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HIV MARKET REPORT

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

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The data sources primarily used for analysis in the report include CHAI country teams, ministry of health counterparts, stakeholder resources and conversations (e.g. Global Fund, PEPFAR, UNAIDS, Unitaid, WHO, and civil society partners), and published research. CHAI has taken precautions to verify the information shared in the report. However, the analysis in the report is not exhaustive, and the responsibility for the interpretation and use of the material lies with the reader. The mention of specific companies or products does not imply CHAI's endorsement or recommendation.

ACKNOWLEDGEMENT

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Front Cover: A health worker performs a heel prick on an infant in Cambodia. Blood is then added to a dried blood spot specimen card, which will be used to perform a test for early infant diagnosis of HIV.

Back Cover: A pharmacist in Zimbabwe dispenses pediatric dolutegravir to caregivers.

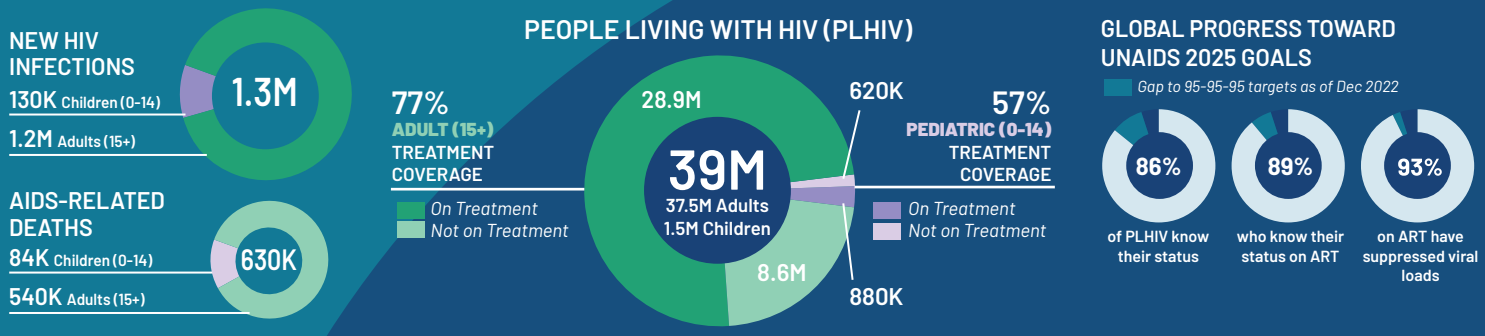
TABLE OF CONTENTS

ACRONYMS

1L	First-line
2L	Second-line
3TC	Lamivudine
3HP	Three months of weekly RPT+INH for TPT
5FC	Flucytosine
ABC	Abacavir
AGYW	Adolescent girls and young women
AHD	Advanced HIV disease
AIDS	Acquired immunodeficiency syndrome
AMP	Antibody mediated prevention
ANC	Antenatal care
APWG	ARV Procurement Working Group
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BIC	Bictegravir
bNABs	Broadly neutralizing antibodies
CAB	Cabotegravir
CAB-LA	Long-acting cabotegravir
CHAI	Clinton Health Access Initiative
CLHIV	Children living with HIV
CM	Cryptococcal meningitis
CrAg	Cryptococcal antigen
DBS	Dried blood spot
DOR	Doravirine
DPP	Dual prevention pill
DRT	Drug resistance testing
DRV/r	Darunavir/ritonavir
DSD	Differentiated service delivery
DTG	Dolutegravir
DVR	Dapivirine vaginal ring
EFV	Efavirenz
EID	Early infant diagnosis
EXW	Ex-works
FDC	Fixed-dose combination
FTC	Emtricitabine
GA	Generic-accessible
GAP-f	Global Accelerator for Pediatric Formulations
HBV	Hepatitis B virus
HBC	Hepatitis C virus
HIV	Human immunodeficiency virus
HIVST	HIV self-test
IM	Intramuscular
INH	Isoniazid
INSTI	Integrase strand transfer inhibitor
ISL	Islatravir
KPs	Key populations
L-AmB	Liposomal amphotericin B
LEN	Lenacapavir
LEVI	Long-acting early viral inhibition
LFA	Laterial flow assay
LGBTQ	Lesbian, gay, bisexual, transgender, queer or questioning
LMIC	Low- and middle-income country
LPV/r	Lopinavir/ritonavir
MAP	Microarray patch
MDR	Multi-drug resistant
MOH	Ministry of health
MPP	Medicines Patent Pool
MPT	Multipurpose prevention technology
NCD	Non-communicable diseases
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OBR	Optimized background regimen
OI	Opportunistic infection
PADO	Pediatric ARV Drug Optimization
pALD	Pediatric ABC+3TC+DTG
pDRV/r	Pediatric darunavir/ritonavir
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
PPPY	Per person per year
PQ	Prequalification
PrEP	Pre-exposure prophylaxis
pTAF	Pediatric tenofovir alafenamide fumarate
RIF	Rifampicin
RPT	Rifapentine
RPV	Rilpivirine
SC	Subcutaneous
SRH	Sexual and reproductive health
SSA	Sub-Saharan Africa
TAF	Tenofovir alafenamide fumarate
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TLD	TDF+3TC+DTG
TLE	TDF+3TC+EFV
TPT	TB preventive therapy
U=U	Undetectable equals untransmittable
US FDA	United States Food and Drug Administration
UNAIDS	Joint United Nations Program on HIV/AIDS
WHO	World Health Organization
VL	Viral load
VMMC	Voluntary medical male circumcision
XTC	Emtricitabine or lamivudine
YOY	Year-over-year

AT-A-GLANCE

HIV Overview, 2022



HIV Prevention

10 LMICs
approved CAB-LA for PrEP, though cost and production capacity remain barriers to access

1.9M People
in LMICs received oral PrEP at least once in 2022

>4 Doses/week
of oral TDF/FTC found to be associated with high PrEP effectiveness in cisgender women, demonstrating a comparable adherence-efficacy relationship to cisgender men who have sex with men

HIV Testing

40 Countries
include the dual HIV/syphilis test in national policy for either pregnant women or key populations

50% Increase in POC
early infant diagnosis (EID) test sales between 2021 and 2022

Advanced HIV Disease

8.6M CD4 Tests
run in 2022, ~30% of which were estimated to be run on point-of-care (POC) devices

75% Increase in 5FC and 51% Increase in L-AmB
order volumes between 2021 and 2022 as seen by the APWG and driven by the Unitaid-CHAI Optimal project

Only 46% of PLHIV
who developed TB in 2021 were receiving ART, highlighting a critical gap

Adult HIV Treatment

91% on DTG-Based Regimens
among adults on ART in generic-accessible LMICs in 2022

PEPFAR Procuring DRV/r (400/50 mg)
and is expected to discontinue procurement of LPV/r (200/50 mg)

Long-Acting Lenacapavir
administered semi-annually with a daily oral optimized background regimen approved by the US FDA for adults with multi-drug resistant HIV; no generic licensing limits access in LMICs

Pediatric HIV Treatment

Generic pALD
from Aurobindo and Viatris granted tentative US FDA approval for CLHIV > 3mo, 6-24.9 kg; negotiated prices of US$14.85 and US$15.00 per 180-pack, respectively

160K Children
on pDTG as of Q3 2023, with

>80 LMICs
procuring the product

62% on DTG-Based Regimens
among CLHIV on pediatric treatment backbones in 2022 (estimates from CHAI analysis based on data from 17 LMICs)

HIV Treatment Monitoring

No Risk of Sexual Transmission
when PLHIV have an undetectable viral load (VL) and negligible risk when VL is suppressed but detectable (under 1,000 copies/mL), according to a new WHO brief

Flatlining POC VL Test Sales
indicates a gap in testing for priority populations, such as pregnant and breastfeeding women , CLHIV, and people with AHD or OIs

GENERAL TRENDS

In the two decades since the establishment of PEPFAR and the Global Fund, new HIV infections have reduced by half and AIDS-related deaths decreased by nearly 70 percent. Further, HIV treatment is the most affordable it has ever been. In the HIV prevention, advanced HIV disease, and diagnostics spaces, novel and increasingly effective products hold potential for reducing new infections, mortality, and morbidity. Now, more than ever, is the time to double down on investments in HIV. To make continued progress towards ending HIV, global efforts must prioritize key populations and their partners, bridge treatment disparities between adults and children, and ensure sufficient and sustainable funding, among others.

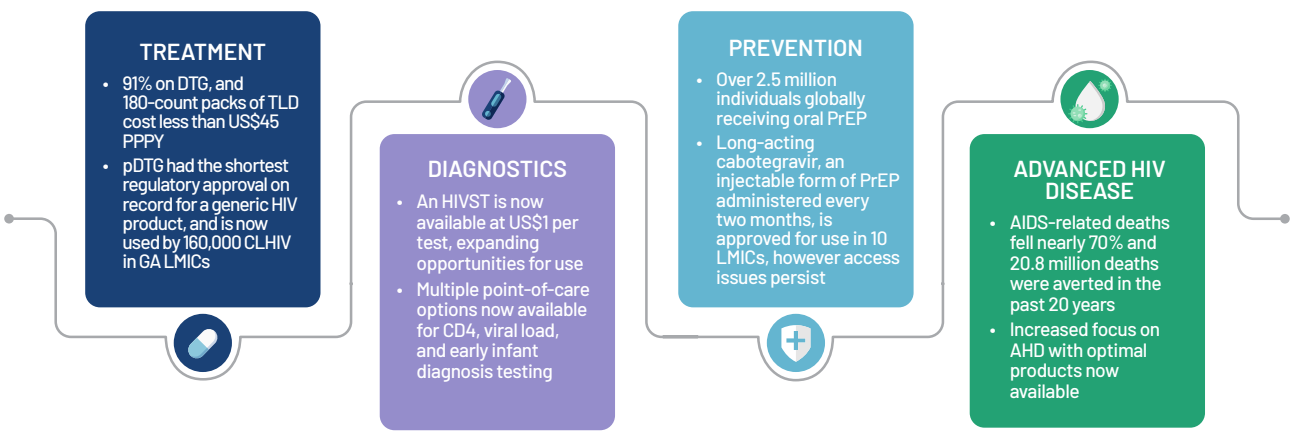
Access to and quality of HIV services continues to improve, but critical gaps remain across the cascade

Today the HIV response is markedly different from that of two decades ago. When the US launched the US President's Emergency Plan for AIDS Relief (PEPFAR) in 2003, globally over 2.5 million people contracted HIV each year and two million people living with HIV (PLHIV) died annually.[i, ii] Exorbitantly priced antiretroviral therapy (ART) was inaccessible to individuals living in lower resource settings. In sub-Saharan Africa (SSA), one of the regions most impacted by the epidemic, child mortality tripled and life expectancy dropped 20 years.[ii]

Since 2003, innovative partnerships between governments, PEPFAR, the Global Fund, and other global partners have significantly improved access to HIV services across the cascade of care [Figure 1]. This was in large part enabled by the development of affordable, generic antiretrovirals (ARVs). Today, a generic version of dolutegravir (DTG) is used by over 90 percent of adults in generic accessible (GA) low- and middle-income countries (LMICs) and is available for less than US$45 per person per year (PPPY).[1, iii, iv] Following the shortest regulatory approval on record for a generic HIV product, 160,000 children are already accessing pediatric DTG (pDTG) at a cost of approximately US$100 PPPY, partly as a result of pricing agreements negotiated by Clinton Health Access Initiative (CHAI) and partners.[2, iv, v, vi, vii, viii] However, despite these successes, some gaps in treatment remain, including slower scale-up of fixed-dose-combination (FDC) darunavir/ritonavir (DRV/r) in second-line treatment and retention of PLHIV in care. As the number of people on treatment increases and prices reduce, the ARV market in GA LMICs remains robust with an estimated US$1.9 billion market size in 2022 based on CHAI calculations of the annual cost of regimens in-use.[iii]

In tandem with advances in treatment optimization, improvements in testing have further expanded access to HIV services. Today, laboratory diagnostics are increasingly decentralized with multiple point-of-care (POC) options for CD4, viral load (VL), and early infant

FIGURE 1: ADVANCES IN HIV SERVICES ACROSS THE CASCADE AS OF OCTOBER 2023



[1] See Appendix C for a definition of generic-accessible

[2] Child pricing based on 10-13.9 kg as the reference weight band

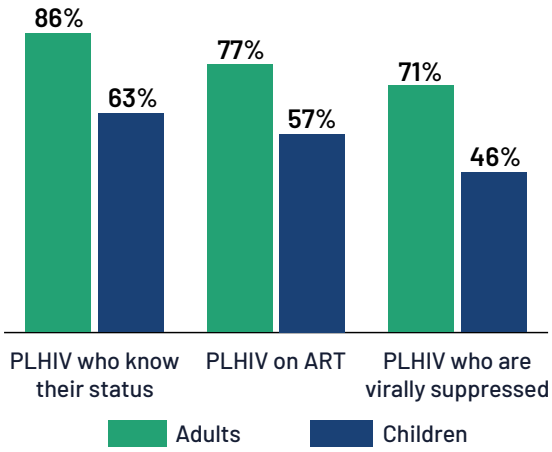
diagnosis (EID) testing. While HIV self-tests (HIVSTs) are now available at just US$1 each, uptake to date has been limited but is growing.[ix]

While progress expanding HIV treatment—alongside more modest primary prevention efforts—has contributed to reductions in HIV transmission, persistently high new HIV infection rates reinforce that treatment alone is insufficient to reach and maintain epidemic control. Global efforts increasingly prioritize effective combination prevention packages that include both socio-behavioral interventions, as well as highly effective biomedical interventions. In 2022, over 2.5 million individuals globally received oral pre-exposure prophylaxis (PrEP).[i] New options like injectable long-acting cabotegravir (CAB-LA) and future pipeline products have the potential to accelerate reductions in new HIV infections. However, the transformational potential of available long-acting products is currently limited by high costs and low production capacity. Targeted donor investment to accelerate generic development of promising long-acting PrEP products is crucial for achieving impact at scale.

In the past 20 years, AIDS-related deaths have decreased by almost 70 percent, resulting in an estimated 20.8 million deaths averted. However, there were still 630,000 AIDS-related deaths in 2022 with tuberculosis (TB), cryptococcal meningitis (CM), and bacterial infections remaining the major causes of death among adults, and pneumonia, TB, bacterial infections, diarrheal diseases, and severe acute malnutrition among the major causes of mortality for children.[x, xi] More work needs to be done to reduce the number of people presenting to care with advanced HIV disease (AHD), identify AHD sooner, and link individuals to treatment and prevention for opportunistic infections (OIs).

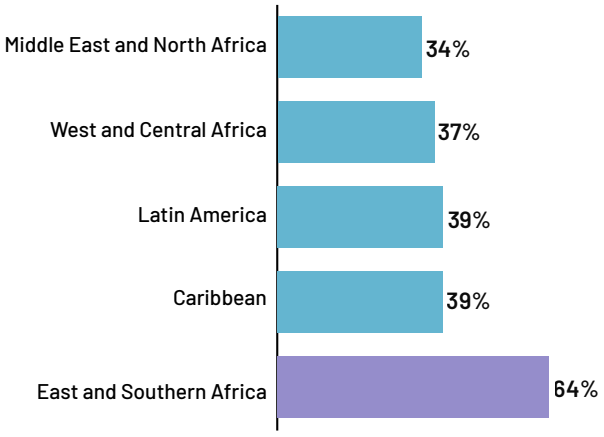
For children living with HIV (CLHIV), urgent action is needed to further reduce AIDS-related mortality and morbidity. In 2022, CLHIV accounted for 13 percent of AIDS-related deaths, despite comprising only four percent of PLHIV.[x] Management of AHD in children is challenging. At least 30 percent of CLHIV present with severe immunosuppression at HIV diagnosis, and those who are hospitalized when they initiate ART have high mortality.[xi] A large portion of CLHIV are not on ART at all. In 2022, only 57 percent of CLHIV were on treatment compared to 77 percent of adults, an unacceptable disparity [Figure 2]. Year-over-year, the gap between HIV treatment coverage for children and adults continues to grow. Due to these gaps in ART coverage, existing (but decreasing) use of less effective ARVs in pediatric populations, and various other contributing factors, less than half of CLHIV are virally suppressed, resulting in over 80,000 AIDS-related deaths among CLHIV in 2022.[x] To reduce these deaths, stepping up efforts to identify and treat pediatric AHD cases is crucial.

FIGURE 2: HIV CASCADE FOR ADULTS AND CHILDREN LIVING WITH HIV, GLOBAL, 2022[x]



These differences are even more pronounced regionally, where 64 percent of children in East and Southern Africa (ESA) were on ART in 2022 compared to less than 40 percent in all other regions reporting data [Figure 3].[i] These disparities often begin before a child is born—despite being home to 20 percent of pregnant women living with HIV, West and Central Africa (WCA) accounts for 52 percent of pregnant women who are not on ART.[x] It is clear that a focus on case identification and treatment retention for both pregnant and breastfeeding women and children is imperative to close the pediatric HIV gap.

FIGURE 3: PERCENTAGE OF CHILDREN LIVING WITH HIV RECEIVING ART BY REGION, 2022[i]



Ongoing funding and resource mobilization threats could hamper continued progress toward epidemic control

International and domestic funding has been crucial to the success of the HIV response over the past 20 years. However, recent funding threats and reductions in HIV investments put these hard-won gains at risk. For example, the PEPFAR program represents the largest investment by a country toward a single disease area, contributing over US$110 billion to end HIV while simultaneously strengthening global health and economic security in 50 countries over the past 20 years.[ii] In Sep. 2023, the program was due for its fourth five-year reauthorization. However, politicization has put the traditionally bipartisan program in peril and reauthorization is not certain. A failure to reauthorize PEPFAR risks lives and the forward momentum needed to address remaining gaps and eliminate HIV as a public health threat.[xii]

Looking across all funding for HIV programs in LMICs, in 2022, a total of US$20.8 billion was provided representing a 2.6 percent decrease from 2021's funding envelope. This continues a years-long pattern of stagnant and decreasing funding [Figure 4].[x] International organizations, governments, and other donors have played a crucial role in providing financial support to HIV programs in LMICs, and continued investment, including PEPFAR reauthorization and meeting the US$2 billion gap in Global Fund targets while also fulfilling the pledges of the seventh Global Fund replenishment, is imperative for reaching global targets on time.[xiii]

Significant challenges remain in ensuring sufficient and sustainable funding for HIV programs. Global economic challenges, competing health concerns, and shifting global priorities have impacted funding availability. This was particularly the case for domestic funding, where decreased revenue due to lockdowns and foreign debt obligations disproportionately impacted many of the countries with the highest HIV burdens.[xiv] A former trend of increasing domestic spending on HIV has since reversed post-COVID-19 pandemic, with two percent less domestic funding available for HIV programs in 2022 compared to 2021, the third consecutive year of decreases.[x]

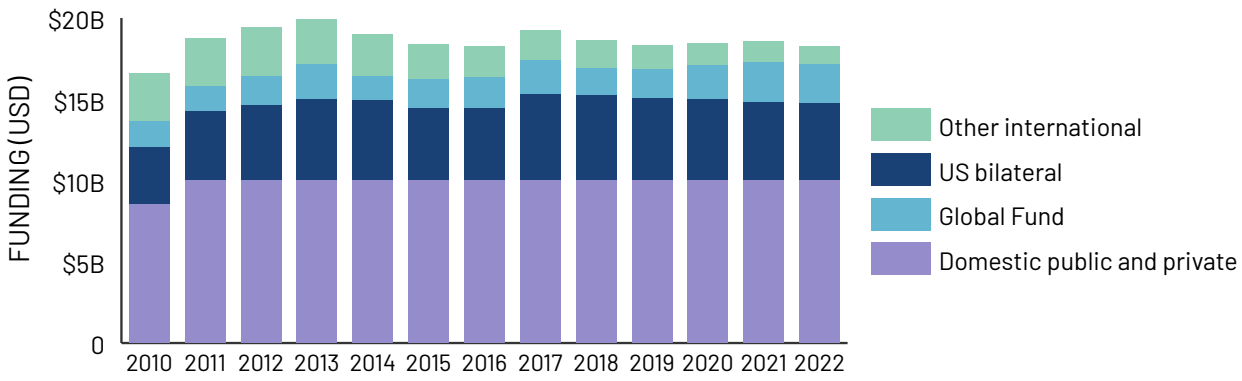
Factors such as stigma, discrimination, and social barriers can also hinder the effective allocation and utilization of funds. Key populations (KPs) remain one of the most underfunded areas in the HIV response, with a 90 percent funding gap for prevention programs estimated in 2022 compared to what is needed to reach 2025 targets in LMICs.[xv, x]

Without urgent and collaborative action to ensure adequate and sustainable funding, the HIV epidemic will continue to have health, social, and economic costs disproportionally impacting key and priority populations, thereby deepening inequality. Crucial to these efforts will be continued support for ending HIV via the Global Fund and PEPFAR, among others. Ensuring a sustainable HIV response will require a range of strategies to enhance financing for the health sector as a whole and maximize the use of existing resources and partnerships.

Overcoming political and social barriers remains critical to sustaining and expanding the HIV response, especially among key populations

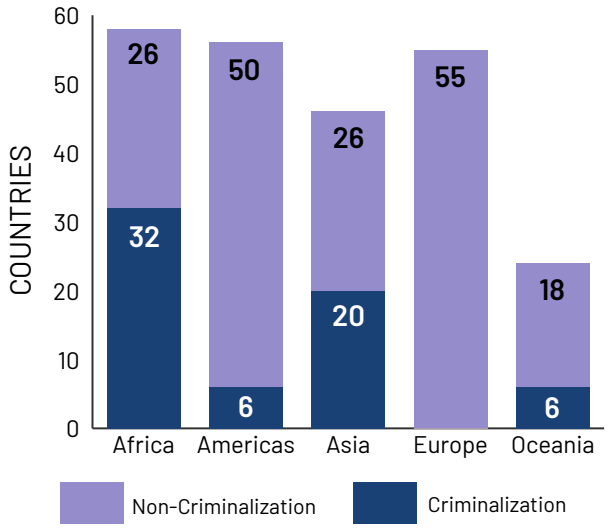
Stigma, discrimination, and criminalization of key populations are also significant barriers to achieving the goals of the HIV response. As a result, key

FIGURE 4: FUNDING FOR HIV IN LMICs BY SOURCE, 2010-2022[x]



populations continue to be among the most at risk for HIV transmission, have a higher prevalence of HIV, and lower treatment coverage when compared to the general population in most countries.[x] Currently, 64 countries criminalize same-sex relationships, and half of these are located in Africa with the death penalty possible in Mauritania, Nigeria, Somalia, and Uganda [Figure 5].[xvi] In countries where these relationships remain criminalized, a study in SSA found HIV prevalence among men who have sex with men was five times higher.[xvii] While some countries are exploring decriminalization, others such as Ghana, Iraq, Kenya, and Tanzania are pursuing harsher penalties, with Uganda recently passing a sweeping anti—lesbian, gay, bisexual, transgender, queer or questioning (LGTBQ) law.[xvi]

FIGURE 5: CRIMINALIZATION OF SAME-SEX RELATIONSHIPS BY REGION, 2023[xvi]



Criminalization of key populations can also negatively impact the ability of governments and partners to provide necessary HIV services to those in need. In Uganda, PEPFAR reported significant drops in weekly attendance by KPs at drop-in-centers providing HIV treatment and prevention services while the Anti-Homosexuality Act was debated in parliament. This attendance has not recovered in all centers despite interventions to improve client access.[xviii] Rising rates of new infections in some regions such as Asia and the Pacific and the Middle East and North Africa, primarily driven by infections among KPs and their partners, further point to the need for KP-friendly services and enhanced efforts to reduce stigma and discrimination.[x]

Global partners are doubling down on their commitments to priority populations, as outlined in PEPFAR's new five-year strategy. Released in 2022, the strategy aims to end HIV as a public health threat by 2030 while prioritizing evidence-based interventions, improving health equity, and sustainably strengthening public health systems [Figure 6].[ii] However, the ability to implement this strategy precariously hinges on congressional approval of the next five-year reauthorization of PEPFAR, threatening progress and putting lives at risk.

FIGURE 6: PILLARS OF PEPFAR'S NEW FIVE-YEAR STRATEGY[ii]

Comorbidities among PLHIV negatively impact HIV outcomes, suggesting opportunities for health services integration

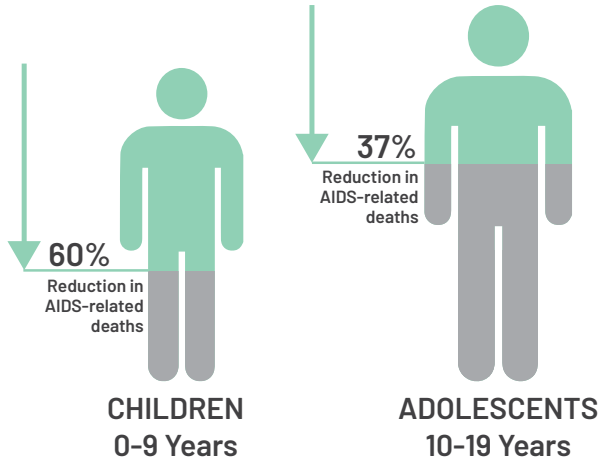
Due to affordable and effective treatment, PLHIV are living longer. Data from a US study found that PLHIV who are diagnosed and treated when CD4 counts are high, maintain adherence to ART, and have access to medical care can anticipate a life expectancy mirroring the general population.[xix] With these improvements in life expectancy come chronic comorbidities such as diabetes and hypertension that commonly affect aging populations. However, for many in LMICs, care for non-communicable diseases (NCDs) is often inaccessible. NCDs can complicate HIV treatment and increase morbidity and mortality in PLHIV. Deaths among PLHIV due to causes other than AHD doubled from 14 percent in 2010 to 32 percent in 2022.[x] Recognizing the evolving health needs of PLHIV, in 2023 the World Health Organization (WHO) released implementation

guidance outlining a holistic approach for integrating NCD prevention and control into HIV, TB, and sexual and reproductive health (SRH) programs.[xx]

Mental health is another neglected health concern that disproportionally impacts and leads to poor outcomes among PLHIV. Poor mental health increases the risk of acquiring HIV four-fold and worsens treatment outcomes.[xxi] Following diagnosis, PLHIV are 100 times more likely to die by suicide than the general population.[xxii] The prevalence of depression in PLHIV in sub-Saharan Africa is estimated at 24 percent, compared with less than three percent for the general population.[xxiii]

Adolescents with HIV are particularly impacted by poor mental health. Globally, there are 3.2 million adolescents and young adults living with HIV between 15 and 24 years of age, and evidence shows that this group has higher rates of mental health challenges than their HIV-negative peers.[xxiv] Among adolescent key populations, poor mental health is exacerbated by multiple stigmas including their youth, minority group association, and HIV status.[xxv] Between 2010 and 2020, HIV-associated mortality declined at a slower pace in adolescents than in children, with a 37 percent reduction in mortality among PLHIV 10 to 19 years as compared to 60 percent among those aged zero to nine years [Figure 7].[xxvi] This limited progress highlights the need for more support to ensure adequate and holistic care for this population.

FIGURE 7: REDUCTIONS IN GLOBAL AIDS-RELATED DEATHS AMONG CHILDREN (0-9 YEARS) AND ADOLESCENTS (10-19 YEARS), 2010-2020[xxvi]



A recently published WHO technical brief recommends integrating psychosocial and HIV services for adolescents and young adults, identifying best practices and strategic actions to support healthy behaviors and bolster mental health. This brief aims to ensure the wellbeing of this important demographic group during a crucial developmental stage in life.[xxv]

However, despite a strong research base of effective, low-cost mental health interventions appropriate for LMIC settings, there are large gaps in translating research into practice.[xxvii] While it is crucial to tackle the substantial comorbidity between HIV and mental health, it is important to pave the way for broader mental health integration to diminish stigma and enhance overall health outcomes beyond PLHIV.

Syphilis and hepatitis B remain common co-infections that particularly impact pregnant women and children. HIV is known to interact with both syphilis and hepatitis B to increase mother-to-child transmission risk, underscoring the need for integrated diagnostics and care for these diseases to improve maternal and neonatal health outcomes. This is especially true in SSA, where the burden of these diseases is the highest. Unequal funding across diseases has impeded efforts to reduce syphilis and hepatitis B infection, with a recent assessment in ten SSA countries showing a gap between HIV and syphilis screening coverage of between five and 52 percent. Newly approved dual HIV/syphilis tests and triple combination diagnostic tests under development have the potential to close this gap, link more women to treatment, and accelerate the triple elimination agenda when paired with differentiated service delivery models.[xxviii]

PREVENTION

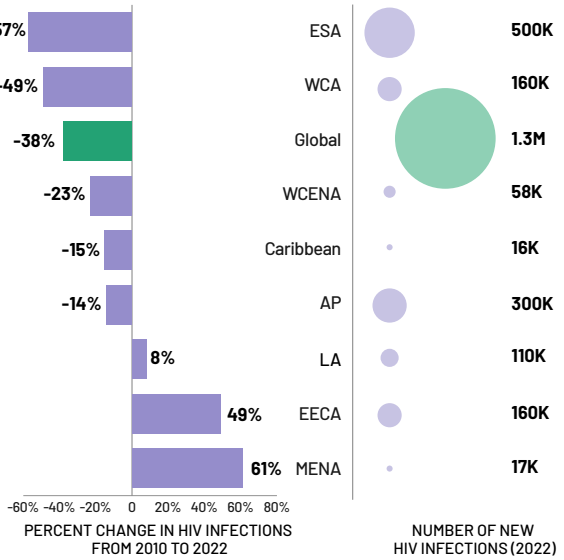
2022 saw the lowest number of new HIV infections in three decades, however, year-over-year reductions are still too low to meet the global target of ending AIDS by 2030. Despite global progress, disparities across populations persist and some regions are seeing an alarming increase in new infections. Increased access to effective primary prevention interventions, particularly among those at highest risk of HIV acquisition—including key populations, adolescent girls and young women, and pregnant and breastfeeding women—will be essential for reducing HIV incidence. Long-acting cabotegravir and other novel prevention products have the potential to enhance user choice, increase uptake and promote effective use, and significantly reduce new HIV infections. However, access barriers such as affordability and generic production capacity must be addressed to realize transformational impact.

Progress in HIV prevention is unequal across populations and geographies

In 2022, there were an estimated 1.3 million new HIV infections globally, the lowest number in the past three decades. However, the global response remains off track from the UNAIDS 2025 target of 370,000 infections.[x]

Further, there are disparities in the distribution of and progress in reducing new HIV infections across regions, sub-national geographies, and populations. For example, while SSA saw large reductions in HIV infections between 2010 and 2022, women and girls continue to bear a disproportionate burden of new infections in the region, representing 63 percent of all new HIV infections in 2022. However, less than half of the districts in high HIV incidence areas have HIV prevention programs for adolescent girls and young women (AGYW). Beyond SSA, HIV prevention progress is slower. Several regions, including Asia and the Pacific and Eastern Europe and Central Asia saw steady or increasing numbers of new infections from 2010 to 2022 [Figure 8].[x]

FIGURE 8: CHANGE IN NEW HIV INFECTIONS BY REGION (2010-2022) AND NUMBER OF NEW INFECTIONS (2022)[x]



Key populations and their partners continue to account for a disproportionate number of new infections, and these populations often lack access to tailored and stigma-free prevention services. Further, discriminatory laws, violence, and stigma continue to pose barriers.[x] Ultimately, these disparities in access are human rights issues, and underscore the importance of integrating human-rights-based approaches into the HIV response to achieve meaningful progress in reducing new infections.

Despite generic licensing for CAB-LA, major access challenges persist requiring urgent action to accelerate generic development

In Dec. 2021, the United States Food and Drug Administration (US FDA) approved long-acting cabotegravir, a highly effective injectable PrEP administered every eight weeks, for use in adults and adolescents at risk of HIV acquisition and weighing at least 35 kg.[xxix] CAB-LA is the first long-acting injectable HIV prevention product on the market, but LMICs continue to face major access challenges.

Following strong community advocacy for rapid, equitable, and affordable access to CAB-LA, ViiV Healthcare signed a voluntary license agreement with the Medicines Patent Pool (MPP) in July 2022.[xxx, xxxi] Subsequently, in March 2023 ViiV and MPP announced sublicense agreements with Aurobindo, Cipla, and Viatris to manufacture generic CAB-LA for use in 90 countries.[xxxii]

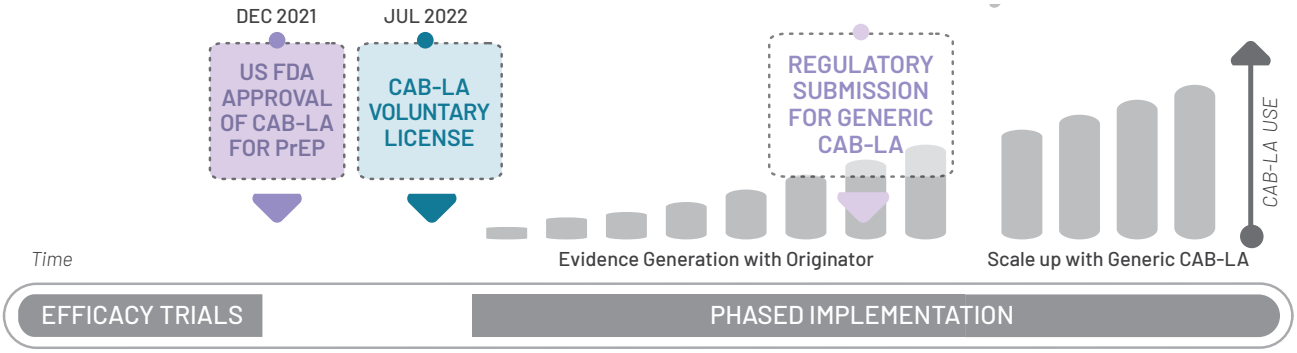
Until generic CAB-LA is available, ViiV remains CAB-LA's sole supplier, impacting available volume and affordability. While CAB-LA has been approved in ten LMICs (Brazil, Botswana, Malawi, Malaysia, Nigeria, Peru, Philippines, South Africa, Zambia, and Zimbabwe) as of Oct. 2023 , these supply constraints continue to represent a challenge for introduction planning.[xxxiii] In the near term, access will be limited outside of implementation projects, planned PEPFAR procurement in Malawi, Ukraine, Vietnam, Zambia, and Zimbabwe, and modest volumes expected to be available through the Global Fund.[xxxiv]

Communities continue to advocate for accelerated generic CAB-LA development, however, as of Oct. 2023, no confirmed donor investment had been announced. Leveraging decades of product introduction experience and input from partners, CHAI created an innovative roadmap outlining potential steps to accelerate generic CAB-LA development and equitable introduction [Figure 9].[xxxv] This roadmap was released as part of a special issue publication on the use of long-acting HIV prevention and treatment regimens.[xxxvi] It is important to note, however, that even if partners, manufacturers, and ministries were to implement these roadmap recommendations, generic CAB-LA availability is likely several years away.

Research indicates potential for three-month CAB-LA dosing among cisgender women, but continues to highlight testing challenges

Regulatory approval of CAB-LA for PrEP is largely based on the large-scale HPTN 083 and 084 clinical trials, which demonstrated CAB-LA's statistical superiority over daily oral TDF/FTC for HIV prevention.[xxxvii] While more research is needed to understand choice and preferences in real-world settings, the open label extensions of both efficacy studies continue to show strong preferences for long-acting injectable PrEP. Among adult cisgender women enrolled in HPTN 084, 78 percent opted for CAB-LA over oral TDF/FTC in the choice period.[xxxviii] Similarly, among African cisgender

FIGURE 9: CAB-LA FOR PrEP ROADMAP AND ACCESS OBJECTIVES[xxxv]



Roadmap Access Objectives

- **Partner Coordination and Alignment:** Ensure coordination and alignment across partners, avoiding redundancy experienced during oral PrEP introduction
- **Generic Development:** Incentivize accelerated, efficient generic product development through a combination of evidence-based and innovative market-shaping interventions
- **National Program Preparation:** Provide targeted support to maximize CAB-LA impact based on health system readiness assessments, including development of national policies, guidelines, and introduction plans and tools; system strengthening; quantification and procurement; and evidence generation
- **Community Engagement:** Support community engagement, ensuring that demand generation and delivery approaches for CAB-LA are person-centered and community-led
- **Regulatory Strategy:** Expedite reviews by regulatory authorities and national medicines regulatory authorities to minimize time to market

female adolescents, CAB-LA was tolerable and preferred as compared to daily oral PrEP.[xxxix] Recent pharmacokinetic data shows protective levels of CAB-LA persist for three months in cisgender women, which could open the window for a future dosing indication that aligns with injectable contraception, reduces delivery costs, and results in fewer clinic visits.[xl]

Analysis of the positive predictive value of single rapid HIV tests in HPTN 084 found higher rates of false positives among CAB-LA users. However, two rapid HIV tests were sufficient to confirm HIV diagnosis and recommend treatment initiation. Based on these results, HIV programs will need to ensure appropriate testing strategies for CAB-LA, potentially including further testing to confirm diagnosis and additional client counseling where testing strategies may differ from other PrEP options.[xli]

Notably, a review of the small number of incident HIV infections recorded during the HPTN studies found that the use of CAB-LA for PrEP led to viral suppression and delayed or diminished antibody expression that can persist for months after infection, a condition dubbed "long-acting early viral inhibition" (LEVI). As a result, HIV rapid tests and antigen tests fail to detect infection in a timely manner. While the cases were rare, these missed diagnoses have the potential to increase the risk of integrase strand transfer inhibitor (INSTI) resistance.[xlii]

Ongoing investigations are exploring testing approaches needed in the context of LEVI. The use of RNA testing for HIV screening could help identify and confirm infections earlier in some cases, but would be expensive for prevention programs and would introduce additional complexity for CAB-LA initiation and continuation, potentially resulting in lower PrEP coverage during periods of elevated risk.[xlii] Given its proven high efficacy and the potentially limited value of adding RNA screening to testing algorithms, WHO guidelines note that CAB-LA should still be considered for HIV PrEP in settings where HIV RNA screening is not readily available.[xliii]

An increasing global focus on user choice drives research and investments in the HIV prevention pipeline

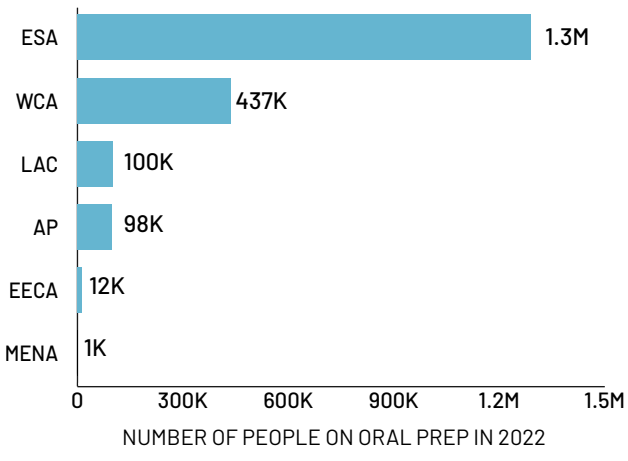
Several implementation studies are underway to explore real-world delivery and demand generation approaches for PrEP products, including CAB-LA, the dapivirine vaginal ring (DVR), and oral PrEP. The Biomedical Prevention Implementation Collaborative's Integrated Study Dashboard details these implementation studies across geographies, populations, and projects.[xxxiv]

Evidence generated from these studies aims to fill important implementation knowledge gaps, such as questions about real-world product choice, feasibility across service delivery channels, integration with other services, and the optimal combination of prevention methods and other services for specific populations. The impact of the growing portfolio of prevention products will depend on their accessibility, affordability, and integration within systems that fully consider the social and political context in which HIV infections take place. A person-centered, choice-based approach will be crucial to ensure efforts are community-led and that prevention strategies better align with the unique circumstances and lived experiences of at-risk populations.

Oral PrEP initiations continue to grow, with new research on effectiveness among cisgender women and opportunities to optimize PrEP delivery

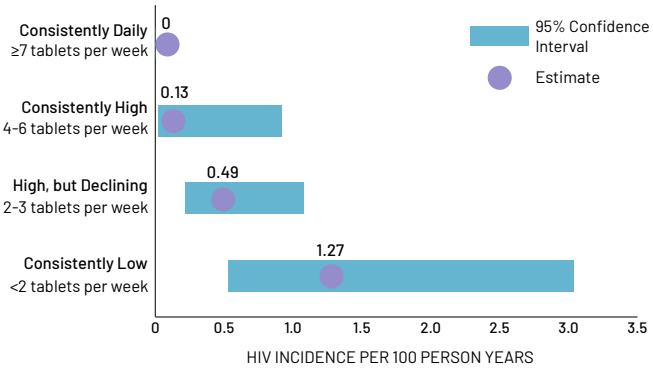
In 2022, approximately 1.9 million people in LMICs received PrEP. While many prevention programs are now rapidly increasing oral PrEP initiations, PrEP provision in LMICs is still limited to a small number of countries and is heavily concentrated in ESA [Figure 10].[i] While most new HIV infections occurred in ESA in 2022, approximately a quarter occurred in Asia and the Pacific, where there is significantly lower PrEP coverage. National programs in these regions have an opportunity to address this disparity by scaling oral PrEP use among at-risk populations.[x]

FIGURE 10: NUMBER OF PEOPLE IN LMICs WHO RECEIVED ORAL PREP IN 2022[i]



Previous studies have demonstrated that daily oral TDF/FTC is more than 99 percent effective for HIV prevention among men and transgender women who have sex with men. However, past findings indicate oral PrEP effectiveness may be lower for cisgender women, potentially due to poorer adherence and/or biological differences.[xliv] Data from a recent pooled analysis of over 6,000 cisgender women on TDF/FTC supports the real-world effectiveness of oral PrEP in cisgender women with consistent adherence (defined as at least four doses per week), indicating that it may be as high as other populations [Figure 11]. However, over half of all participants did not use TDF/FTC consistently, highlighting the urgent need for additional prevention options that improve adherence, such as long-acting modalities.[xlv]

FIGURE 11: HIV INCIDENCE RATES AMONG WOMEN WITH AVAILABLE ORAL PREP ADHERENCE DATA[xlv]



Additionally, efforts are underway to optimize oral PrEP delivery. In Kenya, researchers found that six-month oral PrEP dispensing and semiannual clinic visits resulted in non-inferior adherence compared to the standard quarterly dispensing and visit schedule. Additionally, the use of HIV self-tests every three months was non-inferior to clinic-based testing.[xlvi] This differentiated service delivery model has the potential to optimize oral PrEP delivery and further reduce HIV incidence.

PrEP-specific funding is essential for increasing uptake

Analysis shows that earmarked funding for PrEP is crucial for driving increased uptake. Targeted PrEP investments are likely to continue to play a major role in defining the future prevention landscape.[xlvii] In Sep. 2022, the Global Fund collaborated with the Children's Investment Fund Foundation (CIFF) to establish a catalytic matching fund of US$33 million to drive the scale-up of PrEP, including introducing novel PrEP options, in Kenya, Mozambique, Nigeria, South Africa, Uganda, and Zambia.[xlviii]

VMMC continues to be a cost-effective prevention intervention in SSA

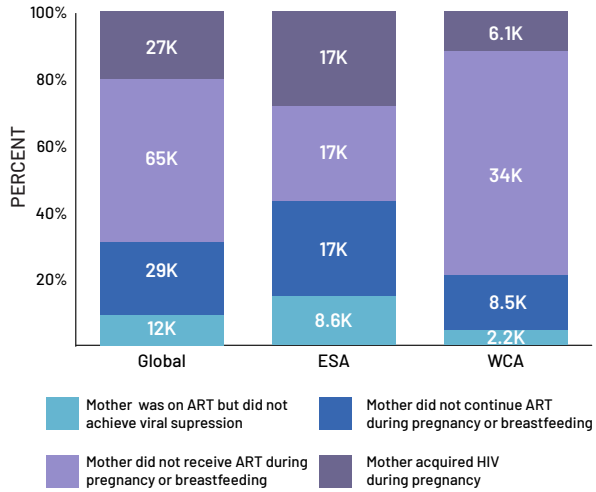
Since 2007, voluntary medical male circumcision (VMMC) has been a WHO-recommended, cost-effective prevention strategy in countries with high HIV prevalence and low coverage of male circumcision.[xlix] However, as ART coverage expands and additional prevention options are made available, there has been renewed interest in evaluating the long-term cost effectiveness of VMMC.

Researchers recently modeled scenarios to better understand the impact of changing epidemic conditions, including reductions in HIV incidence, on the cost-effectiveness of VMMC. Across five mathematical models, researchers found VMMC provides cost-savings over 50 years, while also lowering HIV incidence and mortality rates in men aged 15-49 in Malawi, South Africa, and Zimbabwe.[l] With continued improvements in HIV treatment and prevention, including the introduction of highly effective long-acting PrEP products, further modelling may be needed. Given the widening funding gap in the global HIV response, the development of efficient service delivery and demand generation models, and their integration within routine health services, will be crucial to minimize the cost of delivering VMMC services and enhance accessibility.

Trends in vertical transmission of HIV indicate additional efforts are needed to strengthen existing programs and expand PrEP options

Since 2015, ART coverage among pregnant and breastfeeding women has plateaued around 80 percent. In the same period, HIV infections among children aged zero to 14 years has slowed, from 200,000 in 2015 to 130,000 in 2022. This stagnation is particularly acute in certain regions, such as WCA, where vertical transmission programs reached only 53 percent of pregnant and breastfeeding women in 2022. Globally, and specifically in WCA, lack of access to ART during pregnancy or breastfeeding was the highest contributor to new HIV infections in children [Figure 12]. These findings suggest additional effort is needed to identify and link pregnant and breastfeeding women to treatment, via facility and community-based case finding, and retain them on ART through the end of breastfeeding.[x]

FIGURE 12: CAUSES OF HIV INFECTIONS IN CHILDREN, GLOBAL AND IN SUB-SAHARAN AFRICA[x]



A recent study co-authored by CHAI used a mathematical model to determine the most cost-effective combination of interventions to prevent vertical transmission among pregnant and breastfeeding women in Zambia over a 12-month period. Results showed that the interventions with the greatest reduction in vertical transmission included maternal support groups (35 percent reduction in infant infections), HIV retesting (6.5 percent reduction in infant infections), and infant prophylaxis (4.5 reduction in infant infections).[li]

Women are at substantially higher risk of acquiring HIV during pregnancy and the post-partum period, indicating the importance of access to combination prevention.[lii] Among the limited number of PrEP studies that have included pregnant women, several reinforce the safety of PrEP products for this population and their children. Recent results from a single-site study in South Africa confirm oral PrEP (TDF/FTC) use by pregnant women is not associated with preterm birth or small-for-gestational-age infants.[liii] An extension study in Kenya also found that children exposed to oral PrEP during pregnancy did not have reduced bone density or stunted growth as compared to unexposed infants at 36 months.[liv] These results support existing WHO guidelines encouraging the use of oral PrEP in pregnant and breastfeeding women at increased risk of HIV as part of a combination prevention approach.[lv]

Two phase 3b open-label studies involving the dapivirine vaginal ring, a flexible self-inserted silicone ring for HIV PrEP, reinforced the ring's safety during pregnancy and breastfeeding. DELIVER, a randomized safety trial carried out among pregnant women in Malawi, South Africa, Uganda, and Zimbabwe, found the ring was equally safe to use in the third trimester of pregnancy as daily oral TDF/FTC.[lvi] DELIVER's companion study, B-PROTECTED, revealed women can also safely breastfeed while using the ring. B-PROTECTED found very low levels of dapivirine in participants' breast milk and even lower concentrations in infants' blood, posing no safety risk.[lvii]

A sub-study of HPTN 084 will also explore the impact of CAB-LA for PrEP on pregnant and breastfeeding women and their children following an open-label extension amendment removing a requirement for contraception use during the study.[lviii] Data from close monitoring of women in the blinded phase of trial who became pregnant show that residual cabotegravir was well tolerated and may be safe during pregnancy and breastfeeding.[lix] In the open-label extension, women will be provided the option of continuing CAB-LA throughout their pregnacy, which will generate further safety data.[lviii]

WHO guidance emphasizes that women of reproductive potential should not face barriers to effective PrEP options such as CAB-LA.[xliii] In Kenya and South Africa, oral PrEP-experienced pregnant and postpartum women expressed preference for long-acting injectable PrEP over other modalities, demonstrating potential acceptability among a priority population.[lx] Similar findings from an HPTN 084 sub-study also signalled preference for CAB-LA over oral PrEP among women who were pregnant or intended to become pregnant.[lxi] The above research indicates prenatal and postnatal services may represent appropriate integration opportunities for PrEP services, though additional implementation and safety research is needed. As countries update national guidelines to include CAB-LA and develop introduction plans, it is imperative they are inclusive of women of reproductive potential or those who are pregnant or breastfeeding.

The HIV prevention pipeline includes investigational products with novel delivery mechanisms and MPTs set to increase PrEP options

To meet the diverse needs of at-risk populations, research is underway to better understand the needs and demands of potential end users. A dynamic and robust pipeline of novel HIV prevention products has the potential to increase user choice and expand the prevention market by delivering easier to use, more tolerable, and discreet products. The section below features several HIV prevention products currently in development:

Lenacapavir

In Dec. 2022 the US FDA approved lenacapavir (LEN) in combination with other ARVs for the treatment of people with multi-drug resistant HIV.[lxii] This capsid inhibitor is also being studied as a twice annual subcutaneous injection for HIV prevention. PURPOSE 1 is a two-pronged study that aims to evaluate the efficacy of LEN as well as tenofovir alafenamide fumarate/emtricitabine (TAF/FTC) for HIV PrEP in AGYW at risk of HIV infection. TAF/FTC is an oral PrEP product that is currently only approved for use in men. Initial results from this study are expected in 2024.[lxiii] The PURPOSE 2 study is evaluating the efficacy of LEN for HIV PrEP in men who have sex with men, with primary results expected in 2025.[lxiv]

Dual Prevention Pill

There are several multipurpose prevention technologies (MPTs) under development that combine contraception with HIV PrEP. If successful, such MPTs have the potential to offer benefits such as reducing pill/product burden, improving motivation and adherence, reducing stigma, and accelerating service delivery integration.[lxv]

Viatris is currently developing a novel dual prevention pill (DPP) for the prevention of pregnancy and HIV. The co-formulated daily pill will be packaged in a 28-pill blister pack with 21 pills containing TDF, FTC, levonorgestrel, and ethinyl estradiol, and seven pills containing only TDF/FTC. Viatris is tentatively expected to submit the DPP for regulatory review to the US FDA in 2024.[lxvi]

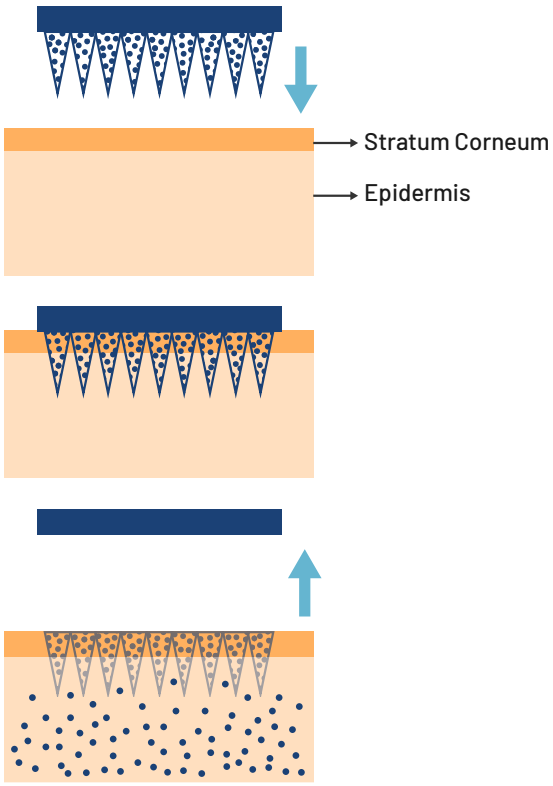
Clinical cross-over acceptability studies using an encapsulated combination pill began in late 2022 in South Africa and Zimbabwe to compare adherence, acceptability, and preference to separate oral PrEP and contraception pills. A follow-up version of this study will also be conducted once co-formulation is complete.[lxvii]

A recent cost-effectiveness study co-authored by CHAI indicates that among women not already using PrEP, the DPP is likely to be cost saving in sex workers and serodiscordant couples, though further studies on real-life adherence are needed.[lxviii]

Other Novel Delivery Modalities

MICROARRAY PATCHES: Microarray patches (MAPs) are a novel platform being developed for the delivery of ARVs, which may be co-formulated with hormonal contraception for certain populations [Figure 13]. MAPs offer an easy, discreet, self-administered option with one to three months of protection. Building on previous user research from South Africa and Uganda, a recent early-stage product development assessment in Kenya found MAPs were acceptable across stakeholder groups, including adolescent girls and young women, female sex workers, men who have sex with men, service providers, and policy makers.[lxix]

FIGURE 13: MICROARRAY PATCH DRUG DELIVERY SYSTEM EXAMPLE[lxx]



SUPPOSITORIES: New data from a pair of phase 1 trials show that a rectal/vaginal suppository combining the antiretrovirals TAF and elvitegravir is safe in humans, with high concentrations of drug present in rectal and vaginal tissues over the course of 24 hours.[lxxi, lxxii]

IMPLANTS: Qualitative end-user research from South Africa indicates potential acceptability of a long-acting, implantable form of PrEP by clients and providers.[lxxiii] All subdermal forms of HIV PrEP are currently in preclinical stages of development and are likely years away from availability.

BROADLY NEUTRALIZING ANTIBODIES: Long-acting, injectable broadly neutralizing antibodies (bNAbs) are being explored for HIV prevention in a range of populations and may offer a particularly promising intervention during the breastfeeding period for HIV-exposed infants. However, outstanding questions on

cold chain requirements and duration of efficacy could impact utility in resource-limited settings. Researchers modeled various scenarios and found bNAb product characteristics would ideally include a three-month or longer duration of effect, cost US$60 or less per dose, and have efficacy of at least 50 percent to be cost effective for use in infants in SSA.[lxxiv]

Results from the Antibody Mediated Prevention (AMP) Trials found that a bNAb (VRC01) tested did not prevent HIV among cisgender men and transgender persons in the Americas and Europe and at-risk women in SSA. However, in HIV isolates sensitive to the bNAb used in the trial, prevention efficacy was shown to be 75 percent.[lxxv] Further investigations of bNAbs informed by the results of the AMP trials continue in a range of early phase, pre-drug studies.[lxxvi, lxxvii, lxxviii]

VACCINES: In Jan. 2023, the Mosaico study, a large phase 3 HIV vaccine efficacy study, was stopped due to high HIV incidence in the trial arm.[lxxix] This is the third vaccine efficacy study to conclude early since 2020. While the early termination of Mosaico represents a setback for vaccine research, several innovative technologies are under investigation, including an experimental protein nanoparticle and a DNA/protein/modified virus combination vaccine.[lxxx] PrEPVacc, an African-led prevention study, is currently testing the efficacy of the combination vaccine.[lxxxi]

Additional African-led vaccine efforts include the Multisite Adolescent Girls and Young Women study based in Zambia. Supported by the International AIDS Vaccine Initiative, this program will collect and analyze a wide range of data from AGYW volunteers to inform the development of HIV vaccine and antibody products.[lxxxii]

TESTING

HIV diagnosis remains the largest gap among the UNAIDS 95-95-95 targets despite the central role of HIV testing across the cascade of HIV care, including within prevention services. Price reductions for HIV self-tests and expanded use of combination tests could improve screening rates and catalyze service integration. Persistent gaps in early infant diagnosis testing continue to delay progress toward epidemic control and contribute to inequities in outcomes for children, although increasing sales volumes of point-of-care early infant diagnosis tests in 2022 provide a point of optimism.

Rates of HIV status awareness are stagnating, but data show testing services remain a critical pathway for engagement in the HIV cascade of care

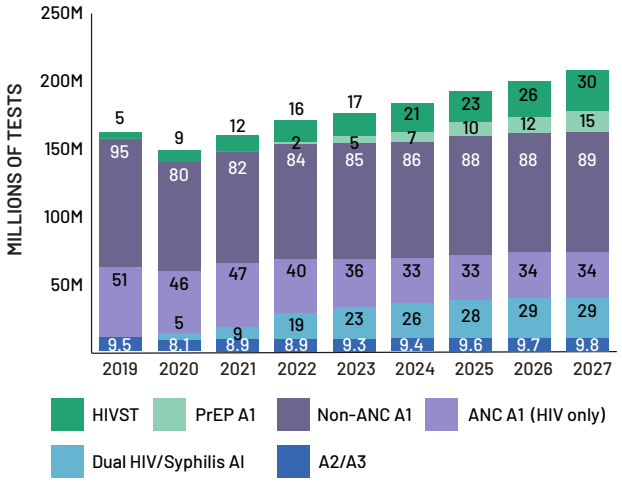
In 2022, 86 percent of PLHIV globally knew their HIV status, only a two percentage point increase compared to 2021.[i] Certain populations also continue to fall behind, with testing rates for children and adolescents significantly below those of adults.[x] As the global community pushes toward the last mile in HIV diagnosis, those who remain unaware of their status will likely be the hardest and most expensive to reach. However, testing services remain a critical part of a complex and often non-linear continuum of lifelong care, acting as a point of re-entry for clients who have disengaged from care, playing a vital and growing position as a gateway to prevention services, and performing a central role in monitoring within prevention programs.

Research shows that a significant number of people starting HIV treatment are actually re-initiating to care after a gap. In a review of ten studies across the Democratic Republic of Congo, Ethiopia, Kenya, and South Africa, between 20 and 50 percent of people who presented for ART initiation were found to be previously exposed to ART.[lxxxiii] This highlights the importance of testing as a primary entry point for re-engagement in care and reinforces the continuing need to maintain HIV testing volumes.

Access to low-cost HIV self-tests continues to expand

Adoption of HIV self-testing continues to pick up speed as 102 countries currently include HIV self-testing in national policies and 63 countries are implementing self-testing routinely.[lxxxiv] This represents a five-fold increase in the number of countries with routine HIV self-testing implementation compared to 2017.[lxxxiv] This growth is further reflected in a new HIV testing forecast from Eureka Idea Co. (EIC), which predicts considerable uptake of HIV self-testing even in the status quo scenario [Figure 14]. EIC also includes several other more aggressive forecasts including one where HIVST becomes the predominant testing modality in non-ANC settings.

FIGURE 14: EIC HIV TESTING PRODUCT MIX FORECAST IN DONOR FUNDED LMICs - CURRENT APPROACH SCENARIO[lxxxv]



This expansion in HIVST is expected to be facilitated by the increased availability of lower-cost options: currently, there are several HIVSTs available under US$2 (EXW) per test. Further, the Wondfo HIVST, the newest and lowest cost option, is available at just one US dollar per test thanks to a ceiling price agreement with MedAccess.[ix] In Oct. 2023, Uganda formally adopted the Wondfo HIVST and the first shipment is expected to arrive in Nov. 2023.[lxxxvi, xcvii] Other countries are currently pursuing regulatory approval. There are also two HIVSTs currently in WHO prequalification (PQ) review, with both expected to be priced less than US$2 (EXW). These tests, the Sedia Asante oral fluid HIVST and Premier's First Response HIVST (blood-based), could potentially be available as early as the end of 2023.

Expansion of blood-based HIVST

After a successful pilot among students at seven universities, Uganda has decided to further roll out a blood-based HIVST among peers of previous study participants pending pricing and procurement negotiations.[lxxxvii]

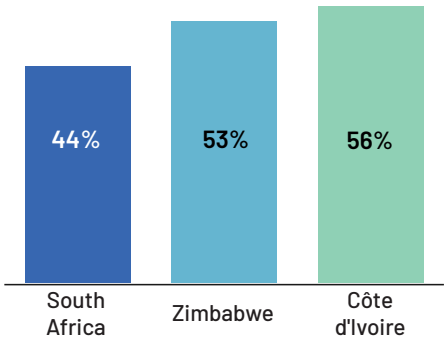
Zambia has also successfully piloted and now adopted blood-based HIVST to provide clients with more testing options and leverage more affordable HIV self-test kits for expansion of secondary distribution at antenatal care (ANC) and community distribution through community-based volunteers.[lxxxviii]

Persistent gaps in early infant diagnosis and pediatric testing stall progress toward epidemic control

Children and infants continue to be left behind in the HIV response across the care and treatment cascade, beginning with stagnating progress in identification of those living with HIV. Data from 16 PEPFAR countries, which represent 80 percent of CLHIV, found that countries only met 17.6 percent of the estimated pediatric testing need.[lxxxix] This data reinforces the need for more testing through a strategic mix of testing modalities.

A recent modelling study using data from Côte d'Ivoire, South Africa, and Zimbabwe projected that across countries, undiagnosed HIV prevalence decreases after age two, with more CLHIV dying than being diagnosed [Figure 15]. Identification during these initial years is critical as the study estimates that unless they are diagnosed and initiated on treatment, almost all children will die before the age of five.[xc]

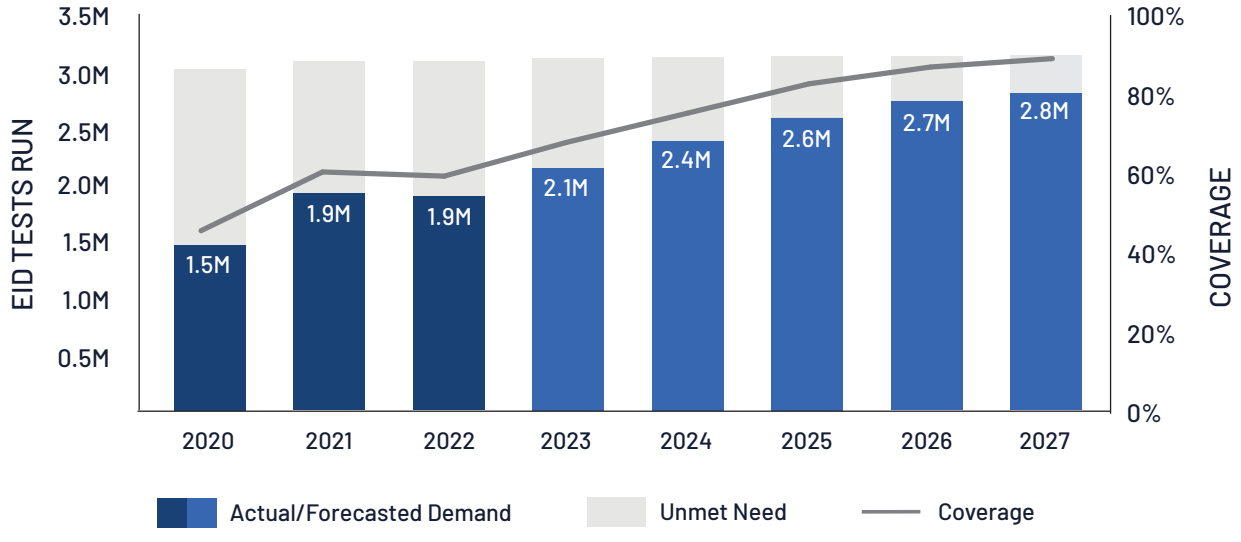
FIGURE 15: MODELED PERCENT OF CLHIV UNDER TWO YEARS OLD UNDIAGNOSED[xc]



Further, while EID remains critical for finding infants with HIV, testing volumes have flatlined over the past few years. In 2022, CHAI estimates that there was no change in EID testing volumes in LMICs compared to 2021, although challenges with POC reporting complicate forecasting [Figure 16].[3, xci]

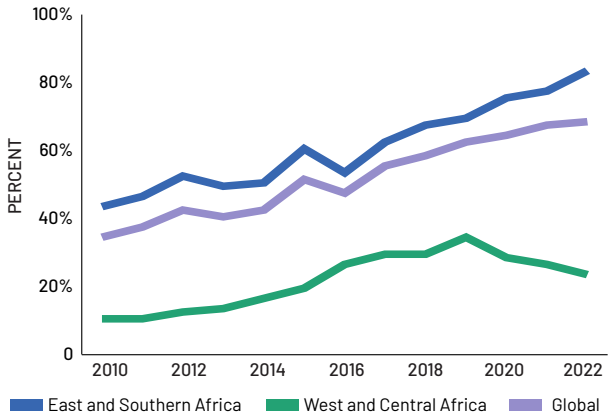
In addition to this overall stagnation, there are also concerning regional gaps in EID coverage. For example, in WCA, only 23 percent of HIV-exposed infants were tested for HIV by two months compared to 83 percent in ESA [Figure 17].[i] Further, WCA shows a three-percentage point decrease from 2021, part of a three-year trend of decline.

FIGURE 16: LMIC EID DEMAND FORECAST[xci]



[3] Lack of supplier sales data disaggregated by quarter or country complicated POC forecasting in 2022.

FIGURE 17: PERCENTAGE OF HIV-EXPOSED INFANTS TESTED FOR HIV BY TWO MONTHS, SELECTED REGIONS 2010-2022[i]



Encouragingly, the use of point-of-care EID—which has been shown to decrease time to result return and increase linkage to care—appears to be increasing. In 2022, 905,000 POC cartridges were sold in LMICs between Abbott and Cepheid, almost a 50 percent increase compared to 2021.[iii]

Further enabling the expansion of POC EID, Cepheid's HIV-1 Qual XC cartridge is expected to receive WHO PQ by the end of 2023. This new cartridge simplifies testing processes by removing the need for a thermomixer by utilizing dried blood spots (DBS) directly and negates the need for high-heat incineration for waste disposal.

Global interest in combination tests is increasing alongside rollout of the dual HIV/syphilis test

Combination tests offer the potential for simultaneous identification of multiple diseases. For example, a systematic review of 175 studies from 56 countries looked at the prevalence of blood-based diseases across over 14 million individuals. The review found that with multi-disease screening, for every one individual diagnosed with HIV, an additional five would be diagnosed with hepatitis B virus (HBV) and three with hepatitis C virus (HCV). There appear to be even greater potential gains for some key populations, with the review estimating that among people who use drugs, over 60 percent would test positive for HIV, HBV, or HIV and almost 20 percent would test positive for multiple infections.[xcii]

There is also increasing evidence that combination tests are acceptable and feasible for end users. A study in Thailand found that 99.8 percent of clients using a HIV/HBV/HCV combination self-test were satisfied with the process and that it simplified and streamlined service delivery.[xciii] With multiple triple combination tests in development and the PQ pipeline, validation and operational research in country contexts would generate important evidence around feasibility and value of integrated screening.[xciv]

Another key combination test for PLHIV is the dual HIV/syphilis test, which is currently available from three suppliers with WHO PQ. One of these tests is available from SD Biosensor at a cost of US$0.95 (EXW) per test as a result of a CHAI/MedAccess ceiling price agreement.[xcv, xcvi] Adoption of the dual test is ongoing with at least 40 countries including it in national policy for either pregnant women or key populations.[xcviii]

In tandem with increasing access to testing, treatment for syphilis is also critical to avoid preventable deaths, particularly among exposed infants. However, global shortages of benzathine G penicillin, an injectable, long-acting form of penicillin used to treat syphilis, have impacted access.[xcix] Global action to address supply chain constraints for this product is needed to ensure that syphilis identification is paired with treatment.

There are overlapping transmission routes and risk factors between HIV, HBV, and syphilis and comorbidity can lead to higher vertical transmission risk. This underscores the critical need for integration of tools and service delivery across disease areas to improve health outcomes and save lives, advancing the global goal toward triple elimination.

Suppliers continue to develop additional combination tests with growing interest in combination lateral flow products for triple elimination of HIV, HBV, and syphilis, and others. Increased access to combination tests could help increase identifications across diseases and catalyze cost-effective opportunities to integrate service delivery across disease areas by simplifying procurement and supply chain processes and improving screening rates across multiple disease areas.

Given ANC systems already serve the majority of pregnant women and include routine HIV screening, there is a huge, unaddressed opportunity to close the testing gap during ANC between HIV, HBV, and syphilis and reduce significant regional disparities in testing coverage. Efforts are needed to strengthen integrated health worker in-service training, strengthen and coordinate timely cross-disease monitoring mechanisms, and engage community members to raise awareness and generate demand. There is an opportunity to build on proven HIV differentiated service delivery models while innovating in community settings to expand access and uptake of comprehensive care.

TREATMENT

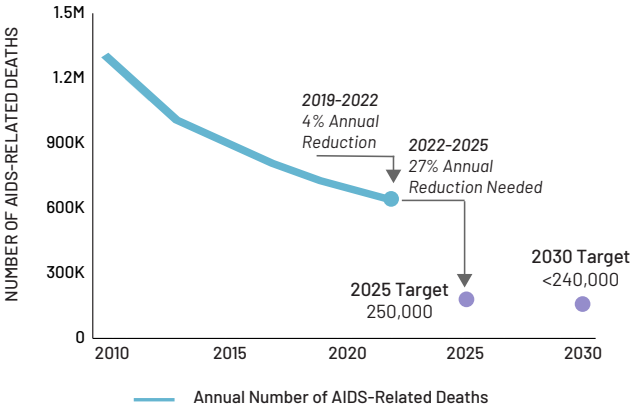
Expanded access to DTG-based regimens, now taken by over 90 percent of adults and hundreds of thousands of children in GA LMICs, has significantly improved treatment outcomes for PLHIV. Treatment optimization continues as introduction of the best-in-class protease inhibitor, DRV/r, begins to scale up and with the US FDA's approval of long-acting lenacapavir, although a lack of voluntary licensing for the latter threatens access in LMICs. Despite these advancements, treatment coverage and viral suppression rates, particularly among children and key populations, fall short of the UNAIDS epidemic control targets, resulting in high rates of mortality and morbidity. The global community must continue to ensure HIV treatment services are person-centered, that they are structured to support client retention in care and keep them virally suppressed, and that they provide timely screening and treatment for AHD and related OIs to reduce preventable AIDS-related mortality.

ADVANCED HIV DISEASE

Progress toward reducing AIDS-related deaths off track from targets, with care interruptions an ongoing challenge

In 2022 there were still 630,000 AIDS-related deaths globally, an unacceptably high number given widely accessible and low-cost treatment and testing.[i] Progress is significantly off track and will likely not meet the 2025 and 2030 Fast-Track targets for reductions in AIDS-related deaths [Figure 18].[x]

FIGURE 18: PROGRESS REQUIRED TO REACH GLOBAL REDUCTIONS IN AIDS-RELATED DEATHS TARGETS[i]



The frequency of clients presenting with AHD at treatment initiation remains high with recent data suggesting that 30 to 40 percent of people starting ART in LMICs have AHD.[c]

As discussed in the Testing section, an increasing number of those presenting to treatment are re-engaging with care after an interruption. A South African study from 2017 and 2018 found that 51 percent of people who tested positive for HIV had been previously diagnosed, and 81 percent of these individuals had been previously initiated on ART.[ci] This is concerning given another South African study found that a longer gap between diagnosis and treatment initiation reduced the chance of viral suppression and increased risk of death.[cii]

Over the past four years, CHAI's efforts to tackle supply and demand barriers in the adult AHD market and introduce the WHO-recommended AHD Package of Care across ten focal countries have significantly improved AHD diagnostic and treatment availability for those who need it most. As part of these efforts, CHAI and partners developed a Global AHD Toolkit that includes community materials, programmatic tools, job aids, and training materials. The toolkit has been used by multiple countries, including many outside of the CHAI project, and includes an AHD Commodity Calculator, which supports the quantification of AHD commodities in countries adopting the AHD Package of Care. While great progress has been made thus far, urgent action and innovation is required to reach the goal of fewer than 240,000 AIDS-related deaths by 2030. Programs and partners must aim to reduce the number of people presenting to care with AHD, identify AHD sooner, and link them to appropriate prevention and treatment for OIs.

Ensuring access to CD4 testing remains critical as supplier shifts impact market dynamics

CD4 testing remains the most critical part of the pathway to accessing the AHD package of care. Without the use of CD4 tests to identify AHD, it is estimated up to 50 percent of AHD cases would be missed as half of patients present as asymptomatic and would not be identified via symptom screening.[ciii] However, the CD4 market is experiencing several significant supplier shifts estimated to impact access to CD4 testing.

In May 2022, Abbott announced that it discontinued manufacturing their PIMA CD4 analyzer, but will continue to supply PIMA cartridges, refurbish existing devices, and honor all existing service and maintenance agreements.[civ]

Similarly, BD announced in Dec. 2022 that they will discontinue production of both the FACSPresto and FACSCount cartridges and devices by the end of 2024, at which time programs must divert any testing currently being done on these devices to other solutions.[cv]

Given the importance of CD4 testing, partners urged suppliers to reconsider production of CD4 tests or to support technology transfer for local production. While Abbott is open to a technology transfer, a redesign of the analyzer is required as some raw materials are no longer being produced, thus requiring a significant investment from any manufacturer who would be interested in producing the analyzer.[cvi] Amidst these discussions, there have been some commitments from suppliers of lab-based tests, as well as AccuBio which produces VISITECT, to stay in the market which will help to ensure future access to testing. Countries should begin to plan for these changes in the CD4 market while ensuring access to testing for those who need it.

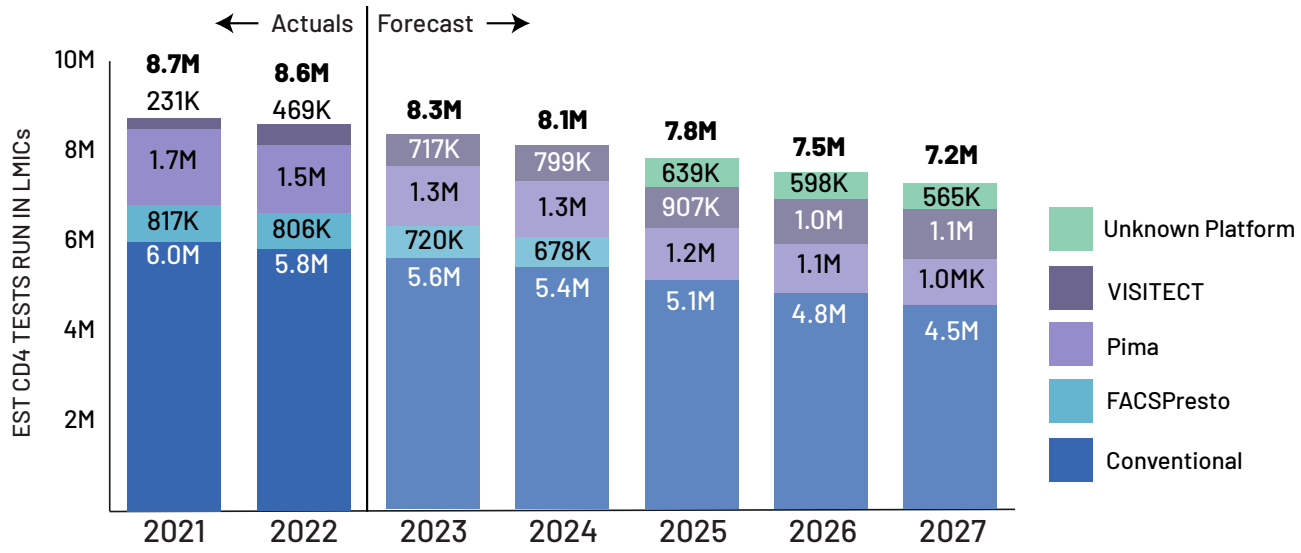
To better inform market visibility, CHAI developed a CD4 forecast split by platform [Figure 19]. CHAI estimates that conventional testing accounts for over 50 percent of total volumes.[cvii] While South Africa comprises around one third of the conventional volumes, this still indicates considerable conventional testing volumes across the rest of LMICs. This forecast is based on historical demand, and future splits across devices may change significantly as these market shifts bear out. Looking forward, CHAI expects increased utilization of VISITECT tests to fill the gaps in POC CD4 testing access.

Given the evolving CD4 market dynamics, limited national and donor budgets for CD4, and persistent high rates of AHD at presentation, demand generation and CD4 network optimization will be needed. Demand generation will help address barriers to access, improve future planning, and facilitate earlier testing and linkage to treatment, ultimately improving access to the AHD package of care and reducing preventable AIDS-related deaths. Similarly, CD4 network optimization will enable a better understanding of gaps and highlight solutions that can optimize CD4 coverage for eligible PLHIV using the existing infrastructure.

New point-of-care tests for cryptococcal meningitis could simplify linkage to care

Cryptococcal meningitis (CM) is a common opportunistic infection associated with AHD, and the second leading cause of death among PLHIV.[cviii] However, currently it is estimated that only a quarter of people in Africa have routine access to cryptococcal antigen (CrAg) testing.[cix] Expanding access to this critical screening tool is a key step in avoiding preventable AIDS-related deaths.

FIGURE 19: LMIC CD4 DEMAND FORECAST SPLIT BY PLATFORM[cvii]



Further enabling future scale-up, a semi-quantitative lateral flow CrAg assay from IMMY is under development and expected to be available in 2023/2024. This test has the potential to simplify linkage to CM treatment by negating the need for a confirmatory lumbar puncture in a subset of patients.[lxxxviii] However, further research is still needed to inform WHO guidance.

Once CM is identified, access to WHO-recommended treatment is critical to save lives. This includes liposomal amphotericin B (L-AmB) and flucytosine (5FC), key components of the induction phase of CM treatment. Between 2021 and 2022, 5FC order volumes increased 75 percent and L-AmB order volumes increased 51 percent, as seen by the ARV Procurement Working Group (APWG) and driven by the Unitaid-CHAI Optimal project. As of publication, 18 LMICs placed orders for 5FC and 30 placed orders for L-AmB [Figure 20].[cx]

Decentralization and price reductions could address critical barriers to histoplasmosis screening

Histoplasmosis is a dangerous opportunistic infection acquired by inhaling spores of a fungus typically found in bird and bat droppings. However, an estimated three quarters of people living in Africa have no access to histoplasmosis diagnostics, and when testing is available it's often only accessible at large central facilities. As a result, histoplasmosis is often misdiagnosed as TB and incorrectly treated, leading to preventable deaths.[cix]

Point-of-care histoplasmosis tests using urine are a promising option to improve access, but pricing and access barriers have limited their use to date.

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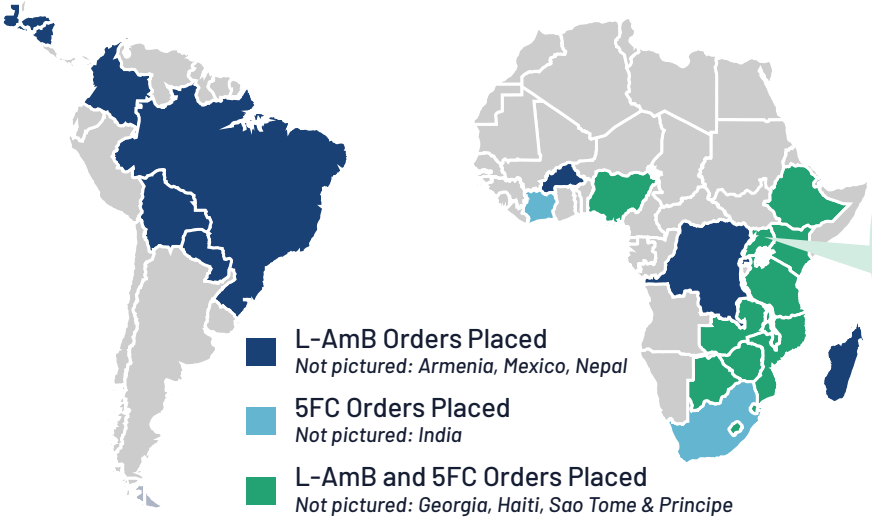
With support from Unitaid, CHAI partnered with the Medical Mycology Society of Nigeria to identify the true burden of histoplasmosis by screening 1,000 AHD patients across 10 sites in Nigeria. This ongoing prevalence study will inform national policy guidelines on histoplasmosis screening for PLHIV with AHD.

Miravista developed the first CE marked urine-based histoplasmosis lateral flow assay (LFA) test, although it is not currently US FDA-approved and is cost prohibitive for many programs.[cxi] IMMY is in the process of developing a LFA test that is expected to enter the market in 2024.[lxxxviii] As LFA products become available at lower prices and significantly reduce complexity compared to existing, lab-based testing options, programs will be able to rapidly expand access.

2025 targets for reductions in TB-related deaths among PLHIV are within reach, bolstered by improvements in TB treatment and supplier capacity

While there have been significant improvements in access to TB care, an estimated 190,000 PLHIV died of TB globally in 2021. However, with concerted efforts, the 2025 target of 150,000 deaths is well within reach [Figure 21].[x] Achieving this goal will require continued optimization throughout the cascade of care, including access to optimal TB prevention and treatment regimens.

FIGURE 20: 5FC AND L-AMB ADOPTION MAP, APWG[cx]



Unitaid

CHAI, with support from Unitaid, helped to introduce L-AmB and 5FC at 19 hospitals in Uganda, saw a reduction in mortality, reduced side effects, and shortened hospital stays.

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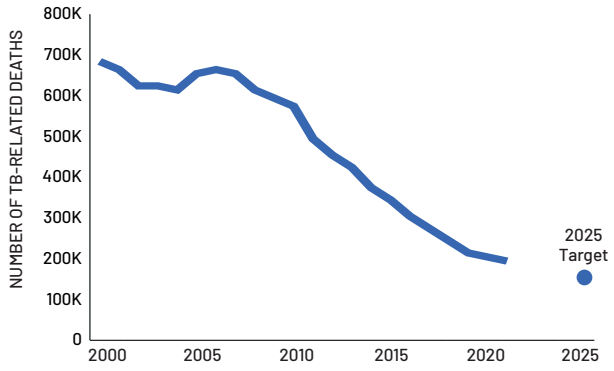
FIGURE 21: NUMBER OF TB-RELATED DEATHS AMONG PLHIV GLOBALLY[i]



One of the first critical steps in reducing deaths is identifying those at risk of TB and increasing access to TB preventive therapy (TPT). A new modeling study estimates that failure to implement contact tracing and tuberculosis prevention in 29 high-incidence countries could result in almost 850,000 preventable deaths from TB through 2035. The study also found that scaling up TPT prevented deaths from TB and was likely to be cost-effective among PLHIV in 29 high-HIV-incidence countries.[cxii]

The supply of 3HP, an optimal TPT regimen comprising isoniazid (INH) and rifapentine (RPT), has stabilized following the easing of several years of supply challenges.[cxiii] As of 2022, 3HP has been adopted by 25 countries, an increase of 39 percent compared to 2021.[cx]

For PLHIV specifically, viral suppression is essential to preventing TB-related deaths. However, only 46 percent of PLHIV who developed TB in 2021 were receiving ART, highlighting another critical gap.[x]

There have also been several advances in TB research that could simplify or shorten treatment timelines. New WHO guidance on multi-drug resistant (MDR) TB now recommends the use of a novel all-oral six-month regimen composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM).[cxiv] For drug-susceptible TB, treatment usually consists of a six-month rifampicin (RIF)-based regimen. However, new research indicates that an eight-week regimen composed of bedaquiline and linezolid is safe, efficacious, and noninferior to standard treatment.[cxv] These shorter regimens could help increase treatment adherence and improve treatment outcomes.

Mpox downgraded from a public health emergency, but remains a concern for PLHIV, especially those with unsuppressed viral loads

In May 2023, the global mpox outbreak was downgraded from a public health emergency of international concern by the WHO.[cxvi] However, according to a recent cohort study, PLHIV remain at increased risk of mpox infection and accounted for up to half the cases in 2022. The study also found that mortality from mpox among PLHIV increases as CD4 count decreases, suggesting particular susceptibility for people with AHD.[cxvii] The WHO continues to recommend PLHIV with AHD as a priority group for mpox vaccination.[cxviii]

Continued disparities in morbidity and mortality among CLHIV demonstrate the need for additional investments in pediatric AHD care

Children living with HIV continue to be disproportionately affected by AHD. In 2022, CLHIV accounted for 13 percent of AIDS-related deaths, despite comprising only four percent of PLHIV.[x] The youngest CLHIV are particularly at risk, with PEPFAR program data showing that CLHIV on ART under five have an increased likelihood of death compared to older age groups.[cxix] To better address the needs of CLHIV, it is critical to understand key gaps and challenges in identifying and managing AHD for this group and improve monitoring of drivers and outcomes.

A recent article co-authored by CHAI provides an overview of common clinical presentations of AHD in children and adolescents, and articulates that the prevalence and presentation of opportunistic infections vary significantly between adults and children living with HIV.[xi] It also highlights the pressing need for additional investments in research and evidence generation to support the AHD package of care for CLHIV.[xi]

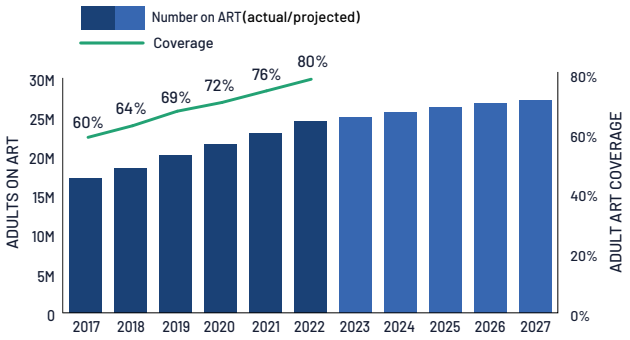
Continued prioritization and increased funding is needed to close the pediatric AHD gap and avoid preventable deaths among CLHIV. Further real-world evidence generation and research alongside concrete actions to address these inequalities remain critical moving forward.

ADULT TREATMENT

Nearly 29 million adults on treatment globally in 2022, representing a diverse group of PLHIV with unique needs

In 2022, an additional 1.7 million adults (1.5 million in GA LMICs) were on treatment globally compared to 2021, for a total of nearly 29 million on ART.[i, iii] Adult treatment coverage in GA LMICs is now 80 percent in 2022, a four-percentage point increase from 2021 [Figure 22].[i]

FIGURE 22: ADULTS ON ART AND COVERAGE IN GA LMICs[i]



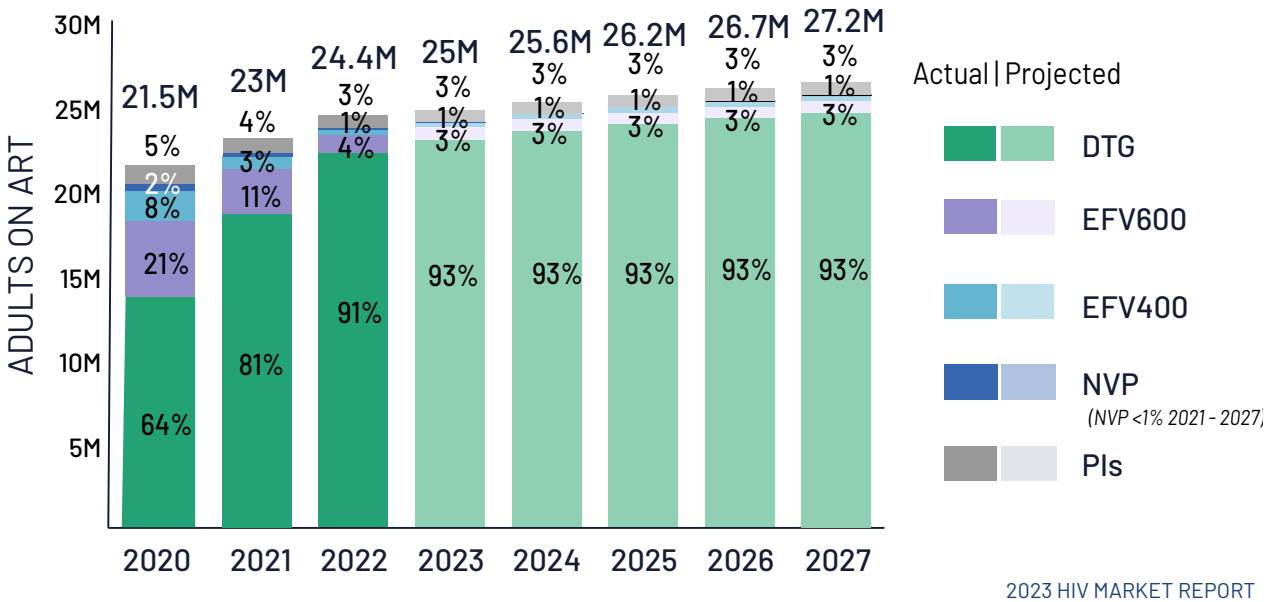
However, despite the increasing number of PLHIV on treatment, some geographies and populations still face barriers to accessing care. Adult treatment coverage rates in the Middle East and North Africa, Eastern Europe and Central Asia, and Asia and the Pacific are lower than those of other regions.[i] Furthermore, key population groups in many countries have lower treatment coverage rates compared to the general population. Stigma and discrimination (including violence and harassment), punitive laws and policies, sparse key population-specific HIV data, and poor funding for key population programs contribute to the gaps in ART initiation and retention in care. In at least one-third of reporting countries, concerns about stigma, confidentiality, or other issues resulted in over 10 percent of key populations avoiding the use of healthcare services, as documented by UNAIDS.[x] To bridge these disparities, UNAIDS recommends that countries should implement inclusive HIV programs that prioritize the involvement of key populations, repeal discriminatory laws and policies, enhance healthcare provider accountability, and strengthen community engagement.[x]

Beyond key populations, men continue to be less likely to be on ART than women in sub-Saharan Africa, the Caribbean, and Eastern Europe and Central Asia, likely a result of harmful gender norms and structural barriers.[x, cxx] UNAIDS has published a framework outlining strategies to address these challenges, including targeted awareness campaigns and partnerships with community leaders, and support networks to dispel gender-related myths and stereotypes that hinder men from seeking and adhering to treatment.[cxx]

Over 90 percent of adult PLHIV on ART in GA LMICs now take DTG-based regimens

CHAI estimates that DTG use among adults in GA LMICs has reached 91 percent, a ten-percentage point increase from 2021, with an estimated 22.2 million adults on DTG-based regimens in 2022 [Figure 23].[iii]

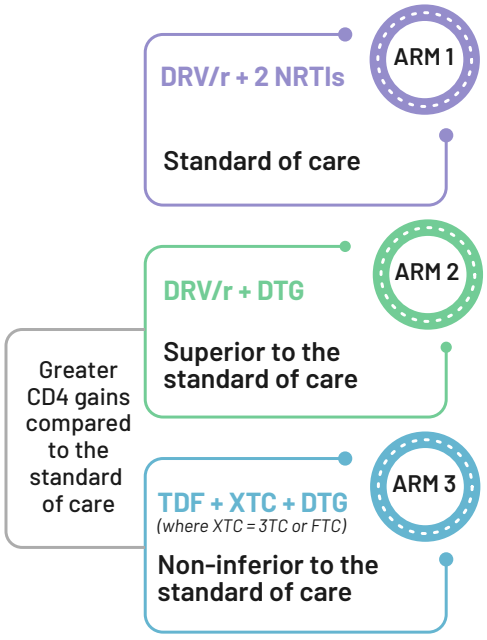
FIGURE 23: ADULT INSTI/NNRTI/PI USE IN GA LMICs[cxxi]



Given the widespread use of DTG across first- and second-line treatment, and the data challenges programs face in differentiating between DTG used in various lines of therapy, CHAI's estimates are aggregated across lines of treatment. The global community may need to revisit the traditional treatment classification structure utilizing lines of therapy and consider categorizing clients based on prior drug exposure instead.[cxxii]

New research continues to show that recycling tenofovir disoproxil fumarate (TDF)-based nucleoside reverse transcriptase inhibitor (NRTI) backbones is effective when used with DTG, which could have implications on treatment sequencing and DTG use. Results from D²EFT, a randomized open-label study, showed that a switch to TDF+XTC+DTG without universal access to genotyping was non-inferior to using DRV/r and two NRTIs following treatment failure on a non-nucleoside reverse transcriptase inhibitor (NNRTI).[cxxiii] The study also found a second-line regimen comprised of just DTG and DRV/r to be superior to DRV/r and two NRTIs [Figure 24], although more research is needed on two-drug regimens in LMICs, especially those that do not contain TDF which is used to cross-treat hepatitis B.

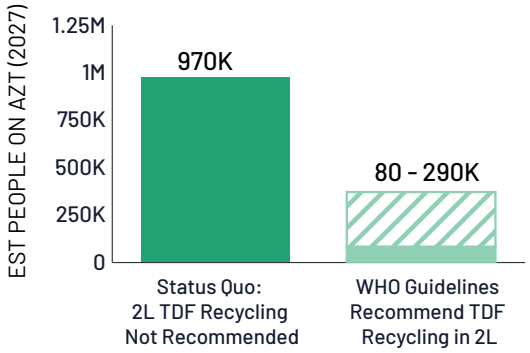
FIGURE 24: D²EFT STUDY RESULTS[cxxiii]



Similarly, in the Second-Line Switch to DTG (2SD) prospective trial in Kenya, researchers found that switching virally suppressed clients on second-line treatment from a ritonavir-boosted protease inhibitor (PI)-based regimen to a DTG-based regimen (without genotypic resistance information) was non-inferior to a continuation of the PI-based regimen.[cxxiv] A transition from PI-based regimens to DTG-based regimens offers benefits such as fewer side effects, lower pill burden, reduced risk of drug-drug interactions, and lower costs. These findings supplement evidence from the NADIA, VISEND, and ARTIST studies supporting the use of DTG plus recycled TDF/3TC for people failing a NNRTI-based regimen.[cxxv, cxxvi, cxxvii] While WHO guidelines have not been updated to reflect this, the WHO has committed to re-evaluating TDF recycling and other "second-line" recommendations.

Adoption of TDF recycling could have major implications on NRTI use in GA LMICs. CHAI estimates that zidovudine (AZT) use will be significantly reduced with widespread adoption of TDF recycling [Figure 25]. Consequently, ensuring the availability of low-volume products, including AZT for use in cases of TDF intolerance, will be critical for equitable and uninterrupted access to treatment.

FIGURE 25: POTENTIAL IMPACT OF TDF RECYCLING ON ADULT NRTI BACKBONE USE IN 2027[iii]



Recent studies reevaluate current recommendations on DTG and rifampicin dosing during TB coinfection and address weight-gain concerns

DTG has proven to be safe and effective when used during rifampicin-based TB treatment, and the WHO currently recommends doubling the dose of DTG for TB coinfected clients for the duration of RIF-based treatments.[cxxviii, lv] Recent research, however, suggests that this may be unnecessary. RADIANT-TB, a non-comparative randomized controlled trial, found similar virological outcomes in once-daily DTG versus the recommended twice-daily dosing for clients on rifampicin-based TB treatment.[cxxix] While further research is required in this area, these findings could potentially improve ART adherence, minimize unnecessary ARV exposure, and reduce program costs.

A recent study involving a secondary analysis of NAMSAL and ADVANCE trial data, both of which reported increased weight gain with DTG use compared to efavirenz (EFV), found that hypertension associated with ART can be effectively treated with low-cost generic anti-hypertensive drugs.[cxxx, cxxxi, cxxxii] The findings suggest that weight gain, rather than specific ARVs, accounted for the observed blood pressure differences. Notably, the study also found that the weight gain initially ascribed to DTG use in the ADVANCE trial was instead a result of the absence of weight-gain *suppression* due to EFV-induced nausea and other side effects, which did not occur with DTG use.[cxxxii, cxxxiii]

Slow initial uptake of DRV/r (400/50 mg) gains momentum with PEPFAR procurement and potential WHO guideline revisions

Historically, the adult second-line market in GA LMICs has been dominated by the protease inhibitors atazanavir/ritonavir (ATV/r) and lopinavir/ritonavir (LPV/r). From 2012 to 2022, ATV/r's market share within the PI category increased from six to 59 percent due to its lower cost, better clinical profile, and significantly lower pill burden compared to LPV/r.[lxxxviii]

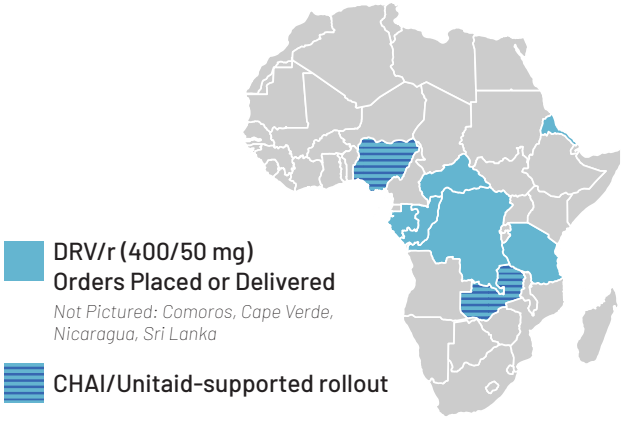
A third PI, darunavir (DRV), is considered the best-in-class protease inhibitor due to its high genetic barrier to resistance, improved viral suppression rates, better tolerability, and lower pill burden compared to LPV/r. However, no affordable generic product co-formulated with ritonavir was available in LMICs until Hetero Labs' DRV/r (400/50 mg) product received WHO PQ in July 2021 and was launched at US$17.50/pack thanks to a CHAI-Unitaid pricing agreement.[cxxxiv] Despite this availability, and pricing below that of LPV/r, uptake in GA LMICs has been slow to date.

A major challenge limiting DRV/r uptake at scale is its status in the WHO guidelines as an alternative second-line option following treatment failure with DTG. PEPFAR had also been unable to procure Hetero's DRV/r product given that it is WHO prequalified and not US FDA-approved, thus limiting access to DRV/r in PEPFAR-supported countries.

However, these barriers are beginning to fall. PEPFAR can now procure Hetero's product and has initiated orders. CHAI expects this will result in increased adoption beyond the 12 LMICs currently procuring DRV/r [Figure 26].[cxxxv]

Additionally, PEPFAR has signaled that it will no longer procure LPV/r (200/50 mg) tablets as it looks to scale optimal DRV/r in line with recent COP guidance. However, it is important to note that some use cases remain for LPV/r, such as in the treatment of TB/HIV co-infected clients who need a PI, as DRV/r and ATV/r cannot be used alongside rifampicin-based TB treatment.

FIGURE 26: DRV/r (400/50 MG) ADOPTION MAP, APWG, AS OF Q3 2023[cxxxv]

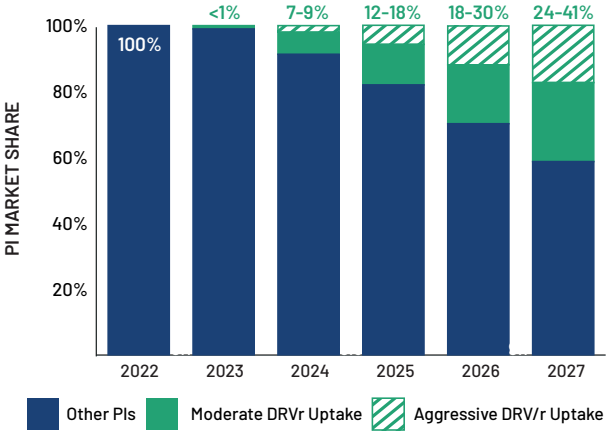


In addition to PEPFAR's ability to procure, the WHO has committed to reviewing its second-line treatment guidelines, including DRV/r's positioning and NRTI recycling, following strong community advocacy. In Dec. 2021, Afrocab issued a community position statement calling for an update to the WHO guidelines to promote DRV/r to the preferred PI for second-line use.[cxxxvi] Following this, in Mar. 2023, Afrocab issued a follow-on letter demanding WHO leadership on the issue and continuing to call for a guideline update.[cxxxvii]

> **"We call on the WHO to urgently remedy the current status of DRV/r and replace LPV/r as the preferred regimen with immediate effect... There is no justifiable reason to maintain the current second-line regimen now that a fixed-dose combination of DRV/r is available at an affordable price."**
>
> ~Kenly Sikwese
> Afrocab Treatment Access Partnership[cxxxvii]

Based on these market shifts, CHAI has modeled the following scenarios for DRV/r uptake in the coming years [Figure 27]. The first scenario portrays the current state with PEPFAR's decision to procure DRV/r and discontinue LPV/r (200/50 mg) procurement. The second scenario envisions a situation where the WHO updates its guidelines by early 2024, promoting DRV/r to the status of preferred second-line treatment option.

FIGURE 27: DRV/r (400/50 MG) FORECAST (EXCLUDING SOUTH AFRICA)[iii]



Development of treatment pipeline products continues, and US FDA approval of lenacapavir adds another long-acting product to the mix, but further optimization is needed

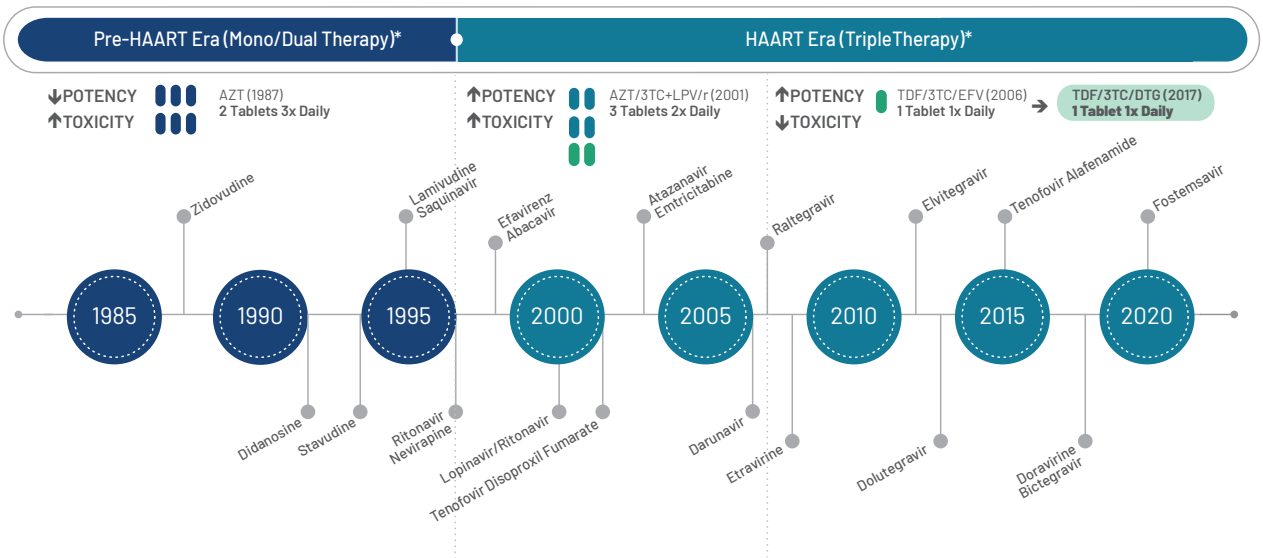
Decades ago, AZT monotherapy (the first ARV for HIV) showed positive impacts on outcomes for PLHIV but was not sufficient for sustained improvements in clinical outcomes.[cxxxviii] Advances in antiretroviral therapy, including combination therapies, NNRTIs, PIs, and INSTIs, led to the WHO's endorsement of TDF/3TC/DTG (TLD) as the preferred first-line regimen in 2018 [Figure 28].[cxxxix, cxl] TLD offers rapid viral suppression, a high genetic barrier to resistance, fewer side effects, and a lower price compared to TDF/3TC/EFV (TLE), enhancing treatment outcomes.

Currently available optimal ARVs are effective, well tolerated, and safe. However, given all available options in LMICs consist of daily oral pills, there are still challenges associated with daily (and lifelong) adherence. Long-acting options, including those in the development pipeline, hold the potential to improve adherence and discretion [Figure 29]. Dual therapy with novel agents has re-emerged as a potential option both for long-acting non-oral combinations and more traditional shorter acting oral regimens. Dual therapy in LMICs will have to account for cross-treatment of hepatitis B, which cannot be achieved without the presence of tenofovir in two-drug treatment regimens.

One such long-acting product with the potential to positively impact HIV treatment is injectable lenacapavir (LEN)—the first capsid inhibitor. In Dec. 2022, Gilead received regulatory approval from the US FDA for LEN, based on results from the CAPELLA trial,for six -month subcutaneous injections alongside other ARVs in treatment-experienced adults with multidrug-resistant HIV.[lxii, cxliii] However, the absence of generic licensing at the time of publication poses a major challenge to access in LMICs.

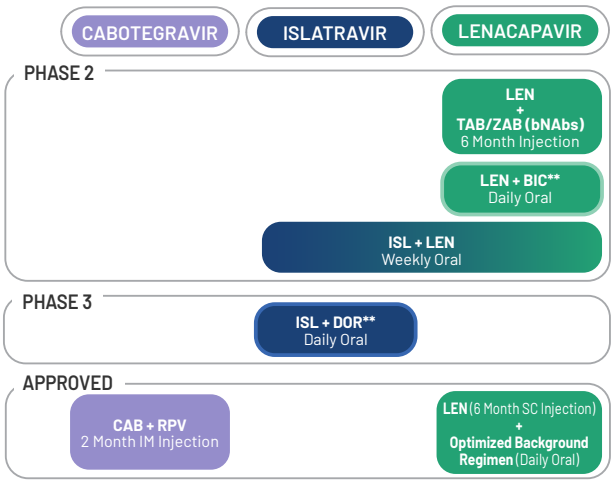
The phase 2 CALIBRATE trial provided evidence on the efficacy of LEN in treatment-naïve PLHIV. Results demonstrated that subcutaneous LEN in combination with other oral ARVs maintained high rates of virologic suppression through week 80 in the study population.[cxliii]

FIGURE 28: ARV APPROVAL HISTORY[cxli]



Adapted from WHO; approval dates based on US FDA approval; ARVs listed are not exhaustive

FIGURE 29: ARV PIPELINE PRODUCTS AND TRIALS[lxxxvi]



**Not exhaustive, further combinations in Phase 1 trials*
***Daily oral combinations, not long-acting ARVs*

However, it is not known when Gilead will file an application for an updated label to include LEN's use in treatment-naïve PLHIV, or when the US FDA will approve it.

Despite LEN's benefits, it requires coadministration with an optimized backbone regimen, all of which currently available are daily oral pills. To reap the full benefits of long-acting treatment in terms of reduced clinic visits and improved adherence, development of novel long-acting ARVs to be paired with LEN, or studies evaluating novel combinations of existing long-acting products such as CAB and LEN, are necessary.

In Feb. 2023, Gilead announced results from a phase 1b trial that assessed the safety and efficacy of LEN in combination with the broadly neutralizing antibodies, teropavimab (TAB) and zinlirvimab (ZAB), as a potential long-acting treatment.[cxliv] The combination was well tolerated and highly efficacious. Phase 2 of the study commenced in May 2023.[cxlv] While this development appears promising, stakeholders need to address potential issues, such as the high cost of bNAbs, the need for appropriate selection and ongoing monitoring, and the required health infrastructure for storage and distribution, to ensure equitable access in LMICs.

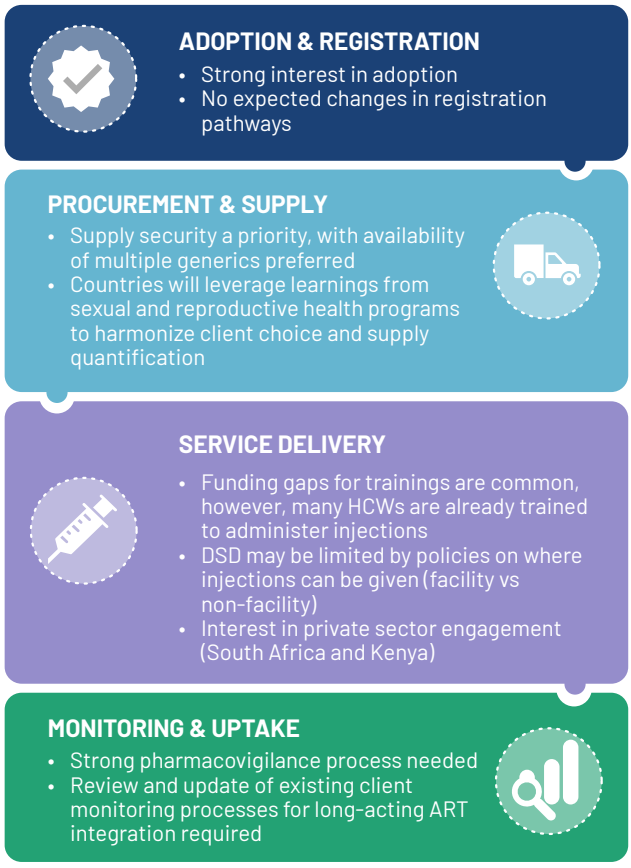
A phase 2 study sponsored by Gilead and in collaboration with Merck is underway to assess the efficacy of oral weekly islatravir (ISL) in combination with bi-annual subcutaneous LEN in virologically suppressed PLHIV.[cxlvi] Notably, ISL remains a weekly oral pill, reinforcing the need for development of longer-acting non-oral formulations to be administered with LEN.

CHAI assessment shows that key stakeholders have a strong interest in adoption of long-acting HIV treatment, but introduction likely to be complex

CHAI, funded by Unitaid and in partnership with ministries of health (MOHs), conducted a landscape assessment in Kenya, Nigeria, and South Africa to evaluate country readiness and outline next steps for the introduction of long-acting ART.[iii] The assessment involved data collection and consultations with MOH personnel/key opinion leaders, community activists, and discussions with healthcare workers. In all three countries, stakeholders expressed their excitement at the transformational potential of long-acting products, but recognized that health systems will require key changes to facilitate broad access to long-acting products.

Across countries, stakeholders held varying opinions on the use of innovator products, selecting initial sub-populations for prioritization, seeking local evidence, and anticipated implementation of client choice. Key similarities are summarized in Figure 30.

FIGURE 30: LONG-ACTING HIV TREATMENT LANDSCAPE ASSESSMENT FINDINGS[iii]



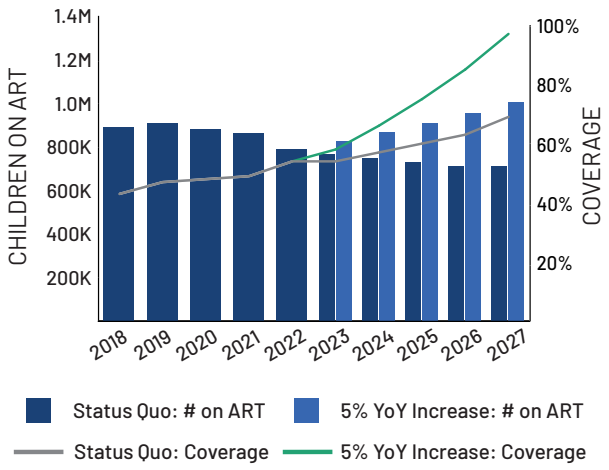
PEDIATRIC TREATMENT

The number of children on ART globally continues to fall, reinforcing the need for renewed focus on this underserved population

In 2022, only 880,000 of the 1.5 million children living with HIV were on lifesaving ART, continuing a three-year downward trend in treatment coverage. Although some decline is expected as children age into adulthood, pediatric treatment coverage remains concerningly low with over 600,000 CLHIV not accessing care due to gaps in pediatric case-finding, linkage to treatment, and retention in care. In 2022, global pediatric ART coverage increased only marginally to 57 percent, significantly lower than adult coverage at 77 percent, and posing a large inequity for this vulnerable group.[i]

Similarly, in GA LMICs, pediatric ART coverage is 54 percent, compared to an adult coverage rate of 80 percent.[i, iii] If the current stagnant and downward trends in both case-finding and retention continue, CHAI estimates that pediatric ART coverage in GA LMICs will only reach 69 percent in 2027. However, achieving a five percent year-over-year (YoY) increase in the number of CLHIV on ART could drastically increase pediatric coverage to close to 100 percent by 2027 [Figure 31].

FIGURE 31: ACTUAL AND FORECASTED CHILDREN ON ART AND PEDIATRIC ART COVERAGE IN GA LMICS[cxxi]



The consequences of poor treatment coverage are evident with 50 percent of children estimated to die by age two without treatment.[xc] Globally, viral load suppression among CLHIV was 46 percent in 2022 compared to 67 percent and 76 percent in adult males and females respectively.[x] The number of AIDS-related deaths in children was 84,000 in 2022, accounting for approximately 13 percent of all AIDS-related deaths despite children making up only four percent of all PLHIV.[i] This is concerning, especially considering that optimal low-cost treatment is now available, and underscores the need to intensify pediatric case-finding and break down barriers hindering access to sustained, high quality care.

To reverse this current trend, urgent and coordinated efforts from national and international stakeholders are required to address the unique challenges faced by pediatric populations.

Continued adoption and scale-up of pediatric DTG has improved adherence and viral suppression rates two years post rollout

The widespread availability and affordability of generic pediatric formulations of DTG marks a significant achievement in the pediatric HIV response.[viii] At the time of publication, more than 80 LMICs have commenced procurement of pediatric DTG, with 160,000 children accessing the product [Figure 33]. Beyond just adoption, data from PEPFAR-supported countries show improved viral suppression rates in children below 15 years old following rollout of pediatric DTG.[cxlvii]

CHAI estimates that, in 2022, 62 percent of children on pediatric treatment backbones were on DTG-based regimens based on data from 17 LMICs representing 64 percent of CLHIV on ART globally [Figure32].

FIGURE 32: ESTIMATED PEDIATRIC THIRD-POSITION DRUG USE IN GA LMICs[iii]

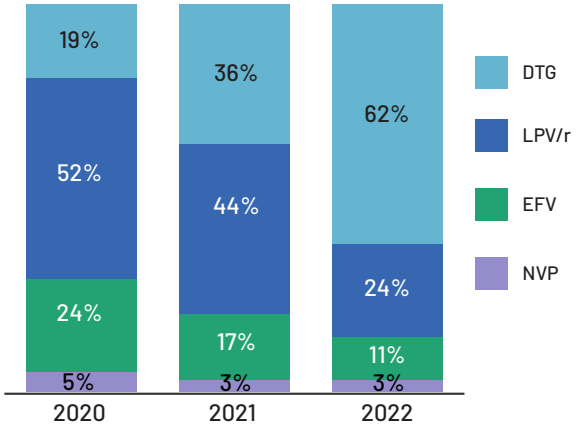
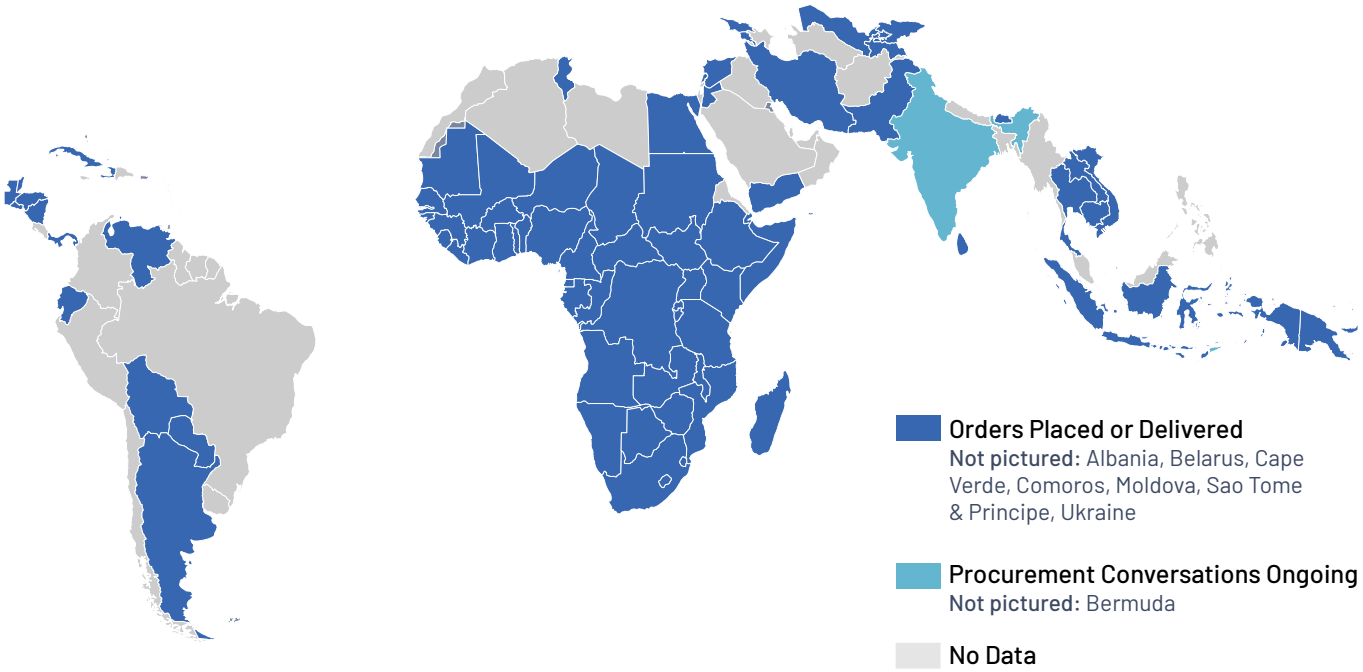


FIGURE 33: PEDIATRIC DTG ADOPTION MAP, APWG, AS OF Q3 2023[cxxxv]



In parallel to increased adoption, research continues to indicate a preference for, and improved viral suppression with, DTG use in children. The TORPEDO study (conducted in Benin, Nigeria, and Uganda), which assessed client, caregiver, and healthcare worker treatment preferences, found a strong preference for pDTG compared to previously used regimens.[cxlviii] Most of the ART-experienced study participants were previously receiving LPV/r tablets (83 percent) or LPV/r pellets (14 percent). Most healthcare workers noted an improvement in adherence due to pDTG's enhanced palatability and ease of administration. Healthcare workers responded to an open-ended question about their experience with prescribing pDTG, and over two-thirds noted improved weight gain and adherence for their clients, aligned with findings from the ODYSSEY and CHAPAS-4 trials.[cxlix, cl]

Additionally, after the transition to DTG, the proportion of CLHIV in the study with an undetectable viral load increased by 25 and 18 percentage points in Benin and Nigeria respectively at 6 months. The proportion of CLHIV with undetectable viral load at baseline in Uganda was higher as compared to the other countries and did not see the same increase at six months [Figure 34].

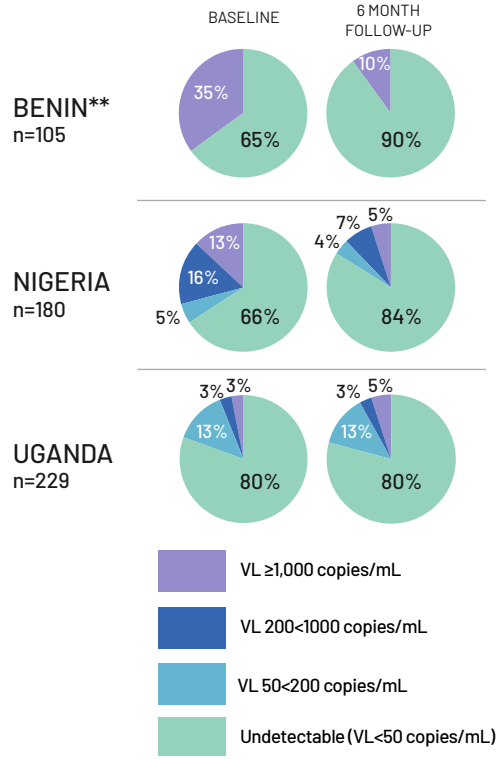
Such real-world evidence from LMIC settings will serve as a catalyst for continued uptake of optimal pDTG-based regimens, further improving adherence and viral suppression, leading to improved treatment outcomes in children.

FIGURE 34: TORPEDO STUDY RESULTS[cxlviii]

TORPEDO Client Statistics

- 51% male and 94% treatment experienced, on treatment 6+ months prior to initiating pDTG. Mean time on treatment was 3.2 years.
- Most (97%) were switched from a LPV/r regimen that was tablets (83%) or pellets (14%).
- The average age was 5.2 years old.

6 Month Viral Load Results for Each Country*



*Results may not add up to 100% due to rounding
**Benin viral load was measured as above or below 1,000 copies/mL

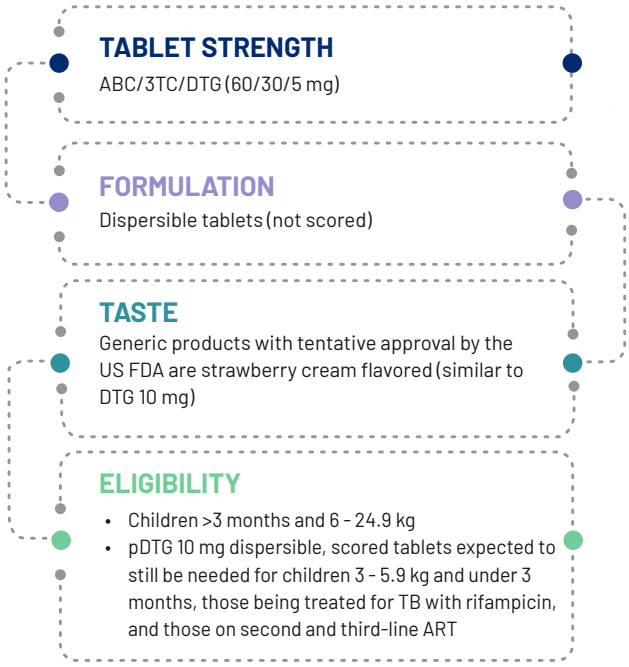
First ever generic pediatric triple FDC containing DTG is now available, with benefits for supply chain planning and administration

Generic DTG-containing pediatric formulations continue to evolve. Pediatric ABC/3TC/DTG (60/30/5 mg) (pALD) is a novel, dispersible fixed-dose combination with DTG for CLHIV aged at least three months and weighing 6-24.9 kg that was initially developed by ViiV Healthcare. pALD is clinically identical to the separate products (ABC/3TC 120/60 mg and DTG 10 mg) at equivalent doses, and provides the complete WHO-preferred first-line treatment for CLHIV.

Aurobindo and Viatris, working as part of a Unitaid-funded development partnership with CHAI and ViiV, both received US FDA tentative approval for generic pALD in Aug. 2023.[cli, clii]

The negotiated price per 180-pack of pALD is US$14.85 (EXW) and US$15.00 (EXW) from Aurobindo and Viatris respectively. pALD product characteristics are summarized in Figure 35 below.

FIGURE 35: pALD PRODUCT CHARACTERISTICS[lxxxvi]



pALD's pill burden is the same as the separate products for most weight bands, and it is simpler for caregivers to administer, as the tablets are taken orally and dispersed in liquid once a day. Additionally, pALD comes in a single bottle, thus simplifying administration and prescription for caregivers and prescribers respectively. The FDC product prevents clients from continuing treatment with either of the separate products when one runs out, thus reducing the risk of developing drug resistance.

With these generic approvals, countries can begin planning for the introduction of pALD, with some key considerations in Figure 36. However, it is important to note that pDTG 10 mg dispersible/scored tablets will still be required for clients 3-5.9 kg and under three months, those on RIF-based TB treatment, and those on second and third lines of therapy.

FIGURE 36: pALD INTRODUCTION CONSIDERATIONS AND KEY STEPS[cliii]

Resources to support pALD introduction such as the Global Accelerator for Pediatric Formulations (GAP-f) pALD Introduction and Rollout Planning Considerations for National Programmes and CHAI's pALD Product Profile are available on the CHAI HIV New Product Introduction Toolkit (www.newhivdrugs.org/pediatric-dtg).

Novel formulation of pDTG may improve administration for certain groups, but affordable pricing will be critical

In April 2023, Laurus Labs received US FDA tentative approval for the first pediatric ARV oral film, developed in both DTG 5 mg and 10 mg strengths.[cliv] The oral film,

a thin flexible strip containing DTG and flavored with mint, is administered via placement on the tongue or inside of the cheek where it sticks and dissolves in saliva. This new technology could have benefits in terms of ease of drug administration but is unlikely to replace pDTG tablets given its expected higher price and higher "pill" burden. However, it may prove useful for drug delivery in neonates (clinical data will be needed to support dosing in this group), the elderly, or others who have trouble swallowing.

The PETITE-DTG study, an ongoing clinical trial in South Africa to assess the pharmacokinetics and safety of DTG for neonatal prophylaxis, was amended to include the oral film in addition to the dispersible tablets.[clv, lxxxviii]

Pipeline products on the PADO-5 priority and watch lists hold the potential to further optimize pediatric treatment

The future of pediatric HIV treatment optimization holds promise with additional optimal products in the development pipeline. Emerging technologies, novel fixed-dose combinations, and tailored approaches to meet the unique needs of CLHIV are poised to improve outcomes and enhance quality of life in this population. Immediate opportunities include the introduction of pALD, and future opportunities include the introduction of pediatric DRV/r for use by children failing on DTG and newer, more tolerable NRTI backbone options that include TAF [Figure 37]. More details on these pipeline products can be found in this section.

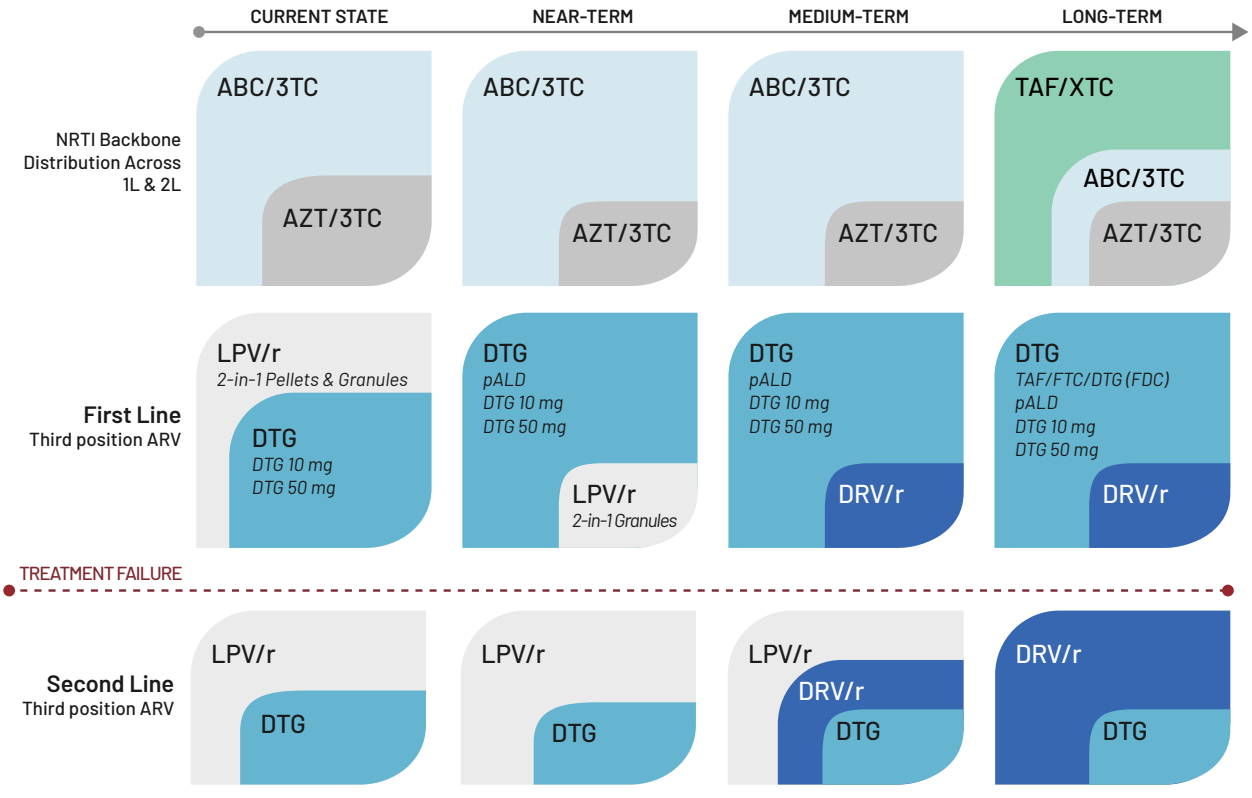
Pediatric DRV/r 120/20 mg (pDRV/r)

CHAI, with funding from Unitaid, is working with Laurus Labs to develop generic pDRV/r (120/20 mg) tablets with the goal of filing with the US FDA in the first half of 2024.[clvi] pDRV/r is a best-in-class protease inhibitor with improved viral suppression rates and improved tolerability compared to LPV/r. pDRV/r has proven efficacy in both treatment-naïve and experienced groups, including children previously exposed to protease inhibitors. Given these benefits, pDRV/r, when available, will replace LPV/r and significantly improve the management of CLHIV ≥3 years old and over 10 kg who fail DTG-based regimens or who are unable to take DTG. CHAI's pDRV/r Product Profile is available on the CHAI HIV New Product Introduction Toolkit (www.newhivdrugs.org/resource-library/tags/pdrv-r).

Pediatric TAF (pTAF)

CHAI is working as a formulation development partner with support from Unitaid, in collaboration with Penta Infectious Diseases Network and Gilead, for the

FIGURE 37: ILLUSTRATIVE OPTIMAL PEDIATRIC REGIMEN DISTRIBUTIONS (<30 KG)*[clvii]



*Includes only regimens with pediatric backbone formulations

development of generic pediatric TAF by generic manufacturers.[clviii] The product is under development as a triple fixed-dose combination with TAF, FTC, and DTG.[lxxxviii]

This will enable children to access a tenofovir-containing regimen (which provides cross-treatment for hepatitis B) without the renal and bone toxicity concerns associated with TDF. Given these benefits and a higher barrier to resistance, pTAF could replace abacavir and become the primary backbone ARV for children.

Other Pipeline Products

Microarray patches and broadly neutralizing antibodies are also on the PADO-5 watch list but are earlier in the development process than pDRV/r and pTAF.[cxxii] As the research and development of these future-looking options progresses, it will be critical to proactively address potential access barriers in LMICs during development and in advance of regulatory approval.

MAPs may have particular benefits in children under two years old, especially in the first six months of life due to challenges with oral drug administration in this age group, but careful evaluation of dose adjustments for growing children will be necessary. They may also be used among adolescents desiring discretion if patch size and placement is acceptable. MAPs are being evaluated for long-acting prevention and treatment. [cxxii]

bNAbs are a unique class of antibodies with the ability to neutralize a diverse range of HIV strains and are under investigation for potential uses including HIV prevention, treatment, and post-natal prophylaxis.[clix, cxxii]

Ending pediatric AIDS will require comprehensive scale-up of proven case-finding strategies, optimal product access, prevention of opportunistic infections, and closing the tap on new infections

To dramatically reduce AIDS-related morbidity and mortality for children, ensuring the availability and scale-up of optimal ARVs is critical. However, optimal ARVs alone are not sufficient. A comprehensive and multifaceted strategy is essential to ensure that CLHIV are identified, linked, and retained in high-quality care.

Public health programs must implement high-quality service delivery strategies including precision, data-driven approaches to improve pediatric HIV case-finding and linkage to care, drive uptake of available optimal ARVs, diagnose and prevent comorbidities such as tuberculosis and pneumocystis pneumonia, and ensure retention in care for CLHIV and their caregivers. Youth-friendly services, including decentralized mental health screening and treatment, are essential to enhance retention in care and reduce risk of HIV infection.

With rapid diagnostic technologies, optimal pediatric ARVs, and proven service delivery strategies, we now have all the tools to end pediatric AIDS for the first time. Strong leadership, global coordination and commitment, and sufficient and sustained investment are needed to make this a reality. Immediate action and global investment are required to save lives and transform the pediatric HIV landscape.

TREATMENT MONITORING

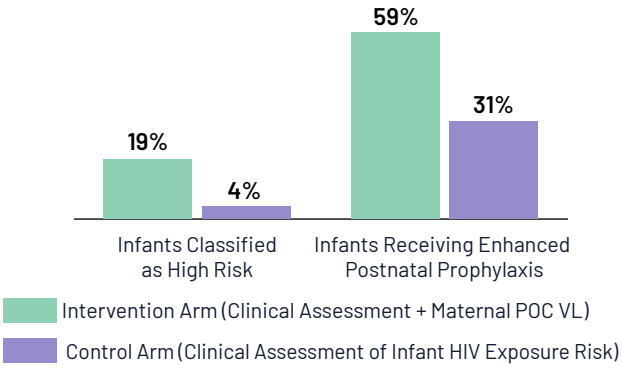
VL testing volumes continue to rebound post-COVID, however, POC volumes are flatlining after a period of growth

In 2022, CHAI estimates that VL testing volumes in LMICs exceeded 25 million (77 percent coverage), continuing a trend of year-over-year increases following stagnation during the first year of COVID. While conventional VL testing has steadily increased in LMICs, POC VL testing volumes have flatlined following a surge from 2020 to 2021. Estimates suggest there was only a slight increase from 1.3 to 1.4 million POC VL tests sold between 2021 and 2022 [Figure 38].[iii]

WHO guidelines recommend POC VL testing for priority populations such as pregnant and breastfeeding women, CLHIV, and people with AHD or OIs.[lv] While CHAI estimates that these populations comprise upwards of 30 percent of PLHIV, currently only five percent of VL testing is conducted via POC, indicating significant potential for growth and increased opportunity to bring VL testing and timely results closer to clients.[iii]

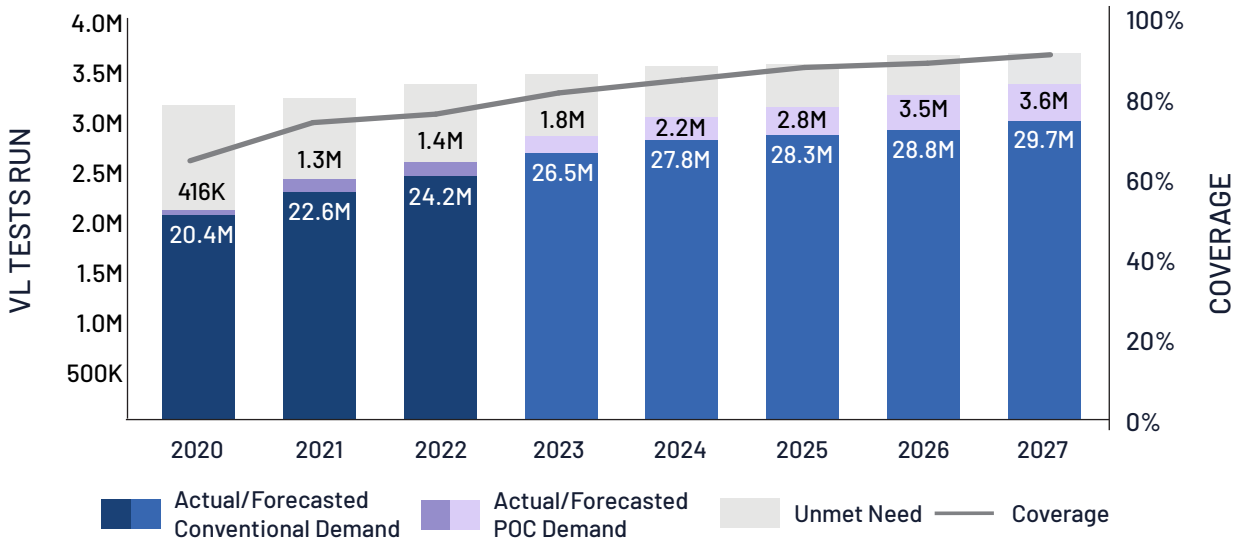
POC VL testing is especially important for pregnant women and neonates. High maternal VL at delivery is one of the strongest risk factors for mother-to-child transmission of HIV. The LIFE trial in Tanzania found that conducting maternal POC VL testing at delivery significantly increased both the proportion of infants identified as high risk for HIV transmission and the percent that received enhanced postnatal prophylaxis [Figure 39].[clx]

FIGURE 39: LIFE STUDY – INFANT PROPHYLAXIS OUTCOMES FOLLOWING MATERNAL POC VL TESTING AT DELIVERY[clx]



New models of VL monitoring could also promote uptake, such as decentralized collection, task sharing, and leveraging short message service (SMS) for reminders or result notification. With support from the Bill & Melinda Gates Foundation, the Zimbabwe Ministry of Health and Child Care and CHAI are conducting a study of DBS sample collection in the community by lay cadres, with easy-to-use kits designed with Lasec. Results may help inform and enable adoption of innovative client-centric services such as leveraging community health workers for sample collection or self-collection of DBS.[lxxxviii]

FIGURE 38: LMIC VL TESTING FORECAST[iii]

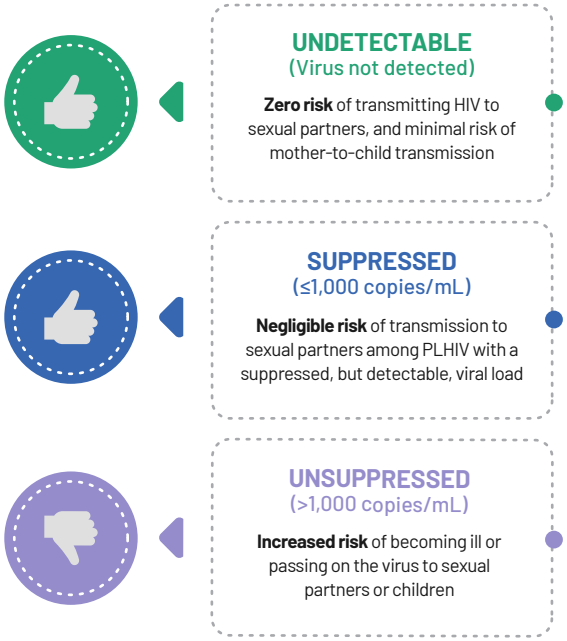


Revised WHO guidance on viral suppression emphasizes negligible risk of transmission for virally suppressed PLHIV

Since 2016 the Prevention Access Campaign's (PAC) 'undetectable equals untransmittable', or 'U=U', messaging has been used to reduce stigma and raise awareness of years-long evidence supporting the effectiveness of ART adherence and viral suppression in preventing HIV transmission.[clxi] In July 2023, the WHO released a landmark policy brief on the role of HIV viral suppression in improving individual health outcomes and reducing both sexual and perinatal transmission, thereby supporting PAC's U=U messaging.[clxii]

Based on evidence from a systematic review on the risk of transmission at varying levels of HIV viral load, researchers concluded there is no risk of sexual transmission when PLHIV have an undetectable VL and negligible risk when VL is suppressed but detectable (under 1,000 copies/mL) [Figure 40].[clxiii]

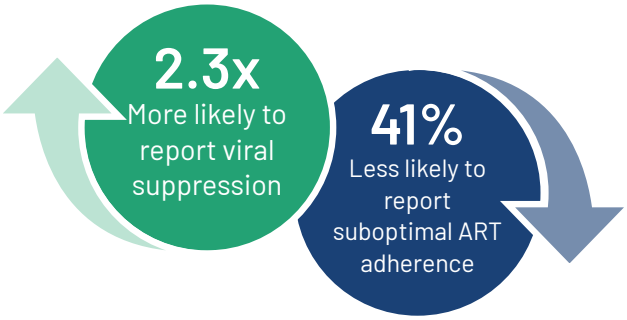
FIGURE 40: RISK OF HIV TRANSMISSION BASED ON VL MEASUREMENTS[clxii]



The WHO brief emphasizes that undetectability is the goal of ART, and access to VL testing is paramount. Furthermore, all WHO-prequalified VL tests, including POC VL and tests using DBS samples, are acceptable and important components for ensuring and expanding VL access.[clxii]

WHO encourages clinical providers to communicate the personal and population-level benefits of viral suppression at ART initiation and throughout treatment, as U=U messaging has been shown to reduce stigma and improve overall health outcomes.[clxii] In a study with clients in 25 countries who reported receiving U=U counseling from providers, self-reported viral suppression was more than twice as likely and clients were 41 percent less likely to report suboptimal adherence compared to those who were unaware of U=U [Figure 41].[clxiv] Similarly, studies of peer and community-led messaging on viral suppression and the transmissibility of HIV in SSA demonstrated reductions in stigma related to HIV testing and improved rates of HIV testing among men.[clxv, clxvi] Critical messaging such as U=U is essential to achieving the UNAIDS 95 targets and ensuring improved health for PLHIV.

FIGURE 41: CHANGES IN SELF-REPORTED SUBOPTIMAL ADHERENCE AND VIRAL SUPPRESSION AMONG THOSE RECEIVING U=U INFORMATION FROM HCWs, 2019-2020[clxiv]



Simple urine tests under development to detect tenofovir drug levels could support treatment and oral PrEP adherence monitoring

For individuals on tenofovir-containing ARVs for treatment or prevention, a urine-based lateral flow assay currently in development may be used to monitor adherence. The test, which provides a real-time yes or no response if TDF has been taken in the last five days, has the potential to objectively inform adherence interventions and improve viral suppression rates in PLHIV.[clxvii, clxviii] This anticipated low-cost urine assay test is expected to be commercially available from Abbott in 2024.[clxix]

As countries complete transitions to DTG, affordable drug resistance testing will be important to expand testing access and understand real world DTG resistance

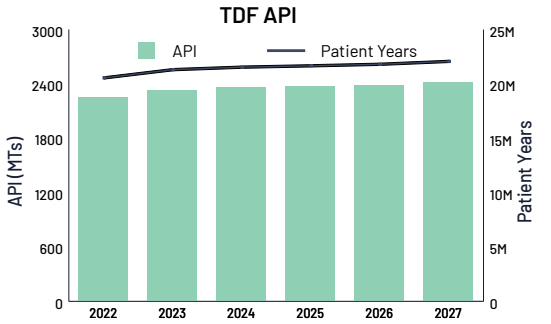
Although DTG has a high genetic barrier to resistance, some INSTI resistance is to be expected with over 22 million PLHIV on DTG-containing regimens.[iii] Improved access to drug resistance testing (DRT) will be useful to identify true cases of resistance-based treatment failure while avoiding unnecessary switches to more expensive and higher cost PI-based regimens due to adherence issues.

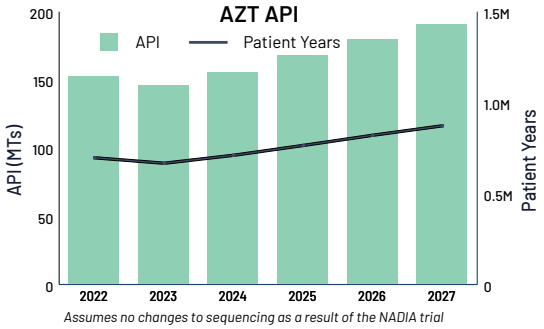
Several countries, including Kenya, Malawi, and Zambia have updated their treatment failure algorithms to include resistance testing following DTG failure.[lxxxviii] However, real world implementation of these guidelines remains difficult, given limited laboratory capacity in LMICs and the financial resources required for large-scale DRT. Thermo Fisher's DRT genotyping kit for Sanger sequencing machines, with CE mark and a starting price point of US$40 (EXW), is already in use in 42 LMICs, albeit at low volumes.[lxxxviii] This comparatively low-cost assay has the potential to significantly reduce the cost of DRT in LMICs.

To assist in establishing a market for affordable DRT for HIV, the WHO recently released their first ever target product profile guidance for the development of new tests for use in African LMICs. This guidance provides diagnostic manufacturers with information on a test's intended use, performance targets, and technical specifications at an early stage of the development process. Importantly, the WHO indicates a per test price of less than US$10 (EXW) as optimal.[clxx]

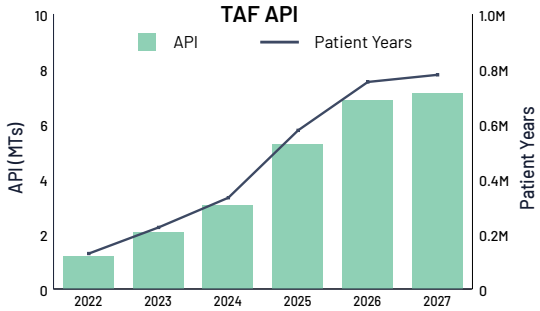
APPENDIX A: FORECASTED API DEMAND IN GA LMICs

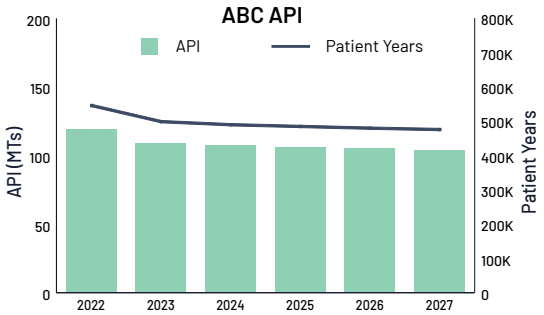
The graphs below show the estimated generic-accessible patient demand and active pharmaceutical ingredient (API) volume (in metric tons) for key adult ARVs. Patient years represent the effective number of patients on treatment for a full year and are used to calculate yearly API demand. Patient years 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.

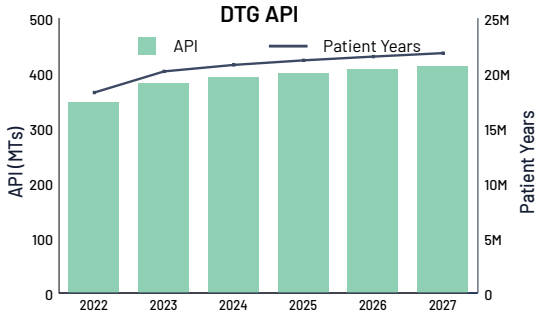


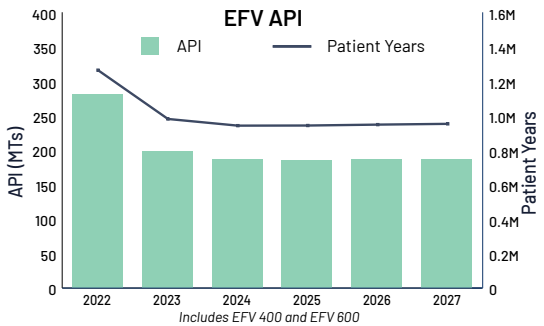


Assumes no changes to sequencing as a result of the NADIA trial

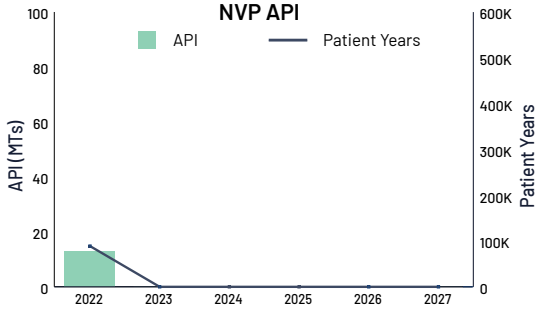


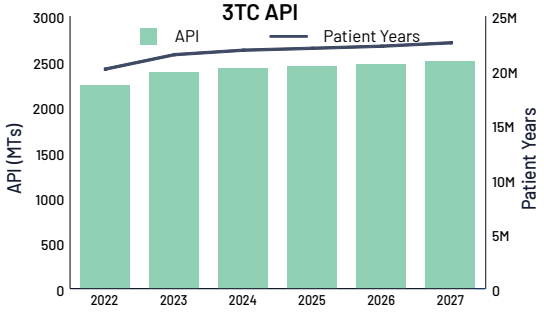






Includes EFV 400 and EFV 600





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. 2023[1]	GHSC-PSM E-CATALOG PRICE JUL. 2023[2]	RSA WEIGHTED AVE TENDER PRICE 2022-2025[3]
Adult Products				
ABC/3TC (600/300 mg)	30 tablets	$7.85	$9.00	$5.85
ATV/r (300/100 mg)	30 tablets	$10.95	$13.45	$11.20
AZT/3TC (300/150 mg)	60 tablets	$5.35	$6.10	$4.37
DRV/r (400/50 mg)	60 tablets	$17.50	$17.50	
DTG (50 mg)	30 tablets	$1.90	$1.80	$1.50
DTG (50 mg)	90 tablets		$7.75	
LPV/r (200/50 mg)	120 tablets	$17.95		$13.68
RTV (100 mg) heat-stable	60 tablets		$7.00	$4.05
TAF/FTC/DTG (25/200/50 mg)	30 tablets	$5.00	$4.95	
TDF (300 mg)	30 tablets	$2.40	$2.40	$1.94
TDF/3TC (300/300 mg)	30 tablets	$3.20	$3.15	
TDF/FTC (300/200 mg)	30 tablets	$3.80	$3.85	$2.89
TDF/3TC/DTG (300/300/50 mg)	30 tablets	$3.60	$5.49	$3.75
TDF/3TC/DTG (300/300/50 mg)	90 tablets	$10.20	$10.15	$10.04
TDF/3TC/DTG (300/300/50 mg)	180 tablets	$21.10	$20.20	
TDF/3TC/EFV (300/300/400 mg)	30 tablets	$4.95		
TDF/3TC/EFV (300/300/400 mg)	90 tablets	$14.75	$15.85	
TDF/3TC/EFV (300/300/600 mg)	30 tablets	$5.25		
TDF/FTC/EFV (300/200/600 mg)	30 tablets	$5.40		$4.38
Pediatric Products				
Optimal Formulary				
ABC/3TC (120/60 mg) disp. scored	30 tablets	$2.70	$2.70	$2.59
ABC/3TC (120/60 mg) disp. scored	60 tablets	$5.35	$5.75	
ABC/3TC/DTG (60/30/5 mg) disp.	90 tablets	$7.50		
ABC/3TC/DTG (60/30/5 mg) disp.	180 tablets	$15.00		
AZT (50/5 mg/ml) oral solution	240 mL bottle	$2.15	$4.25	
AZT/3TC (60/30 mg) disp. scored	60 tablets	$1.70	$1.90	
DTG (10 mg) disp. scored	30 tablets		$1.45	
DTG (10 mg) disp. scored	90 tablets	$4.30	$4.50	
LPV/r (100/25 mg) heat-stable	60 tablets	$5.50	$6.50	$3.63
LPV/r (40/10 mg) oral granules	120 sachets	$16.90	$17.95	
NVP (50/5 mg/ml) oral solution (with syringe)	100 mL bottle		$1.75	$0.95
Limited-Use List				
3TC (50/5 mg/ml) oral solution	240 mL		$2.15	$1.19
DRV (75 mg)	480 tablets	$65.00	$54.00	$50.07
DRV (150 mg)	240 tablets	$65.00	$54.00	$44.92
LPV/r (40/10 mg) oral pellets	120 capsules	$17.25		$11.71
NVP (50 mg) disp. scored	60 tablets		$1.60	
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, 2023. Link
2) Global Health Supply Chain - Procurement and Supply Management (GHSC-PSM) E-Catalog: ARVs, July, 2023. 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.

APPENDIX C: 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 2023. 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 2023 ARV demand forecast for current drugs includes data from: Burkina Faso, Cambodia, DRC, Ethiopia, India, Kenya, Laos, Malawi, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Togo, Uganda, Zambia, and Zimbabwe. These countries represent approximately 73 percent of adult patients on ART in GA LMICs in 2022.

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 2022, and assumes that the countries CHAI has data for are representative of the remaining 27 percent of the market in GA LMICs. It is not an estimate of the cost of ARV procurement in 2022. 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 Global Fund Pooled Procurement Mechanism (PPM) Q2 2023 pricing 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 (2022) testing volumes from CHAI country teams, 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).

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