CLINTON HEALTH ACCESS INITIATIVE

THE ROAD TO ZERO

Report on the Implementation of the Advanced HIV Disease Package of Care in Low- and Middle-Income Countries

With support from

Unitaid
Innovation in Global Health

CONTACT:

James Conroy, Associate Director, Advanced HIV Disease, Clinton Health Access Initiative, jconroy@clintonhealthaccess.org

DISCLAIMER:

The data sources primarily used for analysis in the report include CHAI country teams, ministry of health counterparts, stakeholder resources (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.

ACKNOWLEDGMENT:

The activities detailed in this report were made possible through the generous support of Unitaid. We would also like to extend our sincere appreciation to the national health programs of Botswana, India, Lesotho, Malawi, Nigeria, South Africa, Tanzania, Uganda, and Zimbabwe for their commitment and close collaboration in implementing the Advanced HIV Disease Package of Care. Additionally, we would like to recognize the dedication of CHAI staff in these countries, who have worked tirelessly on supporting this project. Finally, we are grateful to the many other global and country-specific organizations for their contributions and partnership.

SUGGESTED CITATION:

The Road to Zero: Report on the Implementation of the Advanced HIV Disease Package of Care in Low- and Middle-Income Countries. Clinton Health Access Initiative, 2022.

CONTENTS

ABBREVIATIONS

5FC	Flucytosine
AHD	Advanced HIV disease
AIDS	Acquired Immune Deficiency Syndrome
ANDA	abbreviated new drug application
ART	Antiretroviral therapy
B6	Pyridoxine
CAB	Community Advisory Board
CDC	United States Centers for Disease Control and Prevention
CM	Cryptococcal meningitis
CrAg	Cryptococcal antigen test
CTX	Cotrimoxazole
EMAV	Early Market Access Vehicle
EPN	Enhanced Partner Network
FDC	Fixed-dose combination
GAHDT	Global AHD Toolkit
HCW	Healthcare worker
HIV	Human immunodeficiency virus
IAS	International AIDS Society
INH	Isoniazid
IPT	isoniazid preventive therapy
ISC	Implementation Steering Committee
L-AmB	Liposomal amphotericin B
LFA	Lateral flow assay
LF-LAM	Lateral flow urine lipoarabinomannan assay
LMICs	Low- and middle-income countries
M&E	Monitoring and evaluation
MoH	Ministry of health
MSF	Médecins Sans Frontières (Doctors Without Borders)
NACA	National Agency for the Control of AIDS (Nigeria)
NDoH	National Department of Health (South Africa)
OIs	Opportunistic infections
PLHIV	People living with HIV
SAPHRA	South African Health Products Regulatory Authority
SRA	Stringent Regulatory Authority
TB	Tuberculosis
TB LAM	Lateral flow urine lipoaribomannan assay for tuberculosis
TPT	TB preventative therapy
TWG	Technical Working Group
WHO	World Health Organization

EXECUTIVE SUMMARY

BACKGROUND

Despite progress toward reducing AIDS-related mortality over the past decade, the HIV epidemic remains a persistent global challenge. In 2020, there were still 680,000 AIDS-related deaths— only a six percent decrease from 2019.[1] Of these deaths, 210,000 were from tuberculosis (TB) and 85,000 from cryptococcal meningitis (CM). Advanced HIV disease (AHD) contributes to these deaths, as patients with AHD who present to or re-enter care are at a higher risk of opportunistic infections (OIs) and death. AHD is defined as present in people living with HIV (PLHIV) when they have a World Health Organization (WHO) stage three or four condition, a CD4 +Tcells (CD4) count below 200cells/μL, or are age five years or younger.[2] Seeing patients with AHD is common in sub-Saharan Africa with studies reporting between 32 and 71 percent of patients initiating care with AHD, and up to 60 percent of patients presenting with AHD after disengagement.[3] Despite the persistently high prevalence of AHD at treatment (re-)initiation, screening remains suboptimal at all levels. Patients continue to die from preventable and treatable OIs due to late presentation and poor access to the screening and treatment they need. These deaths can be largely prevented should the necessary diagnostics and medications be obtainable in low- and middle-income countries (LMICs).

WHO GUIDANCE ON MANAGING AHD

In 2017, the WHO published guidelines for the management of AHD. In addition to the rapid initiation of antiretroviral therapy (ART), the guidelines recommend a package of care for managing AHD that includes diagnostics for TB and CM, isoniazid preventive therapy (IPT), pre-emptive treatment for cryptococcal antigenemia, optimal CM treatment medications consisting of flucytosine (5FC), liposomal amphotericin B (L-AmB), and fluconazole therapy, and tailored adherence support. Additionally,

Healthcare worker in Uganda performs a VISITECT® test

following the recent publication of the AMBITION study results[4], the WHO has recommended a single high-dose infusion of L-AmB with two weeks of 5FC and fluconazole as the preferred regimen for CM.[5] These recent advances in guidelines and recommendations for diagnostics and optimal treatments for leading AHD conditions have enabled the rollout of the WHO package of care for AHD in certain countries, but many more countries with high AHD burdens are yet to fully implement this lifesaving package.

The WHO guidelines outline a clear cascade of patient care that should be followed when a person initiates or reinitiates HIV treatment. In accordance with the guidance, each person diagnosed with HIV should receive a CD4 test.[6] Of those with a CD4 count below 200 cells/μL, cryptococcal antigen (CrAg) testing should be offered. TB lipoarabinomannan (LAM) testing in AHD patients should be done in accordance with the 2019 "Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV"[7] policy update. Those with positive test results should be linked to appropriate care and treatment.

Some steps in this patient flow are not always performed in resource-limited settings. This may be due to several factors, including a lack of access or stockouts of key commodities such as diagnostic test kits and OI treatment medicines, lack of healthcare worker (HCW) confidence using new products, and limited HCW training on the management of AHD patients.[8] Patient loss to follow-up also impacts the ability to provide the full package of AHD care, and re-engaging with these patients can be difficult due to inconsistencies in patient contact information and extensive distances between the point-of-care and a patient's home. Despite these barriers that must be overcome for comprehensive implementation of an AHD program, prioritizing the provision of a package of care for AHD is an essential component of the effort towards ending the global HIV epidemic.

THE UNITAID-CHAI AHD INITIATIVE

The formation of Unitaid's AHD Initiative ("the Initiative") and collaboration with CHAI as the implementing partner is unlocking stubborn market barriers and generating

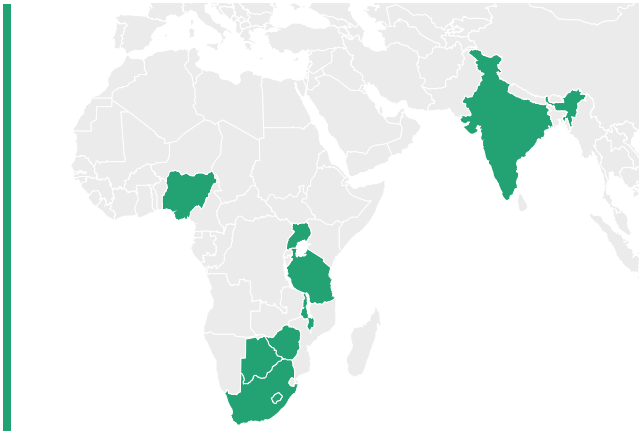
Priority products under the Initiative:

Focal product	Function
DIAGNOSTICS	
CD4 testing	Measures immunological status and is the best predictor for AHD disease status and immediate risk of death, especially useful to identity people presenting with asymptomatic AHD
TB LAM	Rapid test to screen for active TB in HIV-infected individuals with low CD4, particularly those unable to provide sputum
CrAg LFA	Rapid test for detection of cryptococcal antigen, particularly useful in identifying asymptomatic antigenemia before the onset of symptoms
THERAPEUTICS	
TPT	Prophylaxis for preventing TB
L-AmB	Antifungal medication used as backbone in treatment of CM
5FC	Antifungal used in combination with amphotericin B or fluconazole for treatment of CM
Fluconazole	Antifungal medication used for both prophylaxis and treatment of OIs

the momentum among donors and partners that is necessary for accelerated adoption, implementation, and global prioritization of the AHD package of care. Since 2019, the Initiative has sought to renew a global focus on AHD and accelerate access to lifesaving diagnostics and medicines. The goals of the Initiative are to reduce morbidity and mortality from OIs among people with AHD, and improve cost efficiencies for health systems to foster sustainable national AHD programs. In alignment with the 2017 WHO-issued guidance, the Initiative includes key activities around implementing focal products across AHD screening, prophylaxis, and treatment. For diagnostics, the focal AHD products are: CD4 reagents, VISITECT® CD4 Advanced Disease (VISITECT®), TB urine-LAM, and CrAg lateral flow assay (LFA). For treatment and prophylaxis, the focal AHD products are L-AmB, 5FC, fluconazole, and TB preventive treatment (TPT). The Initiative has been increasing global and national awareness of these products to increase advocacy for their availability and use, build support for their adoption into national guidelines, and promote their inclusion into routine country procurement plans. The Initiative covers nine countries: Botswana, India, Lesotho, Malawi, Nigeria, South Africa, Tanzania, Uganda, and Zimbabwe.

On supply, CHAI has targeted three critical levers to accelerate the market: (i) addressing supply-side challenges, including making the products more available and more affordable to partners and country governments; (ii) creating an enabling environment for product introduction and demand creation, including policy work, product registration, forecasting and quantification, etc., as well as catalytic procurement as needed; and (iii) coordinating the global market. To date, the Initiative has galvanized global momentum for AHD and begun to dismantle pricing, supply, and demand barriers to enable access to lifesaving commodities.

The initiative is working in partnership with national health programs in nine countries:



Patient in Uganda has blood taken for AHD screening tests

AHD DIAGNOSTICS

DECENTRALIZATION OF TESTING

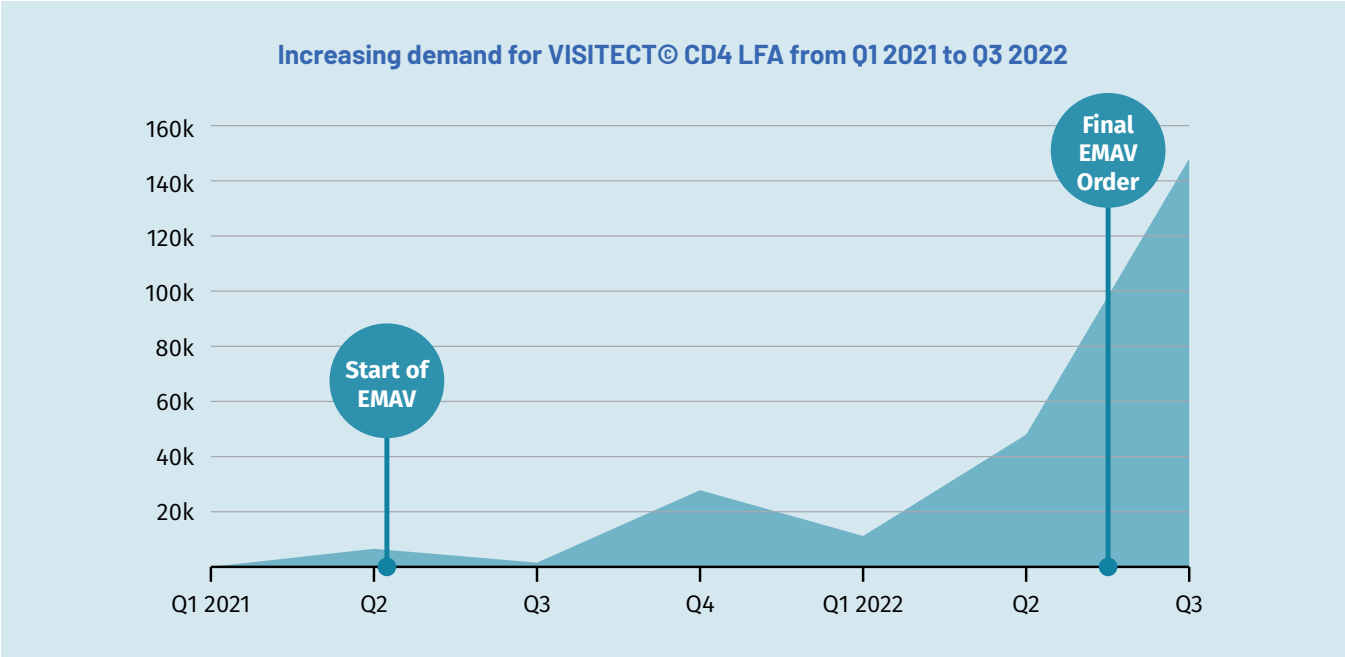
The key to preventing deaths among HIV patients lies in early AHD diagnosis and fast linkage to care. CD4 testing is the gateway to the WHO's recommended package of care for managing AHD. As part of the Initiative, CHAI has been supporting the introduction and decentralization of CD4 testing to enable early diagnosis of AHD and OI screening tests to identify related OIs even at the lowest level of facilities. This package of care includes the following rapid tests that all produce a result in less than one hour allowing for same-day diagnosis (see table below).

EARLY MARKET ACCESS VEHICLE

In April 2020, Unitaid and CHAI launched the Early Market Access Vehicle (EMAV) for the Omega VISITECT® product. The Initiative recognized that VISITECT® could transform CD4 testing and enable same-day diagnosis for patients who need it most. The EMAV sought to catalyze the introduction of VISITECT® by providing the test to interested MoHs and implementing partners. The EMAV was designed to support countries in gaining early programmatic experience, exploring VISITECT®'s role within existing CD4 networks, and sustainably adopting VISITECT® for AHD screening where appropriate. Applications to the EMAV were received, reviewed, and approved from April 2020 through December 2021. Introduction in CHAI's early adopter countries sparked interest in the test in other countries, and now VISITECT®'s reach has spanned across numerous regions, including to Brazil and Eastern Europe.

The 13 countries with participating partners in the EMAV have received over 200,000 VISITECT® tests as of July 2022. Nigeria and Uganda have already adopted, procured, and included VISITECT® in multiyear supply plans for CD4 testing owing to improved turnaround time, as well as ability for use in hard-to reach locations. All participants share a common goal, to use this implementation to catalyze wider access to CD4 testing, resulting in faster, more equitable access to AHD-related OI screening, prevention, and treatment within their respective regions.

Omega VISITECT® CD4 Advanced Disease 	**Abbott Determine TB LAM** 	**IMMY CrAg LFA** 
World's first CD4 test that does not require an electronic device to produce a result	Uses urine samples which are easier to collect than sputum, enables detection of extrapulmonary TB, and does not have the infection control risks associated with sputum production or blood collection	Current market leader and only CrAg test with FDA approval
Produces results in 40 minutes	Produces results in 25 minutes	Produces results in 10 minutes
Retails at US$3.98 ex works *(almost 50% less than the cheapest device-based point-of-care CD4 test)*	Retails at US$3.70 per test ex works	Retails at US$2.50 per test ex works
High accuracy with sensitivity over 95%[9]	Specificity of >98% and sensitivity of 46%[10]	High accuracy with sensitivity of 98% in plasma and whole blood samples and 100% in serum and CSF[11]



A major milestone for sustained implementation of VISITECT® in decentralized settings was the inclusion of the test in PEPFAR's 2022 Country and Regional Operational Plan Guidance as an option for low-cost, quality-assured CD4 testing to diagnose patients with AHD. Building off the catalytic introduction and demand generation of the EMAV, this will catalyze wider access to the test, resulting in faster, more equitable access to AHD and OI screening, prevention, and treatment across LMICs.

Stories from the field: Overcoming barriers to ensure patients have access to CD4 testing

MOZAMBIQUE

While VISITECT® has been decentralized in Mozambique, certain treatments may only still be conducted at regional facilities. To address this, partners have developed a direct phone line between regional and rural facilities to schedule follow-up appointments for patients, with the goal of reducing loss to follow-up and accelerating initiation on appropriate treatment following diagnosis.

> "VISITECT® allows screening in health facilities without PIMA capacity."
>
> ***– The International Training and Education Center for Health (ITECH)***

UGANDA

Access to same-day CD4 testing has rapidly increased due to the introduction of VISITECT® in Uganda. By the end of 2021, three implementing partners and the MoH had collectively provided VISITECT® to patients at 220 facilities. This catalytic access to same-day testing was made possible thanks to the inclusion of clear AHD guidance in the national HIV guidelines and the continued advocacy by communities for CD4 testing. Since the start of the EMAV, over 6,000 patients in Uganda without access to conventional CD4 testing were able to learn of their AHD status through a VISITECT® test.

ZIMBABWE

With the aim of reducing the work burden on facility clinicians in Zimbabwe, partners are task shifting VISITECT® away from nurses to other HCW cadres, including microscopists, counselors, and lab technicians. This was possible following a CHAI-supported training of trainers approach, where selected HCWs partook in centralized training to take learnings back and share them with colleagues in their respective regions and facilities. Since the start of the EMAV, the MoH has successfully implemented VISITECT® in 24 sites and is currently scaling up access to over 100 sites.

DETERMINE TB LAM MARKET DYNAMICS

Despite TB LAM's significant potential for early identification of TB and improved linkage to care, uptake of the test among implementing facilities has been slow due to several factors. One factor was the large pack size of 100 TB LAM tests per pack. Since each pack included only one reference card, it was difficult to split these packs across facilities which led to wastage and expiries, especially in low volume facilities with fewer patients. Following feedback from programs, especially in South Africa, on the wastage of tests due to the inability of many sites to absorb 100 tests before their expiry, CHAI engaged Abbott and made a case to address the pack size. In October 2020, Abbott reduced the pack size of its Determine TB LAM from 100 to 25 tests per pack. This was a major win that opened the door to all countries seeking to decentralize AHD screening efficiently across lower-level and lower-volume sites.

However, in South Africa the change came with an unexpected price increase from ZAR47.99 (USD $3.13) per test to ZAR 94.18 (USD $6.15), representing a 98 percent increase in cost for the same test while the global access price had increased by only US$0.20 (approximately five percent). This price rendered the TB LAM cost-prohibitive to lower-volume facilities across South Africa, threatening uptake of the test and patient screening. CHAI worked closely with the National Department of Health (NDoH) over many months to negotiate a price closer to the global benchmark while provinces in South Africa applied pressure to local suppliers. In January 2021, CHAI succeeded in reducing the local TB LAM price from R94 per unit (~US$6.15) to R68 (~US$4.55) per unit (including all taxes), a price that effectively matches the global benchmark price. Following these negotiations, South Africa placed orders exceeding 190,000 TB LAM tests in 2021 and in February 2022, TB LAM was placed on national tender, now allowing for national procurement and consumption data monitoring via the Republic of South Africa Pharma Dashboard.

A Lab Technician in Uganda collects samples for AHD screening

ZIMBABWE CASE STUDY

As of 2021, Zimbabwe has reached one of the highest antiretroviral treatment (ART) coverage rates (95.8%) in Southern Africa. However, it is still estimated that 35% of PLHIV newly initiating ART present with AHD, and 50% of AHD deaths are due to TB and CM.

The Ministry of Health and Child Care, supported by CHAI, implemented the rapid introduction of the WHO AHD package of care from July 2021 to October 2021 at 24 high ART volumes sites across four provinces in Zimbabwe (11 primary health facilities, 10 secondary, and three tertiary).

During 2021, AHD screening commodities were delivered and HCW were trained on the complete WHO screening package of care at all 24 sites. Additionally, most facilities were conducting point of care CD4 (92%), TB (88%), and CM (79%) screening as of September 2021. Key challenges following implementation included low confidence by HCWs to screen for and provide an AHD diagnosis, treatment knowledge gaps, and staff attrition. Key enablers to addressing these implementation challenges were supportive supervision visits, task shifting CD4 testing to primary care counsellors, dissemination of standard operating procedures, product demonstration videos, and job aids.

Through addressing these known barriers to uptake, the 24 AHD sites in Zimbabwe have demonstrated steady improvement in the uptake of AHD screening (table below).

AHD Screening Improvements at 24 Phase I AHD sites in Zimbabwe

	Q3 2021	Q4 2021	Q1 2022
Percentage of PLHIV newly initiating treatment who received **CD4** test during reporting period	63%	72%	70%
Percentage of PLHIV with CD4<200 who received a **CrAg** test during reporting period	58%	83%	87%
Percentage of PLHIV with CD4<200 who received a **TB LAM** test during reporting period	76%	83%	90%

Zimbabwe has demonstrated an effective stepwise approach and continuous health systems strengthening methodology to implementing the AHD package of care and scale up to additional sites is planned for 2022. National HIV programs can learn from Zimbabwe's experience utilizing a decentralized approach to implementing AHD interventions.

AHD THERAPEUTICS

Prior to the Initiative, there were multiple demand and supply-side barriers limiting access to 5FC and L-AmB. For both products, a lack of product availability, high prices, and poor clarity on manufacturing plans led to prolonged procurement challenges and a lack of access for patients who most needed these lifesaving commodities.

FLUCYTOSINE (5FC)

In 2018, the market for 5FC was plagued by high prices, unclear stringent regulatory authority (SRA) approved manufacturing from a Poland-based manufacturer, limited capacity, long lead times, a lack of consolidated demand, and limited registration all impeding access. Fast forward to 2022 and the picture has dramatically improved for critical CM treatment product. Through the Initiative's partnership with the Global Fund, PEPFAR, and FHI 360, Mylan and Strides' 5FC products were officially reviewed and qualified by FHI 360 in the first half of 2020. Strides' 5FC 250mg and 500mg capsules received approval from the FDA in March 2020. Mylan's (now Viatris) 250mg and 500mg 5FC products received WHO PQ in September 2021 using external API, and using Mylan's own API, received approval by the WHO PQ program in July 2022. These efforts have removed many of the historic access barriers to this critical product by introducing additional suppliers into LMIC markets at affordable prices. The success of this market shaping work has enabled the drug to be eligible for procurement at US$75 ex works across LMICs. As of 2022, 5FC has been procured by the Initiative in eight of CHAI's focal countries and is available in all focal countries as well as additional LMICs thanks to procurement by PEPFAR, Global Fund, and national programs.

5FC ACCESS IN SOUTH AFRICA

Through the Initiative, CHAI has supported NDoH with catalytic procurement and implementation support for 5FC in South Africa, building on successes from the Médecins Sans Frontières (MSF) 5FC Access Program initiated in 2018. In 2021, CHAI distributed 1,840 packs of 5FC to more than 60 sites across all nine provinces in South Africa. In December 2021, the South African Health Products Regulatory Authority (SAHPRA) approved registration for 5FC in-country, advancing efforts to include 5FC in the Essential Medicines List and national standard treatment guidelines, while continuing 5FC training and tendering activities as 5FC access moves from CHAI-supported catalytic procurement to national scale.

5FC Supply Update:

Prior to the project

- Unclear SRA approved manufacturing from a Poland-based manufacturer
- High, unaffordable price
- 6+ months lead time
- Limited supply capacity
- Low, unconsolidated demand
- Very limited procurement

Progress through the initiative

- Two SRA approved generic suppliers in Viatris and Strides
- Significant price reduction to $65-$75 per pack
- Lead-time reduced to ~3-4 months
- Increased adoption and patient access across countries
- Procurement from PEPFAR, GF, and national programs

Ongoing considerations

- Demand must grow to support a long-term sustainable market with two SRA-approved suppliers
- Manufacturing API issues are leading to fractured supply

LIPOSOMAL AMPHOTERICIN B (L-AMB)

Thanks to a Unitaid-negotiated deal announced in September 2018, Gilead offers L-AmB (brand name, Ambisome) at US$16.25/vial for the treatment of CM across 116 LMICs. Under the Initiative, CHAI has now catalytically procured this optimal product in six focal countries (excluding India, Malawi, and South Africa, where catalytic procurement is not required). To facilitate this procurement, CHAI also increased direct engagement with Gilead leading to increased visibility into manufacturing processes and capacity, and stronger lines of communications between parties. This procurement has provided national AHD programs access to the product for the first time, accelerating patient treatment, and enabling early evidence generation to inform national scale-up. Across seven of the focal countries, L-AmB is now recommended and the optimal treatment for CM is available at ministry of health (MoH) led facilities alongside 5FC. Procurement of L-AmB alongside 5FC is transitioning to procurement partners to ensure continued access for patients and sustainable supply across programs.

Despite significant gains made by Unitaid and CHAI towards making L-AmB available to LMICs, there is still a need to improve access to L-AmB, strengthen supply security, and ensure access at US$16.25 for all applicable countries. Because of the supply security concerns for L-AmB, CHAI in collaboration with DNDi undertook a L-AmB scoping exercise to evaluate the potential for the development, SRA approval, and commercialization of an alternate generic L-AmB product that meets the target product profile for LMICs. The findings of this exercise, published in Q3 2021, continue to inform strategies to accelerate access to generic L-AmB in the future.

Additionally, in December 2021 Sun Pharma received final approval from the US Food and Drug Administration for its abbreviated new drug application (ANDA) for generic Amphotericin B Liposome for Injection, 50mg/vial single-dose vial. This is a big step forward for L-AmB supply security and moves the market closer to having an alternative SRA approved supplier.

Vials of Gilead's Ambisome Product

> "Unitaid and CHAI's support to the Advanced HIV Disease program in Uganda has been instrumental over the past few years. Prior to the project, cryptococcal meningitis patients received fluconazole monotherapy, but now through CHAI's catalytic procurement, we have access to flucytosine and liposomal amphotericin B, which has enabled our program to provide lifesaving recommended treatment at 19 regional referral hospitals. In 2021, that meant over 600 patients receiving this regimen, resulting in significantly better treatment outcomes for patients. In 2022, this number is expected to continue to grow as we continue to decentralize CrAg screening across the country to identify as many CrAg positive cases as early as possible. Unitaid and CHAI's support has been instrumental in addressing key gaps in the AHD landscape in Uganda."
>
> ***– Dr Proscovia M. Namuwenge, Senior Program Officer AHD and TB/HIV , Ministry of Health Uganda***

AHD training in Malawi

MALAWI IMPLEMENTATION CASE STUDY

As of 2018, components from the AHD package of care in Malawi were limited, with only partial AHD package interventions at a small number of facilities through partner projects. However, in 2020, CHAI through the Unitaid-CHAI AHD Initiative, supported the Department of HIV & AIDS to introduce the AHD package of care at scale, providing access to AHD screening and treatment at over 100 Phase I sites.

Prior to the project, Malawi reported that only 14 percent (108) of ART facilities in the country provided TB LAM testing. By January 2020, TB LAM implementation had scaled up to 115 sites across 28 districts, representing 43 percent of Malawi's ART cohort. Since introducing TB LAM testing in 2018, Malawi has seen a 20 percent increase in the identification of extra-pulmonary tuberculosis cases. It is very likely that these cases would otherwise have been missed through sputum-based diagnosis.

Supportive supervisions and virtual and in-person mentorship have both been crucial to implementation and led to a steady increase in TB LAM uptake even as the country responded to the COVID-19 pandemic. Before supportive supervision, sites in this country were testing an average of 81 percent of AHD patients for TB. Following supportive supervision visits, this number rose to 98 percent. Scale up by 2.5x from 118 to 301 sites is planned for by the end of 2022, which will ensure the program increases TB screening coverage, identifies, treats additional TB cases, and ultimately saves more lives.

The Malawi program has also demonstrated impressive progress in the screening and management of CM following the implementation of the AHD package of care in 2020. Among a sample of 30 Phase I sites in 2021, 86 percent of patients who received a CD4 result of < 200 cells mm3 also received a reflex CrAg test. Additionally, 24 of those sampled Phase I sites utilized the optimal induction treatment regimen for CM patients in Q4 2021 (L-AmB and 5FC) and 92 percent of CM patients received optimal treatment across the entire site sample in Q1 2022.

In Q1 2022, Malawi updated the national clinical treatment guidelines to include results from the AMBITION trial, now outlining single dose L-AmB as the preferred CM induction treatment regimen in country. Following this update, Malawi has initiated a new round of national clinical trainings to instruct HCWs on proper administration of the new single dose L-AmB regimen. Looking ahead, the CHAI Malawi team will support the MoH in-country to monitor treatment data and conduct supportive supervision visits at CM treatment sites to ensure sustained optimal treatment for CM patients in Malawi.

ROLE OF THE COMMUNITY

Significant progress has been made over the past several years to increase access to AHD services for all PLHIV. However, it became clear that to augment and sustain this success, newly established AHD programs must be further strengthened and momentum around new diagnostics and treatments must continue to be built. In 2019, elaborating on the success of the Optimal Community Advisory Board (CAB) in HIV treatment, CHAI, AfroCAB, and Unitaid expanded the Optimal CAB to include AHD and elevate the community perspective in policy planning and foster demand generation for AHD products and services. Through this work, community leaders have helped shape AHD policies and implementation around the world and contributed to the increased prioritization of AHD within HIV communities. Today, Optimal AHD CAB members are recognized as key stakeholders to the MoH in the planning and rollout of AHD focal products and vital partners to support demand generation for AHD services.

Nationally, AHD CAB members elevate the community perspective through both decision-making at the country-level and demand generation at the regional and individual level. The impact of this approach is evident in Uganda, where CAB representatives are working with partners at the national and district level. CAB members remain active participants on the national AHD technical working group (TWG), which provides them with the opportunity to directly contribute to implementation plans and influence messaging at the national level. At the district level, CAB representatives host workshops across the country with community members and representatives from national PLHIV networks. Trainings focus on general AHD awareness, as well as the importance of CD4 testing and AHD commodities such as TB LAM tests and TB Preventive Therapy. Alongside these activities, CAB members helped develop an AHD Literacy Manual for communities with support from the MoH and

> "There is improved patient satisfaction, reduced turnaround time of CD4 results, improved retention to care, and healthcare worker satisfaction."
>
> ***– Elizabeth Glaser Pediatric AIDS Foundation on VISITECT®***

CAB AHD capacity building in Zimbabwe

frequently write newspaper columns discussing AHD issues and advocating for increased attention on AHD. Overall, the Uganda CAB's activities are helping to solidify AHD as a priority within communities, while also elevating the community voice in AHD policy discussions.

Globally, increasing community awareness and literacy of AHD is a central component of the CAB's work. To support their efforts, the AHD CAB has produced numerous information, education, and counseling resources designed to raise awareness about AHD and encourage clients to seek out AHD services. For example, in 2020, CHAI and the CAB collaborated with HIV i-Base, a treatment activist group, to develop and adapt a set of key AHD materials that provide helpful information on the signs and treatment for AHD. More recently, the AHD CAB formed a working group to develop a multi-media package of AHD literacy and advocacy resources for civil society organizations, community representatives, and national networks of PLHIV. These include numerous posters and graphics on topics ranging from an overview of AHD to the warning signs of TB, as well as an animated AHD advocacy video. These resources were purposefully designed to be adapted and utilized for many different contexts, and they are already being disseminated in focal countries and beyond. These resources can be found on the HIV New Product Introduction Toolkit.

AHD awareness-raising poster developed by the Optimal CAB and partners

AHD radio show led by CAB members in Uganda

IMPLEMENTATION BEST PRACTICES

Through working with MoHs, implementing partners, HCWs, the community, and other stakeholders to rollout AHD services, several best practices have proven essential to accelerate national introduction and scale-up of the package of care for AHD. These best practices include:

National-led governance and coordination

Setting up MoH-led AHD TWGs across focal countries to provide governance and coordination for the rollout of the AHD care package continues to serve as a fundamental best practice. This was critical for building stakeholder consensus on the adoption and update of national guidelines, development of capacity-based implementation plans (in advance of in-country delivery of commodities), and monitoring and evaluation (M&E) rollout efforts. An AHD TWG usually draws membership from MoH, academia/HCW, partners, members of the community, and donors, and ensures that all partners are working towards the MoH led AHD implementation plan. These AHD TWGs continue to oversee and manage the rollout in their respective countries.

Training and adapting to the COVID-19 pandemic

With the COVID-19 pandemic impacting national health systems, close coordination with MoHs and partners in country aided initiation and continuity of AHD implementation. In view of varied levels of COVID-19 restrictions from 2020 to 2021, adopting a mix of virtual and in-person (or hybrid) AHD HCW trainings (keeping with prevailing local COVID-19 restrictions) was critical to minimize the impact of the pandemic on the AHD rollout. In Lesotho, for example, virtual trainings that covered the cascade of care for AHD patients were delivered to over 600 HCWs. The HCWs included doctors, nurses, pharmacists, and M&E data managers. In Nigeria, AHD trainings utilized a hybrid of virtual and in-person training methods to build the capacity of over 300 HCWs. In-person training was essential for product

CM treatment training taking place in Zimbabwe

NIGERIA TRAINING CASE STUDY

To encourage sustainability of the AHD package of care in Nigeria, CHAI worked with the National Agency for the Control of AIDS (NACA) and PEPFAR on AHD implementation across the country via workshops, trainings, and ongoing collaborative discussions. This included identifying lessons learned from the Phase I implementation such as strategies to address gaps identified in CSF CrAg and TB LAM testing that could be applied at a national level. In October and December of 2021, CHAI in partnership with NACA, PEPFAR, and other partners conducted national AHD scale-up trainings of trainers for implementing partners, using a blend of virtual and in-person sessions for the theory and practical modules, respectively. A total of 330 participants joined the theory session and 359 participated in the practical session. In partnership with the AHD TWG, CHAI also instituted an AHD webinar series to reinforce knowledge and cross learning among HCWs. Two webinars focused on CM management and CD4 testing were held in 2021; an additional webinar on TB LAM was held earlier this year. CHAI also supported the national program to complete multiyear (2021 – 2026) quantification for HIV commodities. Following this exercise, CHAI successfully engaged PEPFAR to include AHD commodities in the country operation plan. Volumes have been committed and planned for all elements of the Nigeria package of care for AHD. PEPFAR has confirmed orders for AHD commodities (VISITECT®, TB LAM, CrAg LFA, 5FC, and L-AmB) in preparation for Phase II AHD rollout, which commenced in Q1 2022. Implementing partners were responsible for conducting step-down facility-level trainings following the training of trainers facilitated by CHAI and other partners at the national level. Most states have now completed their facility-level trainings and commenced implementation of the AHD package of care. Throughout the span of the AHD project, CHAI worked extensively with the AHD TWG to ensure commitment to the AHD scale-up and sustainability of the project beyond CHAI's involvement.

demonstration and building of HCW confidence on the proper use of new commodities. In addition to country-level trainings, CHAI collaborated with the US Centers for Disease Control and Prevention (CDC) Foundation and Project ECHO to implement a webinar series focused on AHD sensitization and continuing medical education for HCWs in the context of COVID-19. As of July 2022, the CDC/CHAI/Unitaid AHD Global ECHO Webinar Series had reached over 2,775 unique program participants across 131 countries and continues to serve as an educational resource for frontline HCWs managing AHD.

Timely supportive supervision

Conducting timely and regular supportive supervision visits to facilities, particularly in the months following initial training, is key to mentoring HCWs, identifying and troubleshooting teething issues, and reinforcing HCW confidence on the use of new health products. Capacity building continues to be critical, particularly for CM treatment as countries adopt the new regimen following the AMBITION study results, and to ensure that all diagnosed CM patients are receiving the optimal treatment regimen.

Knowledge sharing and global coordination of AHD activities

As momentum continues to grow around AHD, clear and timely communication with partners and stakeholders across organizations and geographies has become more important than ever to ensure coordinated efforts and efficient activities. At the beginning of the Initiative, CHAI established the AHD Implementation Steering Committee (ISC) to create a comprehensive AHD forum that would ensure effective coordination of efforts among implementers and funders and provide a forum to exchange ideas and troubleshoot programmatic and supply-related issues. In 2021 this group expanded to a larger geographical scope, including Latin America and Southeast Asia— resulting in additional membership from stakeholders in these parts of the world and a wider focus on other AHD-related diseases based on prevalence and neglected areas. Additional populations, including pediatrics, were also included under the expansion. This expanded AHD ISC now includes over 50 members and is co-chaired by Nathan Ford (WHO) and Tom Chiller (CDC), with support from Ajay Rangaraj (WHO) and Angela Loyse (St. George's University of London). The

group continues to meet on a quarterly basis to facilitate collaboration and synergies across partners, identify gaps and challenges in the current AHD landscape, and advocate for increased focus on addressing mortality at both global and country levels.

Creation of the Global AHD Toolkit

To support countries with rolling out the WHO recommended package of care for AHD, CHAI, in collaboration with the AHD ISC, developed the Global AHD Toolkit (GAHDT) to serve as a repository for the much-needed, yet scarce AHD tools. These tools, in many instances serve as foundational resources that national programs use to create country-specific tools from, thereby cutting the development timeframe for context-specific resources. Additionally, the multi-partner approach to the development of the toolkit, and its hosting with the International AIDS Society (IAS) Differentiated Service Delivery Website, certainly helped improve utility and reach to countries. The GAHDT features programmatic resources, training materials (including product demonstration videos), job aids, and patient literacy resources. To date, Nigeria, Uganda, Malawi, Tanzania, Lesotho, and Botswana, are some of the project countries that have utilized the GAHDT to setup AHD programs, with additional countries across LMICs utilizing the resources. Lessons learned from developing the GAHDT were presented at IAS 2021.

Scan QR code to access the Toolkit:

ENHANCED PARTNER NETWORK

To deliver wider impact, in 2021 Unitaid and CHAI launched the Enhanced Partner Network (EPN) to identify and subcontract implementing partners for targeted projects designed to address key gaps in the AHD landscape and widen the reach and impact of the Initiative. As of June 2022, CHAI is coordinating the implementation of 10 additional AHD-related projects with partners across seven countries in Asia, Africa, and South America. The broad range of projects are filling important gaps in the AHD landscape across technology, research, and implementation. These will inform the scale-up of AHD care across LMICs, equip stakeholders with resources to advocate for AHD services, and provide improved decentralized AHD services for more patients.

One project with the Infectious Disease Institute in Uganda is developing a Global AHD Toolkit application that will equip HCWs with accessible AHD guidelines and clinical tools. The app specifications were developed with guidance from HCW and partner feedback through a survey disseminated at the beginning of the year. The app, which is now in final testing, will be available for use in Q3 2022.

DISCUSSION

Priorities ahead

In a short period of time, CHAI galvanized global momentum and made significant progress in addressing pricing, supply, and demand barriers to enable access to lifesaving AHD prevention, diagnostic, and treatment commodities. However, despite the progress thus far, there is still critical work to be done. Several remaining challenges and gaps must be addressed to reach the goal of zero OI-related deaths among PLHIV. The global AHD market still requires coordination and demand to mature into a self-sustaining market. Supply-side interventions are needed to harmonize fragmented procurement and support market entry of new products and generic alternatives at competitive prices. Concurrently, additional demand generation and implementation support are needed at the country level to provide the market with regular and sustainable demand that can support supplier investment. Critical priorities within LMICs and specifically high AHD burden countries are:

1. **Increasing access to screening for AHD and OIs**: Whilst good progress has been made, at least 30 percent of eligible patients in LMICs have no access to CD4 testing. This can be deadly: solely relying on clinical staging can miss up to half of AHD patients. As a result, patients continue to die from preventable and treatable OIs due to late presentation and poor access to the screening and treatment they need.

2. **Increasing procurement commitments for AHD commodities**: Whilst new AHD specific guidance from both PEPFAR and Global Fund on AHD has led to increased orders for certain commodities across several countries, many programs are still not prioritizing sufficient quantities or requesting all commodities in the package of care as part of their procurement requests. This is leading to incomplete screening, or suboptimal treatment options for patients despite the products now being available and affordable.

3. **Strengthening patient knowledge and demand for essential commodities**: Successful uptake of AHD commodities, and positive outcomes of AHD interventions, relies on patient awareness of AHD and associated OIs. Community engagement is also critical for programs to recognize gaps in AHD strategies and service provision, to understand the needs of patients, and to inform the most appropriate interventions to meet these.

4. **Prevention of "drug holidays"**: PLHIV are stopping treatment and returning to care with AHD. Recent evidence suggests there is a "revolving door" of HIV care, as opposed to the linear continuum of care usually used to assess and compare HIV programs. A study in South Africa looking at newly initiating patients found 51 percent of PLHIV had previously been tested, and of those, 71 percent had previously started ART. This data is especially concerning among patients who are extremely vulnerable to OIs which are preventable and treatable – if identified early enough.

5. **Improving data quality**: Countries lack critical information to inform planning and investment in AHD. AHD data on availability and quality of services is constrained by a lack of AHD indicators in national M&E systems. These systems often rely on extensive paper-based registers that are managed by overextended HCWs. As a result, data is often incomplete or out-of-date, painting an incomplete picture of the overall need, access, and provision of care.

6. **Supporting country adoption and implementation of the AHD package of care**: Some country guidelines are still missing optimal diagnostics and treatment regimens. This may be due to slower adoption by some countries, misaligned timelines for national guideline development and release of WHO guidelines, and lack of local evidence or resources to support new guidance.

CONCLUSION

The percentage of patients presenting to care with AHD remains consistently high despite ART scale-up, representing a large and avoidable burden of morbidity and mortality. Rapid linkage to the AHD package of care through CD4 testing must continue to be prioritized in the region. While progress has been made in implementing the package of care in certain countries over the past several years, governments and HCWs will need a continued aggressive focus on how they are combatting AHD to avert additional morbidity and mortality. Accessible and sustainable interventions to identify and care for AHD patients will be essential components of the ongoing HIV response. Countries engaged through the Initiative have demonstrated that through national-led implementation, significant efficient progress can be made scaling up AHD programs. However, the job is far from done, and further collaboration and investment across all stakeholders will lead to more AHD patients being identified, screened, and treated for deadly OIs. The tremendous progress of national programs engaged in the Initiative can serve as tools and lessons learned for additional countries and significantly reduce AIDS-related mortality.

> "After being frustrated with having to visit the health facility twice to receive my CD4 results, I stopped keeping my appointments until a healthcare worker followed up with me. I was astonished when the clinician told me that I do not have to wait for days to receive a CD4 results. Fortunately, I was able to hear my diagnosis in less than an hour. This excited me and I pledge to always keep my appointments."
>
> ***– Patient from Uganda***

REFERENCES

1 The Clinton Health Access Initiative, 2021, 2021 HIV Market Report, https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2021/10/2021-CHAI-HIV-Market-Report.pdf.

2 World Health Organization. (2005). Interim WHO clinical staging of HVI/AIDS and HIV/AIDS case definitions for surveillance: African Region. World Health Organization. https://apps.who.int/iris/handle/10665/69058.

3 Gils, Tinne, et al. "Feasibility of Implementing The Advanced Hiv Disease Care Package as Part of Community-Based HIV/TB Activities: A Mixed-Methods Study Protocol." BMJ Open, vol. 12, no. 2, 2022, https://doi.org/10.1136/bmjopen-2021-057291.

4 Jarvis J.N., Lawrence D.S., Meya D.B., Kagimu E., Kasibante J., Mpoza E., Rutakingirwa M.K., Ssebambulidde K., Tugume L., Rhein J., et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N. Engl. J. Med. 2022;386:1109–1120. doi: 10.1056/NEJMoa2111904

5 "New Guidelines from WHO Recommend a Simpler, Safer Treatment for Cryptococcal Disease in People Living with HIV." 20 Apr. 2022, https://www.who.int/news/item/20-04-2022-rapid-advice-new-guidelines-for-simpler-safer-treatment-for-cryptococcal-disease-in-plhiv.

6 World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. WHO guidelines approved by the guidelines review committee. Geneva: WHO; 2017.

7 Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. Policy update 2019. Geneva: World Health Organization; 2019.

8 Meya, David B. et. al. (2021). Establishing targets for advanced HIV disease: A call to action. Southern African Journal of HIV Medicine, 22(1), 1-5. https://dx.doi.org/10.4102/sajhivmed.v22i1.1266

9 Vidhyavathi V, Iqbal HS, Kanthamani K, et al. Performance characteristics of an instrument-free point-of-care CD4 test (VISITECT®CD4) for use in resource-limited settings. Journal of International Medical Research. September 2020. doi:10.1177/0300060520955028

10 The World Health Organization. (2014, April). High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. https://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf?sequence=1&isAllowed=y

11 IMMY. (2019). CrAg® LFA CRYPTOCOCCAL ANTIGEN. IMMYLabs COVID-19 Testing and Vaccination Services. https://www.immy.com/crag

Clinton Health Access Initiative, Inc. (CHAI)
383 Dorchester Avenue, Suite 400
Boston, MA 02127 USA

www.clintonhealthaccess.org