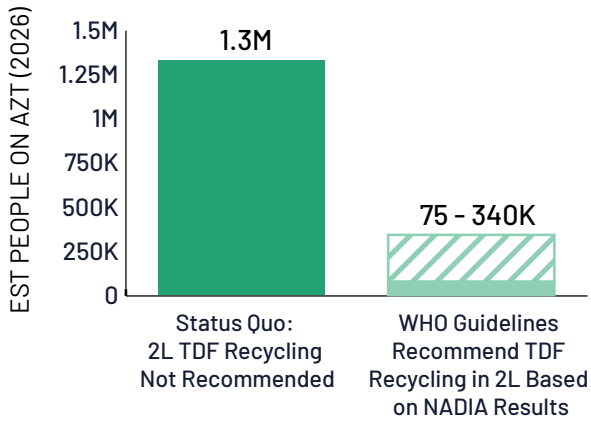


Figure 20: Potential Impact of TDF Recycling on Adult NRTI Backbone Use in 2026[xvii]



96-week results from NADIA and 48-week results from VISEND show continued efficacy when continuing TDF use in 2L after 1L failure

Two trials in SSA are investigating whether switching clients from TDF to AZT following first-line failure (per current WHO guidelines) is clinically necessary, given that retaining TDF over AZT would impart clinical, cost, and administration benefits.

96-week results from the NADIA trial continue to show that recycling TDF in second-line after initial failure on a TDF-containing regimen is superior to switching to AZT, and that DTG is non-inferior to DRV/r.[lxiv] Similarly, 48-week results from the VISEND trial found that remaining on TDF or TAF was non-inferior to switching to AZT following first-line failure.[lxv]

To date, the WHO has not updated their guidelines on TDF recycling, although some countries including Cambodia, Laos, and Tanzania have already begun recycling TDF in second-line. CHAI modelling shows that widespread adoption of TDF recycling would have a dramatic impact on AZT use in GA LMICs [Figure 20], which already accounts for a relatively small proportion of nucleoside reverse transcriptase inhibitor (NRTI) use (4 percent of NRTIs in 2021 compared to 93 percent TDF and 3 percent ABC).[xli] However, it is critical to ensure an uninterrupted global supply of AZT to account for clients who may be intolerant to TDF.

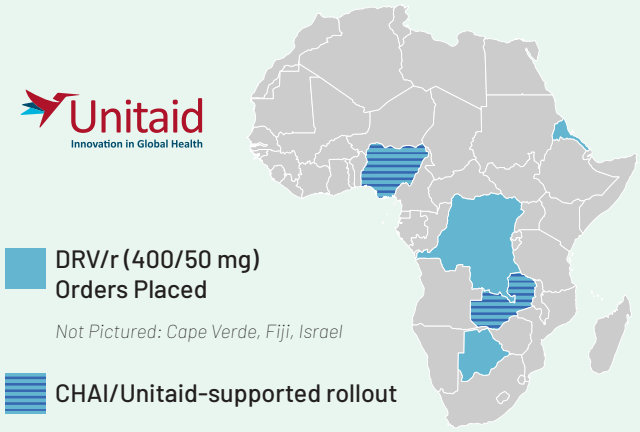
Increased use of TAF, or introduction of the dual regimen 3TC/DTG may impact NRTI use, but broad use of these regimens for now looks unlikely beyond specific sub-populations.

[3] Given changes in country-level regimen reporting, some adults on a DTG-based regimen are included in both Figure 17 and Figure 18.

Generic fixed-dose darunavir-ritonavir (DRV/r 400/50 mg) introduced in sub-Saharan Africa for the first time

For the first time, national programs in SSA are introducing darunavir-ritonavir, the best-in-class PI commonly used in high-income markets, in second-line treatment [Figure 21].[lxvi] This introduction begins to remedy a 16-year access inequity between high-income and low-and middle-income countries. This introduction follows the 2021 announcement of a CHAI- and Unitaid-negotiated pricing agreement with Hetero Labs making generic DRV/r (400/50 mg) available at US$17.50 per pack (EXW), slightly less than LPV/r.[lxvii]

Figure 21: DRV/r (400/50 mg) Adoption Map



Supported by a Unitaid-funded catalytic procurement, in July 2022 Nigeria and Zambia started introducing DRV/r (400/50 mg) for clients experiencing DTG-based treatment failure or intolerance. To date, broader uptake has been limited given that the WHO still lists DRV/r as an alternative second-line regimen, and that PEPFAR is unable to procure Hetero's DRV/r (400/50 mg) product given that it is WHO-prequalified but does not have US FDA tentative approval. With an affordable, fixed-dose combination of DRV/r rolling out in LMICs, treatment advocates are hopeful that the WHO will promote DRV/r to a preferred 2L option.

KEY BENEFITS OF DRV/r

- High barrier to resistance
- Improved viral suppression compared to LPV/r
- Better tolerability compared to LPV/r and ATV/r
- Can be reused in 3L at a higher dose
- Slightly cheaper than LPV/r

BARRIERS TO BROADER ADOPTION

- 'Alternative' status in WHO guidelines
- Inability for PEPFAR to procure with no US FDA-approved supplier
- Other 2L optimization priorities (e.g., DTG)

> *"We call on the WHO to immediately update its guidelines to include DRV/r as the preferred protease inhibitor for use in second-line."*
>
> *Community Position Statement on DRV/r*[lxviii]

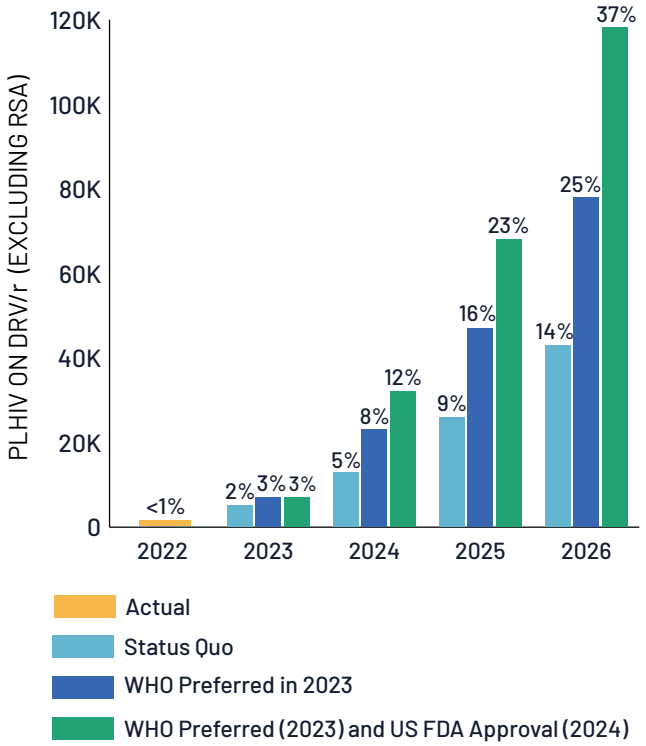
Broader second-line DRV/r uptake dependent on several enabling factors

CHAI modelled several scenarios exploring potential uptake following WHO promotion of DRV/r to preferred status and if the US FDA tentatively approved DRV/r [Figure 22]. Given current tender cycles, Figure 22 excludes uptake in South Africa.

If DRV/r were to receive US FDA tentative approval, it would likely result in the highest uptake as that would enable PEPFAR to procure the product, and PEPFAR's 2022 Country Operational Plan Guidance lists DRV/r as preferred following failure or intolerance to TLD. However, WHO recognition of DRV/r as the best-in-class PI would also likely motivate national programs to adopt and roll out DRV/r.

To support broader adoption, CHAI developed several resources, including FAQs, product profiles, and customizable healthcare worker training slides and prescribing algorithms, which are hosted on CHAI's HIV New Product Introduction Toolkit (www.newhivdrigs.org).

Figure 22: Generic DRV/r Uptake Scenarios (as a percentage of LPV/r use)[xvii]

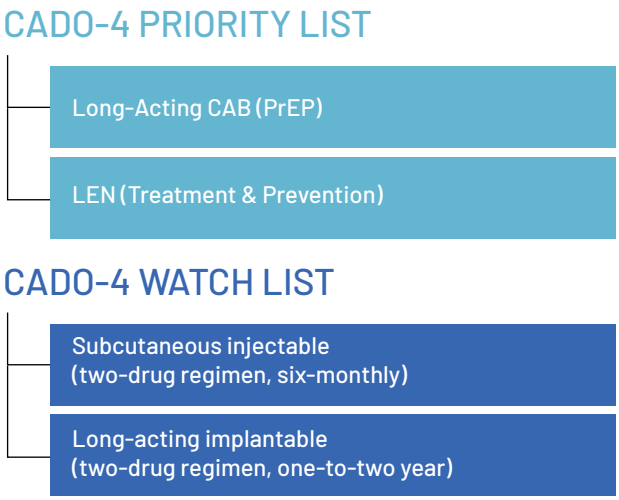


Global HIV treatment priorities heavily feature long-acting products with novel delivery mechanisms

Development of the next generation of ART products is underway, with a heavy focus on long-acting molecules and novel delivery systems such as injections and implants that are set to change ART delivery. These new products have the potential to significantly improve clinical outcomes, with expected improvements in user acceptability, adherence, and viral suppression.

The fourth WHO-convened Conference on ARV Drug Optimization (CADO-4), a meeting of global HIV experts held at the end of 2021, outlined a set of priority and watch-list products for adult treatment and prevention [Figure 23, full report available here]. Long-acting products dominate both lists, signaling a large shift in the future of HIV treatment and prevention.[lxix]

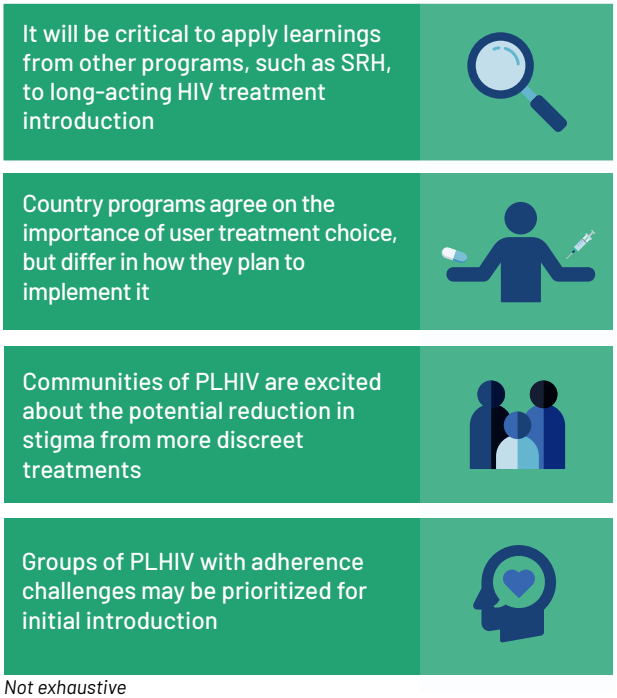
Figure 23: CADO-4 Priority and Watch Lists[lxix]



However exciting these new products are, the systems and structures in place today for delivering HIV treatment are designed around delivery of daily oral ART, and with a public health approach in mind. While these long-acting pipeline products represent an exciting new frontier in HIV treatment and prevention, their introduction will require radical new approaches to all aspects of HIV service delivery to realize their full potential. Additionally, voluntary licensing is a critical enabler of broad access in LMICs, and at the time of publication none of the pipeline products have been licensed with the Medicines Patent Pool (MPP).

CHAI, in partnership with ministries of health (MOH) in Nigeria, Kenya, and South Africa, conducted a long-acting treatment landscape assessment to evaluate country readiness to introduce long-acting HIV treatments. The assessment included desk research, MOH and key opinion leader interviews, and consultations with communities of PLHIV. The primary purpose was to understand enablers and barriers to introduction of these products as well as MOH goals and community preferences for long-acting treatments. Figure 24 contains additional details from this assessment, and CHAI is planning on broader dissemination later in Q4 2022.

Figure 24: High-Level Long-Acting Treatment Landscape Assessment Findings[xvii]



Not exhaustive

Implementation data from first approved injectable ART, CAB+RPV, will be critical to generate evidence for future rollout of more optimal injectables

The US FDA first approved *Cabenuva* (CAB+RPV), ViiV and Janssen's injectable ART, in Jan. 2021 as a monthly injection.[lxx] This was updated to every eight weeks in Feb. 2022, and three-year data from the ATLAS-2M trial continue to show that bi-monthly dosing is non-inferior to monthly dosing.[lxxi, lxxii] In Mar. 2022, the US FDA further expanded the label to include treatment of virologically suppressed adolescents at least 12 years of age and at least 35kg, and to make oral lead-in therapy with CAB and RPV tablets optional.[lxxiii, lxxiv]

Although not an optimal product in LMICs for several reasons, including cold chain requirements, the lack of cross treatment for Hepatitis B, RPV's low barrier to resistance, and others, demonstration projects generating learnings around implementation of long-acting injectable ART will be critical to enable rapid scale-up of other, more optimal injectables once available.

The adult treatment pipeline has seen both progress and setbacks over the past year, highlighting the challenges faced in drug development

Lenacapavir (LEN) and islatravir (ISL) are two of the most promising pipeline molecules for adult treatment and prevention, with multiple formulations at different stages in the development pipeline [Figure 25].

However, development setbacks for both molecules over the past year show how volatile the drug development process can be and highlight the importance of taking a portfolio approach to drug development and prioritization.

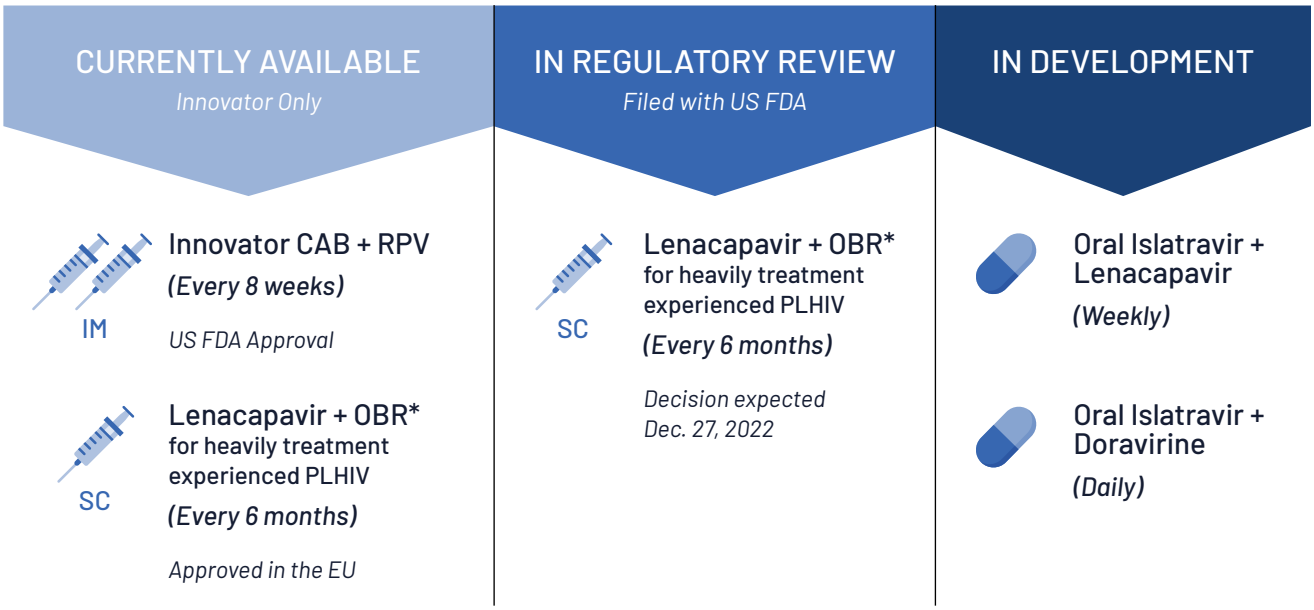
New formulations and long-acting ARVs expected to usher in era of client choice for HIV treatment, but gaps in understanding preferences remain

With recent approvals of long-acting injectable ART, the world now has a new way to treat HIV aside from daily oral pills. A future is now possible where clients have a choice in the way that their HIV is treated, rather than being a passive recipient of treatment in a public health approach. Attendees at the CADO-4 and PADO-5 meetings recognized this paradigm shift and user choice and preferences were part of the discussions.

> *"Community research on end-user perspectives and values and preferences in various regions is needed."*
>
> *CADO-4/PADO-5 Meeting Report*[lxix]

CHAI conducted a literature review to understand the existing body of evidence related to HIV service delivery and treatment product preferences among PLHIV in LMICs. The review found significantly fewer studies looking at preferences for product formulations compared to service delivery.

Figure 25: HIV Treatment Pipeline



*Optimized Background Regimen

LENACAPAVIR

LEN is Gilead's first-in-class capsid inhibitor with potential uses in both HIV prevention and treatment as a long-acting product. Data presented at CROI 2022 from the CAPELLA and CALIBRATE trials showed that LEN, combined with an optimized oral background regimen, produced high-levels of viral suppression in both treatment-naïve and heavily treatment-experienced PLHIV.[lxxv, lxxvi]

In June 2021, Gilead submitted a new drug application to the US FDA for LEN use among heavily treatment experienced PLHIV. However, in Dec. 2021, the US FDA placed a clinical hold on LEN due to compatibility issues between LEN and the borosilicate vials in which it is packaged.[lxxvii] Gilead submitted data to support use of a different vial and the US FDA lifted the clinical hold in May 2022, allowing all research activities to resume.[lxxviii] With the hold lifted, Gilead resubmitted their application to the US FDA in June 2022 with a decision expected by Dec. 27, 2022.[lxxix]

In Aug. 2022, the European Commission granted marketing authorization for injectable LEN for treatment of HIV infection in the European Union, to be used in combination with other antiretrovirals in adults with multi-drug resistant HIV infection for whom it is otherwise not possible to construct a suppressive regimen.[lxxx]

There is also interest from the community in a potential combination of injectable LEN+CAB for treatment, although research on the efficacy and safety of this potential regimen is needed.

At the time of publication, Gilead has not granted a voluntary license for LEN via the MPP.

ISLATRAVIR

Development setbacks have plagued ISL, Merck's first-in-class nucleoside reverse transcription translocation inhibitor (NRTTI) with long-acting potential, since late 2021.

Despite positive data from the ILLUMINATE SWITCH A and B trials showing that ISL and doravirine produced a viral response comparable to existing ART in virally suppressed PLHIV, the US FDA placed a partial clinical hold on ISL in Dec. 2021 based on decreases in total lymphocyte and CD4+ T-cell counts in some trial participants.[lxxxi, lxxxii] The hold applied to all clinical trials studying ISL for prevention and treatment.

In response to these holds, in Sep. 2022 Merck announced the beginning of new Phase III studies investigating daily oral ISL and doravirine for treatment of both treatment-naïve and experienced clients, but using a lower dose of ISL. The Phase II study investigating a weekly oral combination of ISL and Gilead's LEN will resume using a lower dose of ISL, and Merck has discontinued the studies investigating ISL for PrEP.[lxxxiii]

The future of ISL is uncertain, and given the initial clinical holds the CADO-4 lists do not include ISL as a priority product, and the watch list inclusion of ISL includes a specific note about the clinical hold.[lxix] At the time of publication, Merck has not granted a voluntary license for ISL via the MPP.

Further, product preference research in LMICs was particularly limited compared to research among PLHIV in high-income countries. Additional findings are summarized in Figure 26, and it is clear that more LMIC-focused treatment product preference research is critical considering the pipeline of products.

Figure 26: CHAI Long-Acting Treatment Preferences Literature Review Findings[lxxxiv]

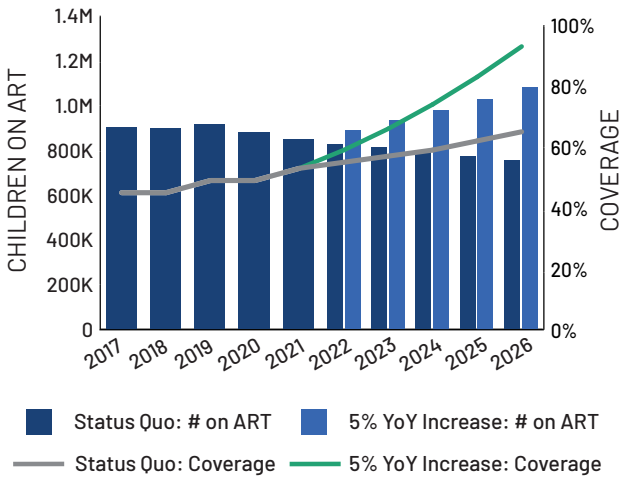
> **"For research on long-acting products, we need community involvement.** We need to make sure ALL are involved – women, men, adolescents, children, pregnant and breastfeeding women. Pregnant and breastfeeding women cannot be left behind."
>
> *-Community member at June 2022 Kampala meeting on CAB-LA access*

TREAT RIGHT WITH OPTIMAL ARVs FOR CHILDREN

The number of children on ART in 2021 fell for the second year in a row, raising concerns about whether the global HIV response is leaving children behind

Despite progress over the past few years, pediatric treatment outcomes are still unacceptably poor and lag far behind those of adults. For the second year in a row, in 2021 the global number of CLHIV on ART decreased with only 880,000 of the 1.7 million CLHIV on lifesaving treatment, representing only a 52 percent coverage rate [Figure 27]. Without major investments in improved case finding and retention, more and more children will be left off lifesaving treatment and die preventable deaths.[ii]

Figure 27: Actual and Forecasted Children on ART and Pediatric ART Coverage in GA LMICs



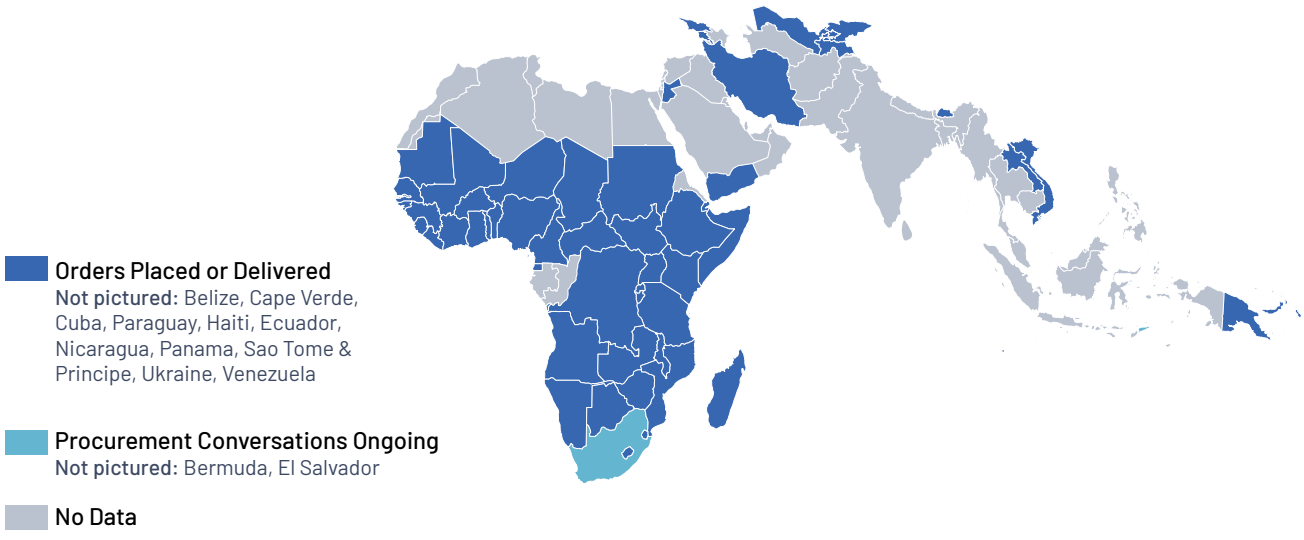
In addition, 160,000 children were newly infected with HIV in 2021 and viral load (VL) suppression among all CLHIV is still only at 40 percent.[i] As a result, children account for 15 percent (98,000) of AIDS-related deaths despite making up only four percent of all PLHIV.[ii] COVID-19 has exacerbated many of the issues contributing to these trends, and it is clear that the pediatric HIV response is going in the wrong direction. A concerted focus from all global partners, especially donors, is needed to ensure that we do not leave children behind in the global HIV response.

Pediatric DTG rollout continues across over 60 countries, but pre-transition viral load requirements have slowed uptake in some programs

Following the record-setting tentative approval of generic dolutegravir 10mg dispersible and scored tablets (pDTG) in 2020, over 60 countries have initiated procurement of this optimal pediatric product [Figure 28].[lxxxv]

At the time of publication, CHAI estimates that country programs have transitioned over 100,000 children to pDTG, with many more on other age-appropriate formulations of DTG such as DTG 50mg singles and TLD.[xxx] However, pre-transition VL testing requirements in some countries have slowed the transition to this optimal product and have left some children on sub-optimal therapies such as LPV/r. Although considered a good practice, the WHO has consistently stated that VL testing should not be a requirement for pDTG transition.

Figure 28: Pediatric DTG Adoption Map, as of Q3 2022[lxxxv]

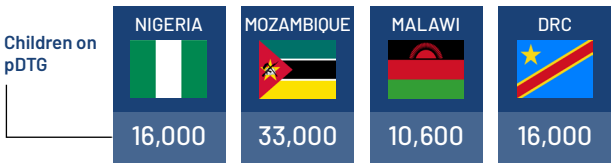


"Viral load testing is not considered a precondition to undertaking programmatic or individual transition to DTG-based regimens."

Transitioning to the 2021 optimal formulary for antiretroviral drugs for children: implementation considerations[lxxxvi]

In countries that do not require VL testing to transition to pDTG, such as Malawi and Nigeria, we have seen incredibly rapid scale-up [Figure 29].

Figure 29: Country Highlights from pDTG Scale Up[xxx]

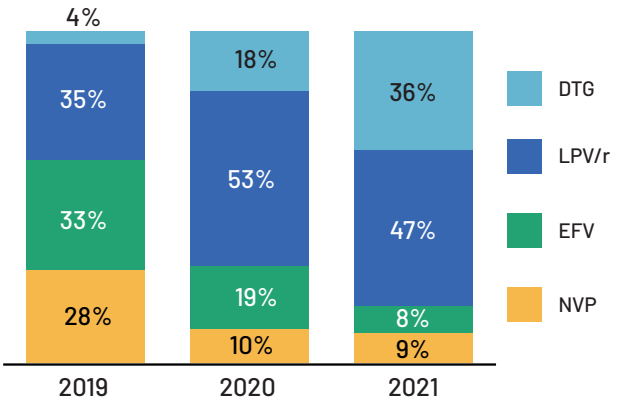


The South African Health Products Regulatory Authority (SAHPRA) approved generic pDTG from both Viatris and Macleods in June 2022, slightly after the July 2022 – June 2025 tender was adjudicated.[lxxxvii] As such, the initial tender award did not include pDTG, but the National Department of Health is planning a supplementary tender to be released later in 2022 to include pDTG to enable introduction in early 2023.

SAHPRA also approved Cipla's ABC/3TC/LPV/r "4-in-1" granules, although these have not yet been approved by the US FDA or received WHO prequalification, which means they cannot be procured with most donor funds.[lxxxvii] The 4-in-1 may help to simplify supply chains and administration compared to existing LPV/r formulations, but LPV/r is not the WHO-preferred option for CLHIV. Based on data from the ODYSSEY trial, it is expected that fewer than five percent of CLHIV will be intolerant to DTG and need an LPV/r-based formulation.[lxxxviii]

In 2021, CHAI estimates that 36 percent of children on pediatric treatment backbones were on DTG-based regimens, based on data from 20 LMICs representing 73 percent of CLHIV on ART globally [Figure 30].[xvii] Although this number is increasing, delayed rollouts in high-volume countries such as South Africa are driving down this global figure.

Figure 30: Estimated Pediatric Third-Position Drug Use in GA LMICs[xvii]



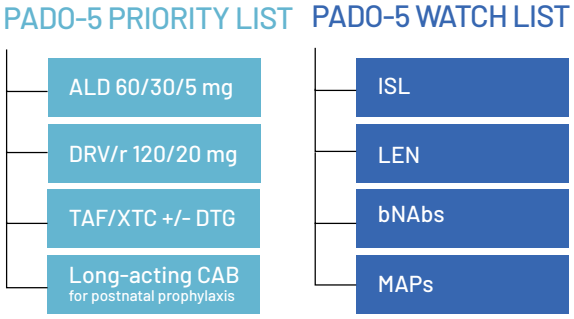
Continuing to transition children to pDTG, without VL requirements and even if it necessitates some LPV/r wastage, should remain a top priority for country programs to begin to bridge the gaps between adult and pediatric treatment outcomes.

The PADO-5 meeting outlined future pediatric HIV treatment priorities, with many in advanced stages of development

The fifth Pediatric ARV Drug Optimization meeting (PADO-5) occurred at the end of 2021 and established updated priorities for pediatric HIV treatment and post-natal prophylaxis [Figure 31]. Attendees also mapped out potential use cases for new formulations (e.g., microarray patches, implants) across different age groups from neonates to adolescents. The full meeting report is available here.[lxix]

With the support of Unitaid, CHAI is working with both generic and innovator ARV manufacturers to accelerate development of three products on the PADO-5 priority list.

Figure 31: PADO-5 Priority and Watch Lists[lxix]



FIXED-DOSE PEDIATRIC ABC/3TC/DTG (pALD)

A fixed-dose combination of ABC/3TC/DTG would provide the WHO-recommended first-line regimen for children in one convenient pill. In March 2022, the US FDA approved ViiV's dispersible FDC of ABC/3TC/DTG (60/30/5 mg) for the treatment of children between 10-24.9kg.[lxxxix] ViiV is planning a filing by the end of 2022 to expand the weight eligibility down to 6kg, and CHAI is working with ViiV and generic manufacturers Viatris and Aurobindo to develop generic versions with filings expected in Q1 2023. Depending on review timelines, generic pALD may be tentatively approved in mid-2023 and ready for introduction into treatment programs.[xxx]

Country programs should not wait for the development and approval of pALD but should continue to scale up pDTG to ensure that children have immediate access to the WHO-recommended treatment regimen, and to move children away from sub-optimal options such as LPV/r, EFV, and NVP. However, with expected approval in mid-2023, country programs should begin to plan for pALD introduction.

PEDIATRIC DRV/r (pDRV/r)

CHAI is also working with generic partner Laurus Labs to develop a pediatric fixed-dose tablet of darunavir/ritonavir for use in second-line or for children who are intolerant to DTG, with development on track and progressing well.[xc] Development of pDRV/r is part of the UNIVERSAL project, coordinated by Penta and supported by CHAI with funding from Unitaid.[xci]

Although likely representing a small market, this is a critical product to replace LPV/r and remedy an access issue between high- and low- and middle-income countries.

PEDIATRIC TAF (pTAF)

Given the bone and renal toxicity concerns surrounding TDF in growing children, a TAF-based regimen, either as a dual with 3TC or FTC or additionally combined with DTG as a triple FDC, remains a PADO priority as a safer, highly effective regimen.[lxix] A TAF-based regimen will also be useful for children intolerant to ABC.

CHAI and the Penta ID network are collaborating with two generic manufacturers to accelerate generic development of dispersible pediatric TAF/FTC. As part of this arrangement, Penta is supporting pharmacokinetic modelling and clinical study development as part of the UNIVERSAL project and CHAI is leading generic product development with funding from Unitaid.[xci]

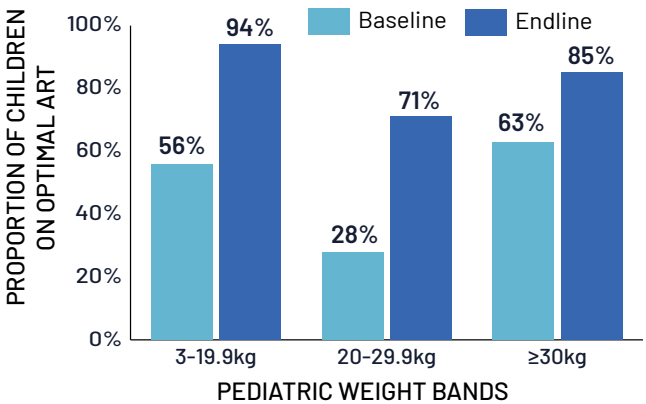
Improving pediatric quality of care goes beyond just optimal products; comprehensive strategies and data are needed to ensure high-quality care

Although introducing optimal treatment products is a key component of improving care quality and ensuring viral suppression, country programs must also have supportive systems in place to support correct product use, deliver accurate and high-quality care, and accelerate uptake.

In particular, understanding a country's pediatric weight band distribution is critical to both accurately quantify ARV needs as well as ensure that facilities are prescribing age- and weight-appropriate ARVs to children. To address this, under the FASTER project funded by PEPFAR through the CDC, in partnership with ministries of health in Nigeria, Tanzania, Uganda, and Zambia, CHAI supported the development and introduction of facility level job aids, tools, and revised monitoring and evaluation processes to better document a child's weight at each visit. Optimal ART uptake at 245 FASTER priority facilities in Nigeria, Tanzania, Uganda, and Zambia increased across all weight bands from baseline to endline [Figure 32].

To aggregate this weight-based ART data at the facility and eventually national level, FASTER built and strengthened pediatric and adolescent quality of care dashboards in Nigeria, Uganda, and Tanzania. These dashboards also monitor additional pediatric and adolescent-specific quality indicators such as VL suppression, and can generate data visualizations and line-lists of clients requiring follow-up to inform clinical decision-making. Country specific, nationally scaled action plans and toolkits developed with FASTER support informed dashboard indicator development, and further aim to improve the quality of care delivered to children. These customized packages of care address specific country gaps in services, including identification and linkage, and aim to capacitate healthcare workers and caregivers to ensure the best possible outcomes for CLHIV.

Figure 32: Improvements in Optimal ART Uptake at FASTER Sites[xcii]



TREAT RIGHT WITH APPROPRIATE TREATMENT MONITORING

After stagnating during the first year of COVID-19, viral load testing volumes in LMICs rebounded significantly in 2021

VL testing volumes in LMICs hovered around 21 million tests per year in 2019 and 2020, with COVID-19 significantly impacting testing volumes in 2020. However, in 2021, CHAI estimates that VL volumes have rebounded significantly with nearly 24 million VL tests conducted in LMICs for a coverage rate of 75 percent [Figure 33].[xciii]

With WHO guidelines recommending point-of-care viral load testing (POC VL) for priority populations in 2020, including pregnant women, adolescents, and people with AHD or OIs, CHAI estimates that POC VL volumes increased to an estimated 1.3 million in 2021.[xciii]

Further adding to the body of evidence supporting POC VL for certain populations, results from a CHAI-supported study in Zimbabwe demonstrated that pregnant women tested on near-POC VL platforms at the facility were four times more likely to receive their results within 30 days of testing and eight times more likely to receive clinical follow-up action within 30 days of testing.[xciv]

However, despite increases in VL volumes and the known benefits of POC VL, a recent large-scale review of 36 observational studies found that clients in SSA wait an average of 17 months between confirmation of virologic failure on first-line and a subsequent switch to second-line treatment. Further, by the time that virologic failure is confirmed, the pooled mean CD4 count was only 187 cells/μL (below the threshold for advanced HIV disease), and the pooled CD4 cell count at second-line switch was even lower at 108 cells/μL.[xcv]

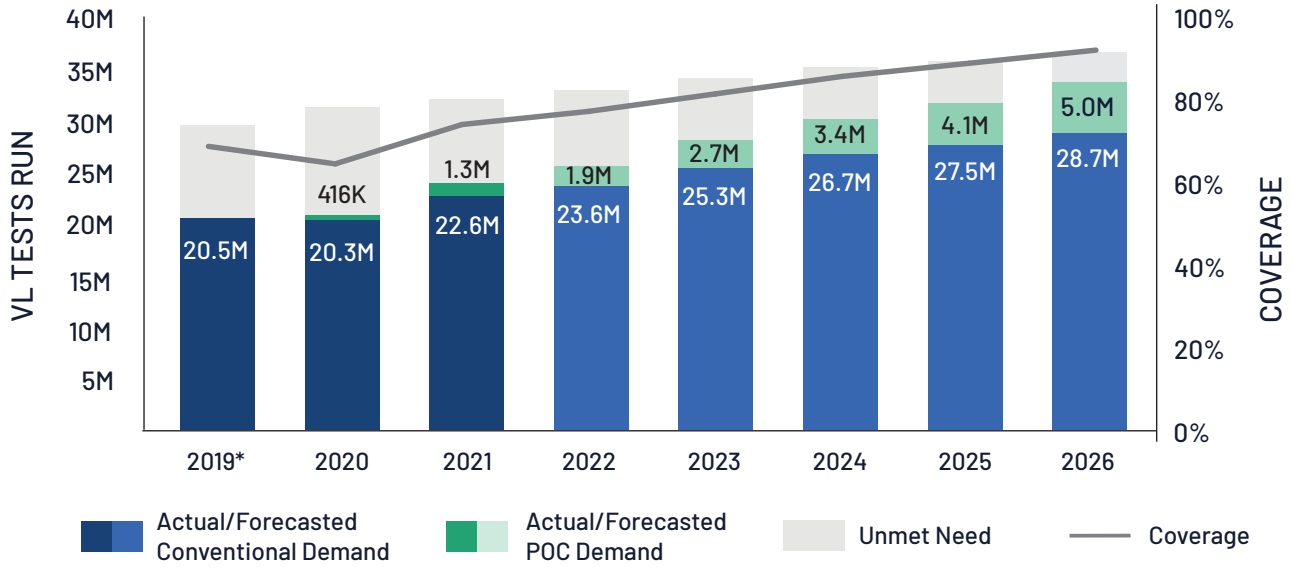
Given treatment monitoring is only useful if it results in timely clinical action, these findings are extremely concerning. Despite the impressive scale-up of routine VL testing over the past decade since the WHO recommended it for treatment monitoring over CD4 testing in 2013, it is clear that a concerted effort is needed to ensure that clients actually receive their test results and appropriate clinical action is taken.

2021 CD4 testing volumes increase from 2020; CD4 access remains critical to link clients to AHD care if needed

CD4 testing remains a critical gateway to the advanced HIV disease package of care and access must be maintained to reduce preventable AIDS-related deaths. Per WHO guidelines, clients should have their CD4 counts tested at treatment initiation and when unstable on ART. CHAI estimates that 12.5 million CD4 tests were run in 2021, an increase compared to 2020, bringing volumes closer to pre-COVID levels [Figure 34].[xcvi]

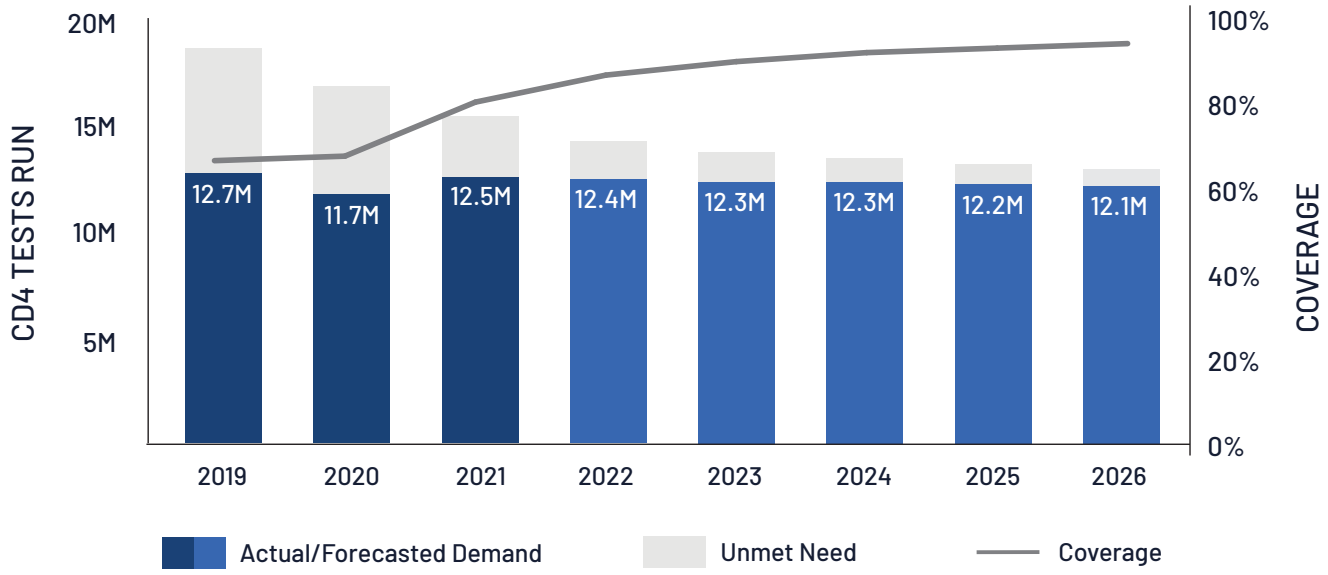
See the Advanced HIV Disease section [Page 14] for more information on CD4 testing.

Figure 33: LMIC VL Testing Forecast[xciii]



**POC tests were not recorded separately in 2019*

Figure 34: LMIC CD4 Testing Forecast[xcvi]



The Integrated Diagnostic Consortium's diagnostic pricing database improves pricing transparency

Despite many global access agreements over the years, national programs often have challenges understanding the true cost of diagnostic testing given the numerous components that go into running each sample (e.g., reagents, controls, additional commodities, platform service and maintenance, human resources). This makes planning, budgeting, and quantification for diagnostic tests challenging.

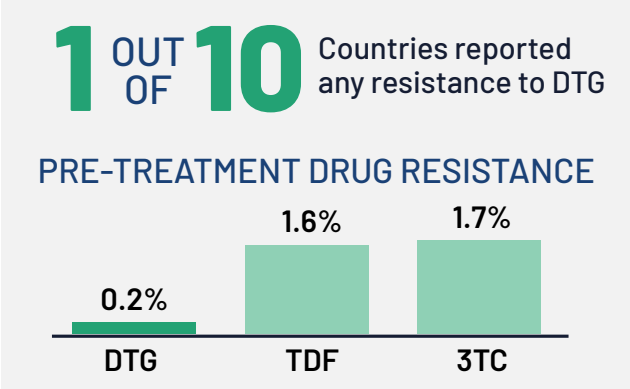
There has been a global push toward "all-inclusive" pricing for diagnostics over the past few years, first with the 2018 announcement of Hologic's US$12 per client sample pricing for HIV, hepatitis B, hepatitis C, and human papillomavirus testing and later in 2019 with the USAID GHSC-PSM global request for proposal (RfP) requiring that suppliers bid with all-inclusive pricing for VL and EID testing kits.[xcvii, xcviii] The USAID initiative began in six initial countries with high procurement volumes and is expanding to more than 20 additional PEPFAR-supported countries. The RfP includes service level agreements and expanded instrument connectivity, and resulted in over US$40 million in savings since it started in 2020.[xcvii]

To improve the transparency of global access pricing options and clarity of components offered, the Integrated Diagnostic Consortium developed a diagnostic pricing database hosted on the African Society for Laboratory Medicine website that clearly outlines access pricing and agreement specifications for key POC and conventional laboratory systems.[xcix] National programs should utilize this resource when budgeting and negotiating with suppliers to ensure that they are accessing competitive pricing and necessary components for diagnostic services.

Drug resistance surveys reassuring with very low levels of INSTI resistance, but ongoing monitoring will be critical given millions of PLHIV now on DTG

Results from the WHO's 2021 Drug Resistance Report are reassuring, especially regarding TLD. Out of ten countries assessing pre-treatment drug resistance to integrase strand transfer inhibitors (INSTIs), only South Sudan reported any resistance to DTG and at a very low level of 0.2 percent. The survey also found very low levels ofpre-treatment drug resistance to TDF (1.6 percent) and FTC or 3TC (1.7 percent) [Figure 35].[c] Although resistance levels were low overall, strong surveillance programs are needed to ensure adequate monitoring.

Figure 35: Select Findings from WHO's 2021 Drug Resistance Survey[c]



Despite low levels of pre-treatment drug resistance to INSTIs, there has been some emerging data on DTG resistance in PLHIV on TLD. A recent study from Malawi found only 6,462 cases (0.7 percent) of virologic failure among those on DTG-based regimens (~838,000); eight (30 percent) of the 27 people with drug resistance testing (DRT) results had mutations associated with DTG resistance.[ci] Although treatment failure and DTG-related mutations are relatively rare, it suggests programs may consider DRT in select cases of treatment failure. This may be increasingly important for individuals at increased risk of drug resistance, such as infants and children or those experiencing 2L treatment failure.

Outside of adults and integrase inhibitors, surveillance data shows high levels of pre-treatment drug resistance among infants and children. While high levels of resistance to NNRTIs such as EFV and NVP are unsurprising, the WHO's 2021 HIV Drug Resistance Report found that levels of pre-treatment ABC resistance ranged from 1.5 percent to nearly 20 percent.[c] This data was further corroborated by other survey data, such as that from Namibia finding pre-treatment resistance rates of 17.7 percent to ABC and 10.1 percent to TDF among infants.[cii] These findings highlight the importance of quickly transitioning children to DTG-based regimens, as well as support the accelerated development of pTAF as an alternative option to ABC for infants and children.

Laboratory system capacity and financial resources to perform DRT remain a challenge in many countries. Service delivery systems may also have barriers, for example in Uganda there was over eight months of delay from sample collection to clinical committee decision prior to targeted interventions reducing it to 73 days.[ciii] Since an AIDS 2022 announcement in August, Thermo Fisher now provides HIV DRT genotyping kits for Sanger sequencing machines for US$20 EXW per assay and an additional US$20 EXW for all required reagents, sample prep, and consumables. This US$40 price point for HIV DRT could help expand access to testing in LMICs.[civ, cv]

STAY NEGATIVE

Despite continued growth in oral PrEP programs and some rebounds in voluntary medical male circumcision volumes, the number of new annual HIV infections remains stagnant. To reach and sustain epidemic control, countries need increased access to highly effective, acceptable prevention options. Cabotegravir long-acting (CAB-LA) injections for HIV prevention represent an important opportunity to expand user choice and drive transformation in the prevention space. However, concerted global effort and intensive country-level planning is needed to support equitable and affordable access to CAB-LA and other promising products in the pipeline to achieve epidemic impact at scale in LMICs.

Progress toward reducing HIV infections is under threat as infections remain stagnant or rise in many regions

In 2021, there were approximately 1.5 million new HIV infections globally. With an estimated decline of only 3.6 percent compared to 2020, this reduction was the smallest annual decline since 2016.[cvi] Even more worrying, infections are increasing in some regions, a reversal of recent trends downward. Globally, the number of HIV infections has increased in 38 countries since 2015.[xx]

Key populations continue to shoulder a disproportionate share of new infections and have a significantly increased risk of HIV acquisition compared to the general population [Figure 36].

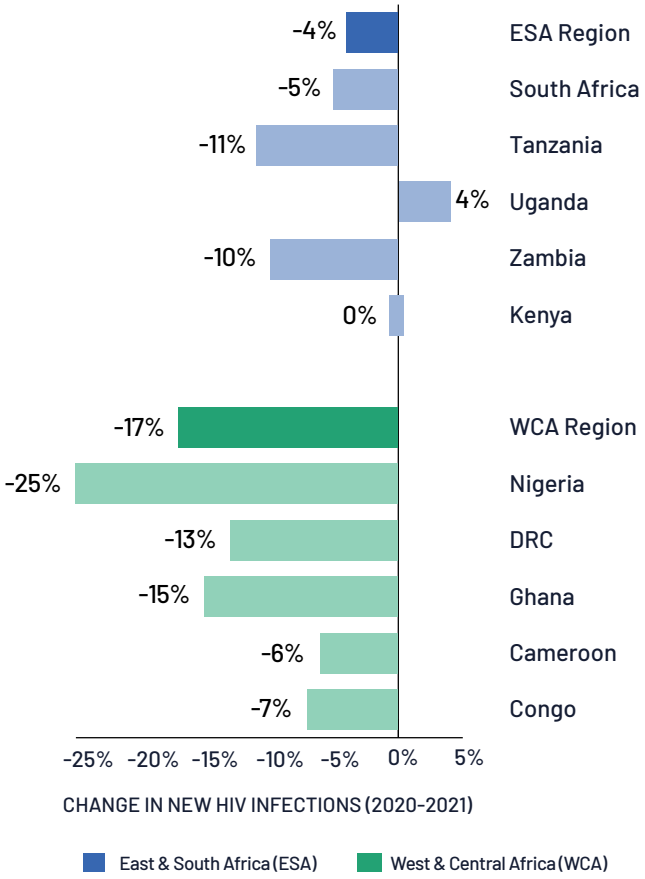
In 2021, key populations and their sexual partners comprised 70 percent of new HIV infections globally and 94 percent of new HIV infections in regions outside of SSA.[xx] These percentages have increased steadily, with key populations and their sexual partners accounting for just 54 percent of global new infections in 2018. To better meet the needs of key populations and their partners, in July 2022 the WHO published consolidated guidelines on HIV, Viral Hepatitis and STI Prevention, Diagnosis, Treatment and Care for Key Populations, which outlines a public health response for five key populations.[cvii]

Figure 36: Relative Risk of HIV Acquisition by Key Population, 2021[xx]

Although there have been some regional declines in new infections, these mask some significant differences across countries. For example, in east and southern Africa, HIV infections declined in South Africa, Tanzania, and Zambia, but increased or remained stagnant in Uganda and Kenya. Further, in west and central Africa, while infections declined in the top five high burden countries in the region, the extent to which infections decreased varied significantly across countries [Figure 37].[ii] Globally, annual new infections remain off track from the 2025 Fast Track target of 370,000 new infections.

Scaling up new and existing prevention interventions will be essential to reversing these trends and accelerating reductions in new HIV infection rates.

Figure 37: Change in New HIV Infections (2020-2021) by Region and Select High-Burden Countries in ESA and WCA[ii]



ViiV grants voluntary license for long-acting injectable cabotegravir for prevention following strong community advocacy

CAB-LA, a highly effective injectable for PrEP, was approved by the US FDA in Dec. 2021 for at-risk adults and adolescents weighing at least 35 kg.[cviii] Administered every eight weeks (after the first two doses administered four weeks apart), CAB-LA is the first long-acting injectable HIV prevention product on the market.

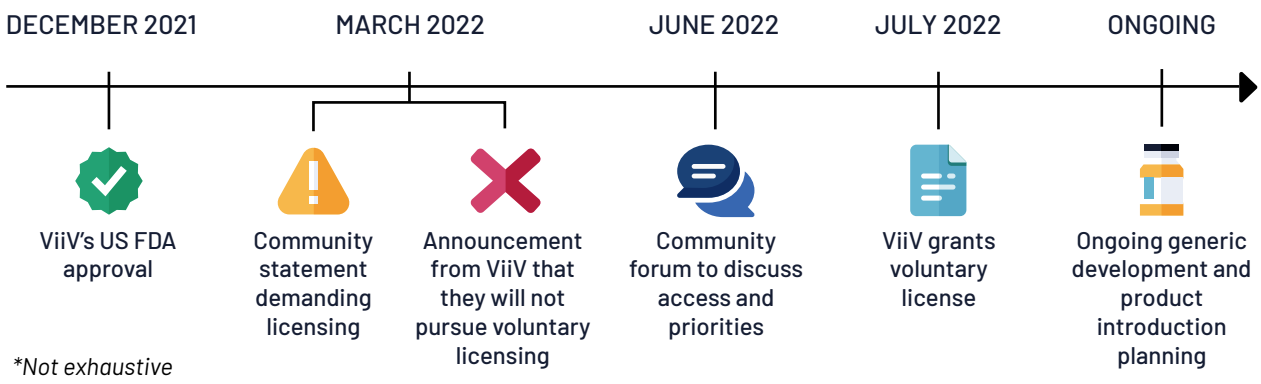
On July 28, 2022, ViiV Healthcare and the Medicines Patent Pool announced a voluntary licensing agreement for patents relating to CAB-LA for HIV PrEP in 90 countries.[cix] While this agreement includes all low-income and lower-middle income countries, as well as all countries in SSA, it does not include several middle-income countries that participated in CAB-LA efficacy trials including Brazil, Peru, and Thailand, a fact that Health GAP activists highlighted prominently at protests during the AIDS 2022 conference.[4] Through this agreement, selected generic manufacturers will have the opportunity to develop, manufacture, and supply generic CAB-LA once approved by relevant regulatory authorities.

While generic development progresses, ViiV will be the sole global supplier of CAB-LA [Figure 38]. As a result, ViiV's price for CAB-LA will significantly influence whether there will be equitable access to the product in the next several years. However, ViiV's ability to set this price will also depend on commitments and investments on the table from large donors in this space.

Community advocacy played a critical role in ensuring voluntary licensing of CAB-LA and remains essential to impactful and equitable introduction. In early March 2022, AfroCAB, along with nearly 200 community organizations and individuals released a statement demanding immediate action from ViiV to grant a license for CAB-LA.[cx]

[4] There is a subset of countries where there is no patent for CAB-LA and where procurement is possible even though they are not included in the license.

Figure 38: Pathway to CAB-LA Generic Development*



*Not exhaustive

> *"The arrival of CAB-LA marks a turning point in the fight against HIV. For years, we have waited patiently for this moment even as we watched our families, neighbors, and communities be transformed forever. We will not wait any longer. We demand ViiV and GSK stand with us and support generic access for CAB-LA."*
>
> *CAB-LA Community Statement, March 2022*[cx]

The group later released an additional statement and formed the CAB-LA Advocacy Forum to drive a coordinated agenda for CAB-LA access.[cxi] In June 2022, following early signs of progress in licensing negotiations, AfroCAB convened a community forum in Kampala, Uganda to discuss key issues around CAB-LA access and align on advocacy priorities and next steps. Participants from this forum released a statement outlining key near-term demands and priorities moving forward.[cxii]

Updated WHO recommendations and continued evidence generation set the stage for CAB-LA implementation

Following the resounding voices from the community calling for access, in July 2022 the WHO released new guidelines recommending CAB-LA as an additional HIV prevention option for people at substantial risk of HIV infection. The new guidelines call for countries to consider adoption of this safe and highly effective prevention option.[cxiii] In line with this recommendation, in Oct. 2022, the Medicines Control Authority of Zimbabwe announced the approval of CAB-LA for HIV prevention, the first national regulatory approval in Africa.[cxiv]

Two large clinical trials, HPTN 084 and HPTN 083, provided key data on safety and efficacy to inform the WHO recommendation. The WHO also conducted a review of values and preferences, finding that injectable PrEP is a highly preferred option, offering users privacy, discretion, and infrequent dosing.

While generic development is underway, implementation and evidence generation with ViiV's product in the next several years must address pending research questions highlighted in the WHO's guidelines. Among these areas for further investigation is the risk of increased INSTI resistance from widespread use of CAB-LA. However, modeling suggests that while CAB-LA is likely to lead to increased rates of resistance, the advantages of CAB-LA in terms of reductions to AIDS-related mortality are likely to outweigh the risk of resistance.[cxiii] This study provides important insights as countries plan for the future of prevention care and ultimately underscores the importance of not limiting access to CAB-LA.

To further inform evidence generation and understand implementation considerations, Unitaid announced it

will include CAB-LA in PrEP introduction studies being conducted in Brazil and South Africa among transgender communities and adolescent girls and young women, respectively. Additionally, the PEPFAR-funded MOSAIC project (Maximizing Options to Advance Informed Choice for HIV Prevention) will deliver CAB-LA alongside oral PrEP and the dapivirine vaginal ring (DVR) in CATALYST, an introduction study being conducted among women at PEPFAR/USAID delivery sites in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe.[cxv] The Bill and Melinda Gates Foundation, the NIH, and other donors are also currently planning CAB-LA studies.[cxvi]

In July 2022, a coalition convened by Unitaid, WHO, UNAIDS, and the Global Fund was announced to coordinate key stakeholder activities on PrEP access, including CAB-LA, DVR, and other future PrEP products.[cxvii] These efforts and studies will provide much needed support and data to inform broader product introduction in the future.

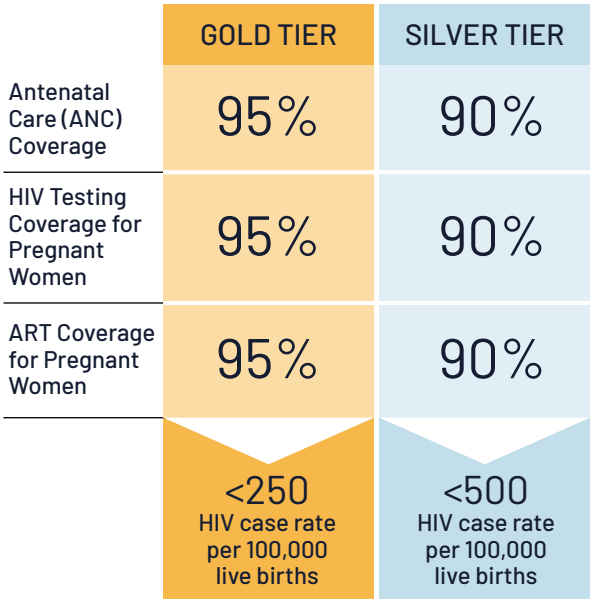
Efforts to eliminate vertical HIV transmission continue with routine engagement in care remaining critical throughout the exposure period

In recent years, reductions in new HIV infections among children have stagnated with only a six percent decrease in 2021 compared to 2020.[ii] There were 160,000 new HIV infections among children in 2021, far surpassing the UNAIDS target of less than 20,000 infections among children by 2020. Further, some regions bear a disproportionate burden, with 85 percent of these infections occurring in SSA. While global efforts to eliminate vertical HIV transmission have resulted in a 52 percent decline in new infant infections since 2010, only 15 countries globally have eliminated vertical HIV transmission.[xx] In Dec. 2021, Botswana achieved a key milestone on this path, becoming the first high-burden country to achieve a vertical transmission rate of less than five percent and reach the WHO's silver tier status for HIV elimination [Figure 39].

Botswana was able to realize this impressive accomplishment through comprehensive HIV testing and late retesting in antenatal care, high rates of retention in care throughout pregnancy and the breastfeeding period, and community engagement and education.[cxviii] Further prevention efforts are ongoing and Botswana aims to achieve a vertical transmission rate of less than one percent by 2024.[cxix]

As other countries aim to eliminate vertical HIV transmission, challenges remain in tracking mother-infant-pairs and retaining them in care through the end of breastfeeding. Lack of retention in treatment during pregnancy or breastfeeding causes an estimated 34,000 new infant HIV infections per year.[xx] To address these gaps, Nigeria and Uganda implemented a tool, supported by CHAI, which sent automated alerts and reminders via short message service to healthcare workers and caregivers for appointments and test results. Additionally, in Zambia, CHAI developed a cohort-monitoring tool within the national electronic medical records system to track mother-infant pairs. Innovations like this could help improve retention in prevention programs for pregnant and breastfeeding women.

Figure 39: Indicators for Certification of the Elimination of Vertical HIV* Transmission[cxx]



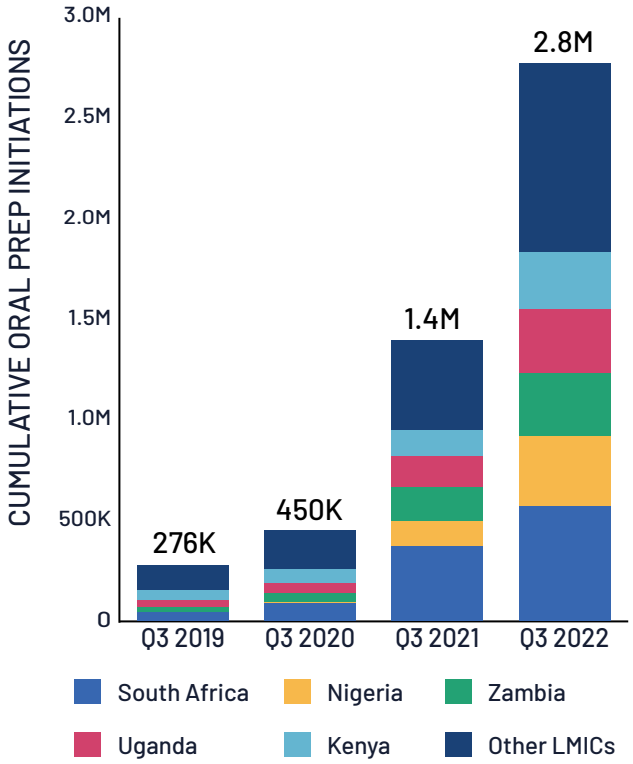
**Indicators for certification of syphilis and HBV elimination not included in the above*

Continued growth in oral PrEP programs despite pandemic challenges

As of Q3 2022, approximately 2.8 million people in LMICs have initiated oral PrEP (either for the first time or as a re-initiation), with 50 percent of these occurring between Q3 2021 and Q3 2022. [Figure 40]. [cxxi]

Expansion in the number of sites offering PrEP continues to drive increases in new initiations. For example, in South Africa, the largest PrEP program globally, the number of facilities offering PrEP increased by 50 percent from 2020 to 2021 and initiations doubled in this period to 205,000 cumulative initiations.[cxxii] Similarly, in Nigeria, as PrEP services expanded to additional states starting in 2020, initiations have risen significantly, from approximately 30,000 cumulative initiations at the end of 2020 to 343,000 in Q3 2022. [cxxiii, cxxi]

Figure 40: Cumulative Oral PrEP Initiations in LMICs and Five Largest Programs as of Q3 2022[cxxi]



Despite the ongoing challenges posed by the COVID-19 pandemic, data published in April 2022 from a study of 21 PEPFAR-supported countries found that the total number of people who initiated PrEP increased by 157 percent in the first year of the pandemic (April 2020 to March 2021) compared to the pre-COVID period (April 2019 to March 2020). This study pointed to adaptations such as multi-month dispensing, virtual demand generation, and decentralized service delivery as key for maintaining PrEP services during the COVID-19 pandemic.[cxxiv] Further, according to the PEPFAR Data Dashboard, in the 2021 fiscal year (Oct. 2020 to Sep. 2021), PEPFAR countries achieved 95 percent of the aggregate target of one million oral PrEP initiations. Initial data from the first half of fiscal year 2022 suggest that programs are on track to exceed targets, with 65 percent achievement against the annual target.[cxxv]

Research shows that non-continuous, risk-informed PrEP use is common and still associated with HIV incidence reduction

While initiations on oral PrEP continue to grow, many people at risk of HIV may not continually use oral PrEP. A meta-analysis of 59 oral PrEP studies found that 41 percent of people who started taking oral PrEP discontinued it within six months. However, among the studies that continued to follow people after they stopped oral PrEP, 47 percent of people followed for more than a year eventually restarted it.[cxxvi] Non-continual PrEP use may reflect changing levels of HIV-risk over time and suggests that individuals may temporarily discontinue use during periods of low risk.

The SEARCH study, which examined HIV incidence in the context of PrEP use, further highlighted the potential for epidemic impact even in the context of non-continuous use. In the study, HIV incidence was 74 percent lower among those who ever initiated PrEP compared to matched controls, despite high rates of discontinuation (only 49 percent of PrEP users received refills at week four) and restarts (half of the participants who discontinued PrEP restarted at some point during the study).[cxxvii] While many early PrEP programs focused on continuation as the primary measure of success, this data highlights the importance of more nuanced approaches for evaluating PrEP programs that account for non-continuous use.

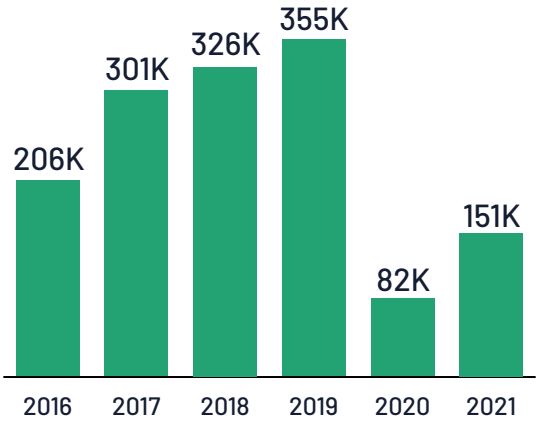
Informed by new evidence on PrEP use patterns, a modelling study assessing the cost effectiveness of easy-access, risk-informed oral PrEP in SSA estimated that risk-informed oral PrEP would reduce HIV incidence by 49 percent over 50 years compared with no PrEP. Further, the study found that oral PrEP was cost-effective in 71 percent of all settings and 76 percent of settings where more than two percent of PLHIV had unsuppressed viral loads.[cxxviii] These studies suggest that non-continuous, risk-informed oral PrEP use can be both clinically and cost-effective.

Further adaptations to service delivery for VMMC needed, especially in the context of ongoing COVID-related disruptions

For countries with high HIV prevalence, voluntary medical male circumcision (VMMC) represents a highly cost-effective, one-time intervention to reduce HIV infections and onward transmission. While uptake and scale up of VMMC slowed in 2020 due in part to the shock of COVID-19 related service interruptions, VMMC service delivery in 2021 began to rebound with program performance improvements across some of the UNAIDS priority countries.[cxxix]

Innovations and adaptations in service delivery have been key to this recovery and the continuity of VMMC services. For example, in Zimbabwe, the number of male circumcisions performed between 2021 and 2021 almost doubled, a significant improvement, but still not reaching pre-pandemic levels [Figure 41].

Figure 41: Number of Male Circumcisions Performed in Zimbabwe (2016-2021) [cxxix, cxxx]



This increase resulted in 83 percent achievement of the 2021 VMMC target, compared to only 20 percent achievement of the 2020 target. Zimbabwe was able to achieve this through community-led demand generation by village health workers, integration of VMMC into broader service delivery, and partnerships with implementers to transport clients to facilities. This reinforces earlier findings in Zambia and Zimbabwe where VMMC programs shifted service delivery from campaign-based models to routinized integrated service delivery models to support program sustainability and overall health system strengthening.[cxxxi]

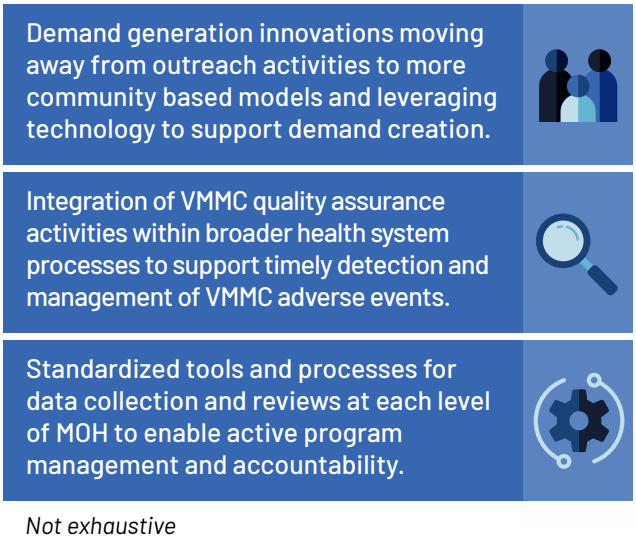
Global and regional guidance and tools outline paths to program sustainability, with programs now defining their own sustainability goals

Sustainability will remain a focus moving forward to ensure resilience of national HIV prevention programs. Reflecting this, the Global Fund and PEPFAR have both released updated prevention strategies that include increased emphasis on sustainability and programmatic resilience.[cxxxii, cxxxiii] These strategies highlight the importance of broader health system strengthening as well as integration of HIV prevention services. Zambia and Zimbabwe have also both developed national sustainability strategic plans and policies that define the country pathway to achieving the sustainability goals across their national program pillars. [cxxxiv, cxxxv]

In addition to global and national guidance, assessing and tracking progress will be critical to achieving sustainability goals. There are a number of diverse tracking and assessment tools based on global definitions of sustainability (including the PEPFAR Sustainability Index Dashboard[cxxxvi] and Prevention Self-Assessment Tools[cxxxvii]).

Building on these to ensure countries can define and achieve sustainability in their local context, Zambia and Zimbabwe developed and implemented VMMC Transition Assessment Dashboards to identify and track system and qualitative opportunities and barriers to achieving country-defined program sustainability targets. Through these tools, both countries have made significant progress with 66 percent achievement of country-defined VMMC sustainability targets in Zambia in 2021 compared to 55 percent at baseline in 2019.[xxx]

Figure 42: Illustrative VMMC Sustainability Enablers



Not exhaustive

Sustainability measurement frameworks such as the VMMC Transition Assessment Dashboards can be expanded to other HIV programs to advance the discourse on qualitative health system requirements to achieve and sustain epidemic control.

The dapivirine vaginal ring experiences regulatory challenges, but introduction studies and research continue

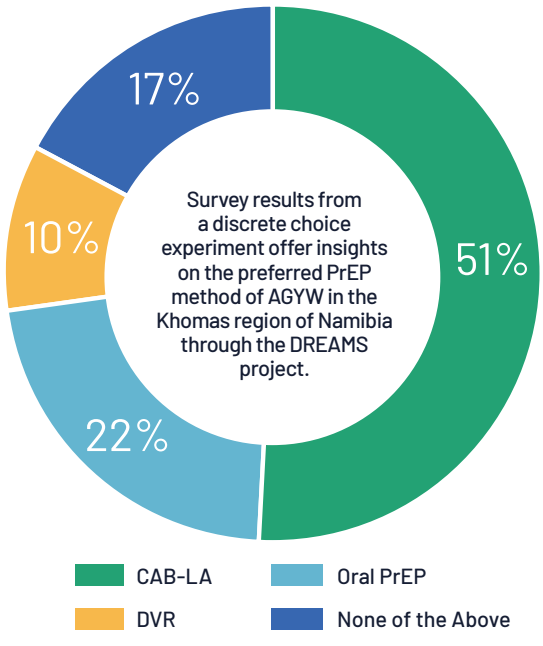
The DVR is a flexible self-inserted silicone ring for HIV PrEP developed by the International Partnership for Microbicides, and recently acquired by the Population Council.[cxxxviii] While efficacy in preventing HIV acquisition during vaginal sex was relatively low in blinded trials, ranging from 27[cxxxix] to 31[cxl] percent, estimated risk reduction in unblinded, open-label extensions was higher with improved adherence (39[cxli] to 69[cxlii] percent relative risk reduction compared to an estimated counter factual). However, in Dec. 2021, the International Partnership for Microbicides announced that it voluntarily withdrew its application to the US FDA for the DVR following feedback that current data are

unlikely to result in US approval at this time.[cxliii] The WHO continues to support its conditional recommendation of the ring alongside oral PrEP as a choice for women who do not want or are unable to take a daily oral tablet.[cxliv]

As more PrEP options become available, including the ring and CAB-LA, user preferences and choice will play an important role in product uptake. Several studies presented at the INTEREST conference in Kampala in May 2022 highlighted concerns of potential end-users around pricing and the lower efficacy of the DVR compared to oral PrEP. However, results from the REACH study presented at CROI 2022 found that more adolescent girls and young women (AGYW) opted for the ring (67 percent) than oral PrEP (31 percent).[cxlv] The REACH results also demonstrated that choice has the potential to increase uptake, as only 2 percent of participants chose neither product.[cxlv] When comparing preferences between oral PrEP, the ring, and injectable PrEP, several recent studies among AGYW have found the strongest preferences and acceptability for injectable PrEP [Figure 43].[cxlvi]

Ultimately, ensuring informed choice among PrEP options, including clear information on relative safety and efficacy, will be critical for supporting person-centered services.

Figure 43: Preferred PrEP Method Among AGYW in the Khomas Region of Namibia[cxlvi]



Prevention products in the development pipeline point to longer-acting options and increased client choice

A number of HIV products in the pipeline offer long-acting protection through new administration forms, expanding the potential for user choice. The following section highlights select products currently in development.

LENACAPAVIR

LEN is a capsid inhibitor currently under investigation in the PURPOSE 1 and PURPOSE 2 trials as a twice-annual subcutaneous injectable for HIV prevention with primary completion dates estimated in early 2024. As mentioned in the Adult Treatment section on page 23, on May 16, 2022, Gilead announced the US FDA lifted the clinical hold placed on injectable LEN for HIV treatment and prevention due to a compatibility issue with borosilicate vials.[lxxviii] The US FDA removed the clinical hold following the agency's review of Gilead's comprehensive plan and corresponding data on the storage and compatibility of injectable LEN with an alternative vial made from aluminosilicate glass. Following this decision, all activity can resume in the clinical studies evaluating injectable LEN including those investigating the safety and efficacy of LEN for HIV PrEP. As mentioned in the Adult Treatment section, injectable LEN received European Commission marketing authorization in Aug. 2022 for the treatment of HIV infection, in combination with other antiretrovirals, in adults with multi-drug resistant HIV infection for whom it is otherwise not possible to construct a suppressive regimen.[lxxx]

ISLATRAVIR

ISL is an investigational NRTTI under evaluation in oral and implant formulations for PrEP. As described in the Adult Treatment section on page 23, in Dec. 2021 the US FDA placed a full or partial clinical hold on all trials investigating ISL based on decreases in total lymphocyte and CD4+ T-cell counts in some study participants.[lxxxii] In Sep. 2022, Merck discontinued development of monthly oral ISL for PrEP, a disappointing blow to the HIV prevention community given earlier excitement and promise of this option. Trial participants will continue to be monitored and Merck will continue to evaluate other long-acting PrEP candidates.[lxxxiii]

DUAL PREVENTION PILL

A dual prevention pill (DPP) to prevent HIV infection and unplanned pregnancy is currently under development by Viatris. Bioequivalence studies are ongoing with US FDA submission estimated for late 2023 based on current time lines. CHAI, with partners, is engaged in advanced planning for introduction of the DPP as part of the broader pipeline of multi-purpose prevention technologies (MPTs).

The development of MPTs represents an important step for integrating sexual and reproductive health (SRH) with HIV services, a critical need for those facing multiple health risks. While the DPP offers protection from unintended pregnancy and HIV acquisition, MPTs for other STI prevention are also in early development.[cxlvii] Recent research highlighting the overlapping risk between HIV and HPV (20 percent increase in risk of HIV infection for every additional HPV infection among women) emphasizes the need for comprehensive, integrated SRH care that includes both STI screening, prevention, and care as well as HIV services.[cxlviii]

mRNA HIV VACCINE

In May 2022 the non-profit scientific research organization IAVI and the biotech company Moderna announced the start of participant screenings for a Phase I clinical trial of an mRNA HIV vaccine antigen (mRNA-1644). The trial is being conducted at the Center for Family Health Research in Kigali, Rwanda and The Aurum Institute in Tembisa, South Africa and is the first trial of an mRNA HIV vaccine to take place in Africa.[cxlix]

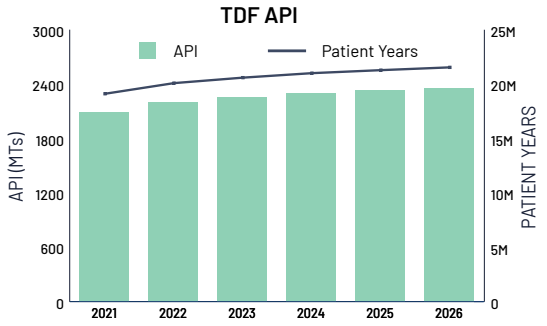
Upcoming prevention products provide an opportunity for transformational change, but will require continued support from the global community

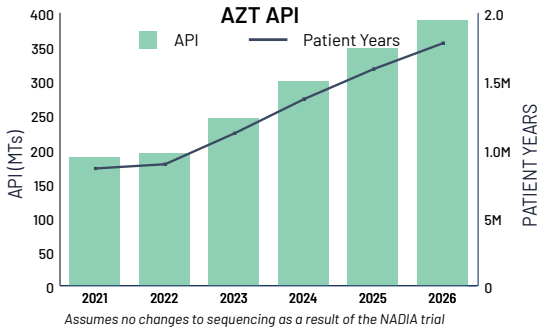
Continued expansion of existing prevention interventions as well as introduction and scale-up of new, highly effective PrEP options provides the opportunity to drastically reduce new infections after years of missed prevention targets and stagnating declines in incidence. In order to be successful, global efforts cannot let up. Action is required now to plan for the introduction and scale-up of new products, including preparing health systems to deliver new HIV modalities such as injectables. Sufficient funding will also be essential to the success of current and future prevention interventions. Partnerships with communities remain critical to ensure community-led and person-centered service delivery. In this new landscape, continued collaboration of stakeholders at the community, regional, and global levels can pave the way for significant progress toward reducing new infections over the coming years.

APPENDIX A:

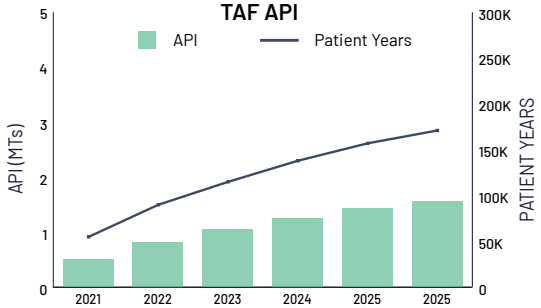
FORECASTED ADULT API DEMAND IN GA LMICs

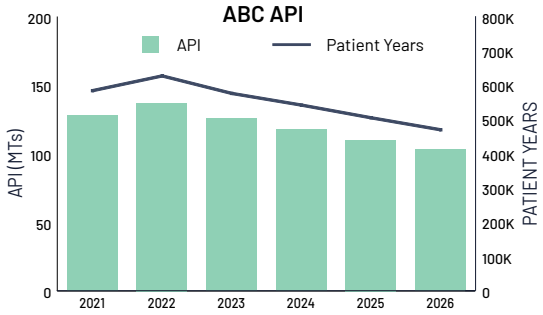
The graphs below show the estimated generic-accessible patient demand and active pharmaceutical ingredient (API) volume (in metric tons) forecast for key adult ARVs. Patient years represent the effective number of patients on treatment for a full year and are used to calculate yearly API demand. Patient 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 is assumed to estimate yearly new initiations. Note that all figures are based on demand for adults only.

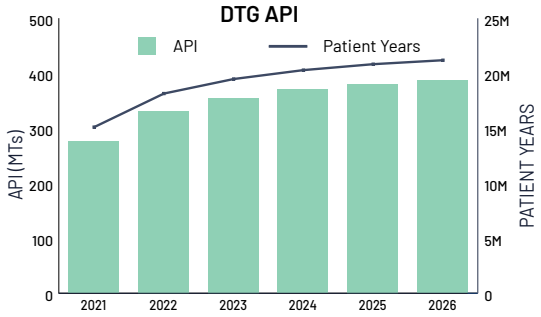


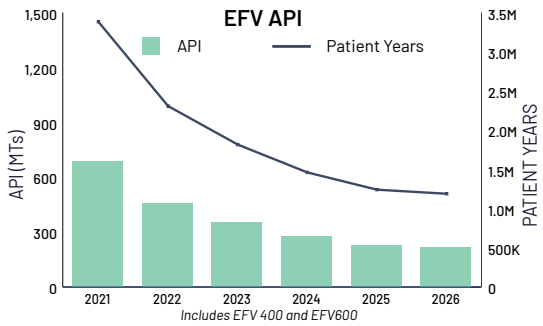


Assumes no changes to sequencing as a result of the NADIA trial

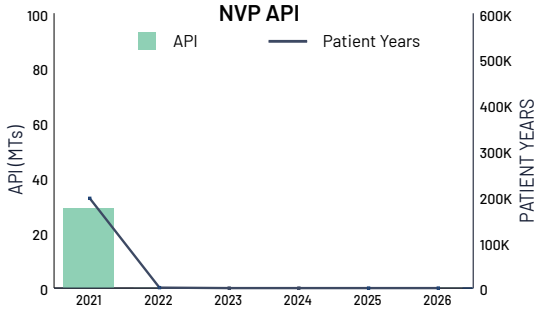


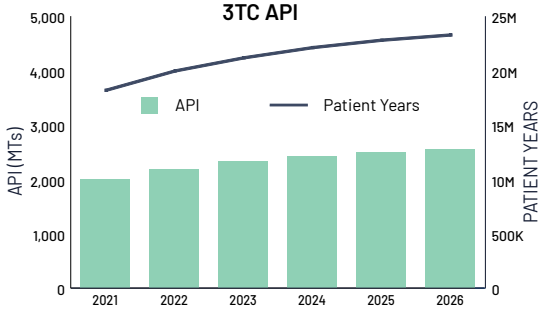






Includes EFV 400 and EFV600





APPENDIX B:

CHAI ARV BENCHMARK PRICE COMPARISON LIST

The table below provides per pack or bottle prices (US$) for key adult and pediatric ARVs. Prices are Ex-Works (EXW).

PRODUCT	PACK SIZE*	GLOBAL FUND PPM PRICE** OCT. 2022[1]	GHSC-PSM E-CATALOG PRICE JUL. 2022[2]	RSA WEIGHTED AVE TENDER PRICE 2022-2025[3]
Adult Products				
ABC/3TC (600/300 mg)	30 tablets	$7.88	$8.90	$5.85
ATV/r (300/100 mg)	30 tablets	$11.80	$13.45	$11.20
AZT/3TC (300/150 mg)	60 tablets	$5.35	$6.05	$4.37
DRV/r (400/50 mg)	60 tablets	$17.50		
DTG (50 mg)	30 tablets	$2.25	$2.35	$1.50
DTG (50 mg)	90 tablets		$7.75	
EFV (600 mg)	30 tablets	$2.50		$2.32
LPV/r (200/50 mg)	120 tablets	$17.95	$18.65	$13.68
NVP (200 mg)	60 tablets			$1.92
RTV (100 mg) heat-stable	60 tablets	$7.00	$7.00	$4.05
TAF/FTC/DTG (25/200/50 mg)	30 tablets	$5.00		
TDF (300 mg)	30 tablets	$2.40	$2.40	$1.94
TDF/3TC (300/300 mg)	30 tablets	$3.37	$3.20	
TDF/FTC (300/200 mg)	30 tablets	$3.97	$3.95	$2.89
TDF/3TC/DTG (300/300/50 mg) No Carton	30 tablets	$4.50	$5.49	$3.75
TDF/3TC/DTG (300/300/50 mg) No Carton	90 tablets	$12.20	$13.50	$10.04
TDF/3TC/DTG (300/300/50 mg) No Carton	180 tablets	$23.50	$25.83	
TDF/3TC/EFV (300/300/400 mg) No Carton	30 tablets	$5.20		
TDF/3TC/EFV (300/300/400 mg) No Carton	90 tablets	$15.40	$15.85	
TDF/3TC/EFV (300/300/600 mg) No Carton	30 tablets	$5.65		
TDF/FTC/EFV (300/200/600 mg) No Carton	30 tablets	$6.06		$4.38
Pediatric Products				
Optimal Formulary				
ABC/3TC (120/60 mg) disp. scored	30 tablets	$2.75	$3.10	$2.59
ABC/3TC (120/60 mg) disp. scored	60 tablets	$6.25	$6.05	
AZT (50/5 mg/ml) oral solution	240 mL bottle	$2.18	$4.25	
AZT/3TC (60/30 mg) disp. scored	60 tablets	$1.70	$1.90	
DTG (10 mg) disp. scored	90 tablets	$4.50	$4.50	
LPV/r (100/25 mg) heat-stable	60 tablets	$6.00		$3.63
LPV/r (40/10 mg) oral granules	120 sachets	$17.00	$17.95	
NVP (50/5 mg/ml) oral solution (with syringe)	100 mL bottle		$2.00	$0.95
Limited-Use List				
3TC (50/5 mg/ml) oral solution	240 mL	$2.05	$2.15	$1.19
DRV (75 mg)	480 tablets		$54.00	$50.07
DRV (150 mg)	240 tablets		$54.00	$44.92
LPV/r (40/10 mg) oral pellets	120 capsules	$17.25	$17.25	$11.71
NVP (50 mg) disp. scored	60 tablets	$1.45	$1.45	
RAL (100 mg) granules	60 sachets		$57.00	
RTV (25 mg) heat-stable	30 tablets	$3.00	$3.25	

1) Global Fund Pooled Procurement Mechanism Reference Pricing: ARVs, October 4, 2022. Link.
2) Global Health Supply Chain - Procurement and Supply Management (GHSC-PSM) E-Catalog: ARVs, July 2022. Link.
3) Republic of South Africa 2022 - 2025 Tender, weighted average price across awarded suppliers, 1 USD = 14.54 ZAR exchange rate used per tender documents; Ex-Works prices have been calculated by removing 15% VAT and 5% in shipping; prices subject to forex-based adjustments; some pack sizes differ slightly from those listed above, see tender for full details.

* 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.

**PPM lists have slightly higher prices with cartons, please refer to latest price list for more information.

APPENDIX C:

2021 OPTIMAL FORMULARY AND LIMITED-USE LIST FOR PEDIATRIC ARVs

OPTIMAL FORMULARY

DRUG	DOSAGE FORM	STRENGTH	RATIONALE FOR USE	PACK SIZE
DTG[1]	Tablet (dispersible, scored)	10 mg	For first-line or second-line ART for infants and children who are ≥ 4 weeks of age and weighing 3 to <20 kg	90-count pack
ABC + 3TC	Tablet (dispersible, scored)	120 mg/60 mg	For preferred first-line or second-line ART for infants and children weighing 3-25 kg	30- and 60-count packs
AZT[2]	Oral Solution	50 mg/5 mL	For postnatal prophylaxis and neonatal treatment only	240 mL bottle
NVP	Oral Solution	50 mg/5 mL	For postnatal prophylaxis and neonatal treatment only	100 mL bottle
LPV/r	Tablet (heat stable)	100 mg/25 mg	For alternative first-line or second-line ART for children weighing ≥10 kg and who are able to swallow tablets whole	60-count pack
LPV/r	Oral granules	40 mg/10 mg	For alternative first-line or second-line ART for children weighing ≤10 kg and who are unable to swallow 100 mg/25 mg tablets whole	120-count pack
AZT + 3TC	Tablet (dispersible, scored)	60 mg/30 mg	For second-line ART for infants and children weighing 3-25 kg	60-count pack

1) DTG 50 mg film-coated tablets are the preferred formulation for children weighing ≥20 kg (and co-formulated DTG 50 mg + TDF 300 mg + 3TC 300 mg, also known as TLD, for those weighing ≥30 kg) to reduce the pill burden, simplify supply chain processes and reduce program costs. Programs should ensure that the ≥20 kg population is accounted for during quantification for DTG 50 mg tablets.

2) As of March 2021, AZT oral solution is only available in a 240 mL bottle. This formulation is only anticipated to be used for neonatal treatment or enhanced infant prophylaxis. AZT oral solution has a four-week shelf life after opening, and if infants use AZT oral solution for longer than this period, a new bottle should be issued after four weeks.

LIMITED-USE LIST

DRUG	DOSAGE FORM	STRENGTH	RATIONALE FOR USE	PACK SIZE
NVP	Tablet (dispersible, scored)	50 mg	Only for postnatal prophylaxis when NVP oral solution is not available	60-count pack
3TC	Oral Solution	50 mg/5 mL	Only for treating neonates	240-mL bottle
RAL	Granules for suspension	100 mg	Only for treating neonates	60-count pack
LPV/r	Oral pellets	40 mg/10 mg	For specific circumstances in which DTG 10 mg dispersible, scored tablets or LPV/r oral granules are not available or clinically indicated	120-count pack
DRV	Tablet	75 mg, 150 mg	For third-line ART regimens for children 3 years and older	480- and 240-count packs
RTV	Tablet	25 mg	For superboosting of LPV/r during TB treatment and required for use when administering DRV	60-count pack

APPENDIX D:

NOTES ON METHODOLOGY

There are several CHAI analyses from which many figures in this report are derived:

ART Patient Forecast: Each year, CHAI develops a forecast for the total number of patients on ART in generic-accessible LMICs (GA LMICs). 'Generic-accessible' denotes countries where global generic manufacturers can register and supply a large proportion of that country's ARVs. For this purpose, CHAI defines GA countries as those LMICs that are covered under voluntary licenses for generic TDF/TAF, or for where there are no patents. The largest *generic-inaccessible* countries are Brazil, China, Mexico, and Russia.

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 at the same rate as the linear trend observed in the last four years and will plateau as universal access (under a "Treat All" paradigm) is approached.

Historical ART coverage rates for GA LMICs are calculated based on data available in the UNAIDS AIDSinfo Database as of September 2022. The numerator and denominator are derived by only including countries with both ART and PLHIV data available for the age category in question (adults vs. children).

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 that data, an internally developed forecasting model, and the ART patient forecast to project ARV demand in GA LMICs over the next five years on a country-by-country level that is then aggregated at the global level. CHAI's 2022 ARV demand forecast for current drugs includes data from: Benin, Burkina Faso, Cambodia, Cameroon, DRC, Eswatini, Ethiopia, India, Kenya, Laos, Malawi, Nigeria, Senegal, South Africa, Tanzania, Togo, Uganda, Vietnam, Zambia, and Zimbabwe. These countries represent approximately 75 percent of adult patients on ART in GA LMICs in 2021.

ARV Market Sizing Analysis: Each year, CHAI combines known regimen splits by country with pricing data to estimate the size of the ARV market in dollar terms. The market size is an estimate of the cost of 1L and 2L treatment (drug costs only) in GA LMICs for all of 2021, and assumes that the countries CHAI has data for are representative of the remaining 25 percent of the market in GA LMICs. It is not an estimate of the cost of ARV procurement in 2021. The assumed price paid for ARVs comes from two sources: 1) South Africa procurement informs the price paid for each respective formulation within a given year for South Africa's regimens; 2) For all other countries, the average Global Fund Pooled Procurement Mechanism (PPM) pricing across 2021 is used.

Diagnostics Forecasts: CHAI's VL, EID, and CD4 diagnostics forecasts have two primary components: 1) diagnostic testing *demand,* and 2) diagnostic testing *need*. While the exact methodology differs slightly between VL, EID, and CD4 tests, the general approach is as follows.

For *demand,* CHAI collects baseline (2021) testing volumes from CHAI country teams, uses publicly available dashboards, or other sources with supplemental data from Avenir Health and the WHO survey. For CD4 and EID, demand is forecasted by applying historical CAGRs to baseline data. CHAI forecasts VL demand by assigning countries to one of five growth analogs based on real-world viral load scale up and hypothetical scenarios. CHAI assigns these analogs based on country intelligence around future scale up plans. Testing *need* is forecasted based on the estimated number of patients each year and country-level testing guidelines for each type of test. For all test types, CHAI forecasts at the country level and then aggregates globally across all LMICs.

Demand, need, and coverage are estimated at the test-level, and not the patient-level (i.e., coverage is estimated as the number of *tests* run divided by the number of tests needed, not the number of patients receiving tests).

APPENDIX E:

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This report was made possible through the generous support of Unitaid, with complementary support from the UK Foreign, Commonwealth & Development Office, and the Bill & Melinda Gates Foundation.

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