Expanding Access to Screening and Treatment for Cryptococcal Infection as a Key Component of the Advanced HIV Disease Package of Care:

Lessons Learned from 10 Pilot Sites in Zimbabwe

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Fighting for an AIDS-free generation

1. Introduction

The World Health Organization (WHO) defines advanced HIV disease (AHD) as adults, adolescents, and children above five years of age with a CD4 cell count <200 cells/mm3, or with WHO clinical stage 3 or 4. All newly diagnosed people living with HIV (PLHIV), patients who have defaulted on ART and are returning to care, and patients on ART with suspected or confirmed treatment failure should be screened for AHD using CD4 testing, or WHO staging if CD4 testing is not available. In addition, all children under five years of age living with HIV are considered to have AHD, except those above two years of age who have been receiving antiretroviral therapy (ART) for more than one year and are clinically stable.[1,2]

In Zimbabwe, approximately one-third of newly-diagnosed PLHIV, and a similar proportion who are already on ART, have AHD.[3,4] Among the estimated 22,000 PLHIV who died from AIDS-related illnesses in Zimbabwe in 2020, the most common causes of death were tuberculosis (TB) and cryptococcal meningitis.[5] Each year, there are an estimated 8,100 cryptococcal cases in Zimbabwe.[6] However, a large proportion of those cases go undetected, resulting in death, because healthcare facilities lack reliable supplies of commodities to prevent, diagnose, and treat cryptococcal disease. Further, healthcare workers (HCWs) lack the guidance, tools, and training needed to effectively use WHO-recommended diagnostics and therapeutics. Finally, there are challenges at the national level to coordinate activities across a range of MOHCC departments (e.g. HIV, TB, Vaccines, Nutrition, Laboratory, Procurement) and relevant national stakeholders to develop and roll out policies, guidance, and tools to address the leading causes of illness and death among PLHIV (Box 1).

Box 1: Leading causes of death globally among PLHIV with AHD[1,2]

Leading causes of death among children and adolescents (0-19 years of age) with AHD

- Pneumonia (including Pneumocystis pneumonia),
- Tuberculosis (TB)
- Bloodstream infections
- Diarrheal disease
- Severe acute malnutrition
- For adolescents 10 years and above: cryptococcal meningitis

Leading causes of death among young people and adults above 19 years of age

- Tuberculosis (TB)
- Severe bacterial infections (SBIs)
- Cryptococcal disease
- Histoplasmosis
- Toxoplasmosis
- Pneumocystis jirovecii pneumonia

Photo: Eric Bond/EGPAF, 2022

2. The EGPAF/CDC Foundation Project in Zimbabwe

The WHO recommends a package of interventions for AHD that includes CD4 testing to identify AHD; screening, treatment, and/or prophylaxis for major opportunistic infections; rapid initiation of antiretroviral therapy (ART) unless there are signs of meningitis; and intensified adherence support.[1] For children and adolescents aged 0 to 19 years old, some elements of the AHD package of care differ from the adult package but are clearly described in the STOP-AIDS toolkit.[2]

To prevent, diagnose, and treat cryptococcal disease within the AHD package of care, all AHD patients 10 years and older should receive a serum cryptococcal antigen (CrAg) test. Patients with a positive serum CrAg test should undergo a cerebral spinal fluid (CSF) CrAg test to screen for cryptococcal meningitis (CM). Patients with a positive CSF CrAg should be treated for CM, while those with a negative CSF CrAg test should receive pre-emptive antifungal therapy to prevent the development of invasive cryptococcal disease. If a lumber puncture is not feasible to collect CSF for patients with a positive serum CrAg test, patients should be assessed for signs and symptoms of meningitis, followed by appropriate treatment, depending on the findings. Figure 1 illustrates the pathway for diagnosing AHD and for screening and treating TB and cryptococcal infection within the Zimbabwe AHD package of care.

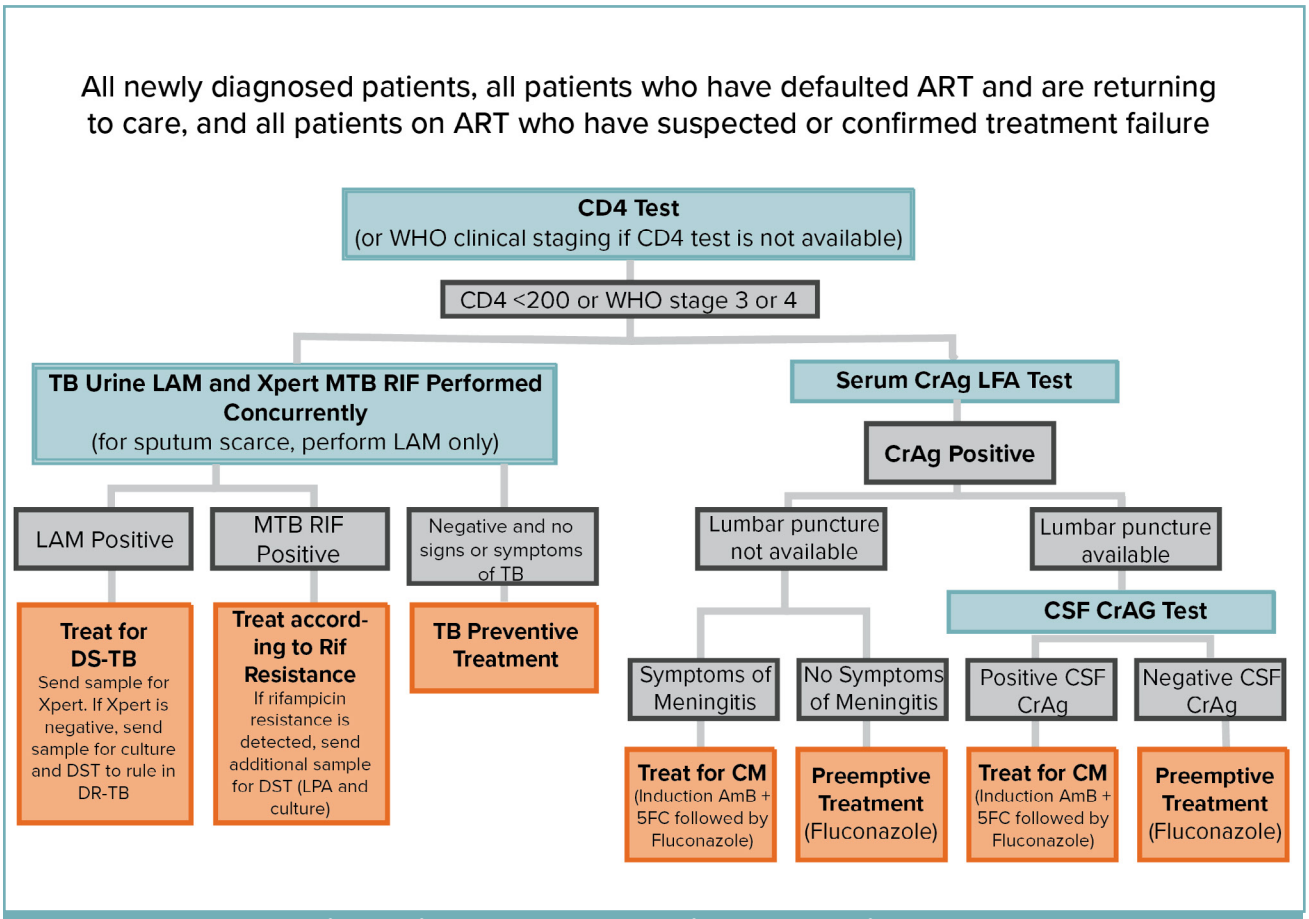

Figure 1. Pathway for diagnosing AHD and screening and treating TB and cryptococcal infection within the Zimbabwe AHD package of care

With funding and support from the CDC Foundation, The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) began collaborating with the Zimbabwe Ministry of Health and Child Care (MOHCC) in 2020 to update national guidelines on AHD and support the early introduction of key elements of the WHO-recommended AHD package of care in 10 selected healthcare facilities, with a focus on preventing, diagnosing, and treating cryptococcal infections and cryptococcal meningitis. The 10 pilot facilities were networked into a hub-and-spoke model that linked provincial hospitals to primary care clinics to extend AHD services to lower-level healthcare facilities. The project generated data and identified challenges, solutions, and best practices to inform future implementation and rollout of the Zimbabwe AHD package of care.

2.1 Establishing a national AHD technical working group

EGPAF supported the MOHCC and partners to draft terms of reference (TOR) for a national AHD technical working group (TWG), which was co-chaired by the MOHCC, EGPAF, and CHAI, and met quarterly. Members of the AHD TWG included representatives from the MOHCC AIDS and TB unit, MOHCC Department of Laboratory Services, Zimbabwe Network of People Living with HIV, Clinicians, Newlands HIV Clinic and implementing partners (EGPAF, OPHID, ZIMTTECH, FHI360, MSF, CDC, CHAI, WHO, UNDP, PANGAEA, BRTI, NAC, AHF, UNICEF, ZVANDIRI).

2.2 Updating national guidelines and materials

To ensure alignment with WHO recommendations, EGPAF supported the MOHCC to develop guidelines and an algorithm for diagnosing and managing AHD, which were published as an addendum to the 2016 Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe. EGPAF also supported the MOHCC and implementing partners (e.g. OPHID, ZIM-TECH, MSF, AHF) to develop materials on the AHD package of care that were used to train HCWs at the 10 project sites.

2.3 Introducing a hub-and-spoke model of care

The project piloted the AHD package of care at one stand-alone hospital in Harare and two networks of primary, secondary, and tertiary healthcare facilities (see table 1).

The main objectives of the hub-and-spoke model were to:

- Decentralize access to AHD diagnostics and therapeutics by making them available at lower-level facilities. This included on-site testing at spoke sites as well as transport of samples and/or referrals of some patients from spoke to hub sites for testing and/or treatment
- Strengthen referral of clients from lower- to higher-level facilities as well as counter-referral of clients from higher- to lower-level facilities for follow-up after testing and/or treatment initiation.

Table 1: AHD Hub-and-Spoke Networks

Province	Hub Sites	Spoke Sites
Midlands	• Gweru Provincial Hospital	• Mkoba Polytechnic • Mtapa Polytechnic
Bulawayo	• Mpilo Central Hospital	• Mzilikazi • Nkulumane • Northern Suburbs • Luveve • Cowdrey Park
Harare	• Parirenyatwa Central Hospital	• None

Figure 2 lists the services provided at hub-and-spoke facilities. When VISITECT CD4 tests were not available at spoke sites, clients were referred to hub sites for CD4 testing. The Omega VISITECT CD4 Advanced Disease Lateral Flow Assay (VISITECT CD4 LFA) is a disposable point-of-care (POC) test that provides semi-quantitative results at a threshold of 200cells/mm. In addition, spoke sites referred specimens to hub sites for Xpert MTB/RIF and clients for CSF CrAg testing. All other tests (e.g. TB LAM, Serum CrAg) were performed at both spoke and hub sites. TB preventive treatment and initiation of TB treatment as well as pre-emptive treatment for cryptococcal infection were provided at both hubs and spokes. However, only hub sites were able to initiate CM treatment, while follow-up for the consolidation and maintenance phase of CM treatment was available at both hub and spoke sites.

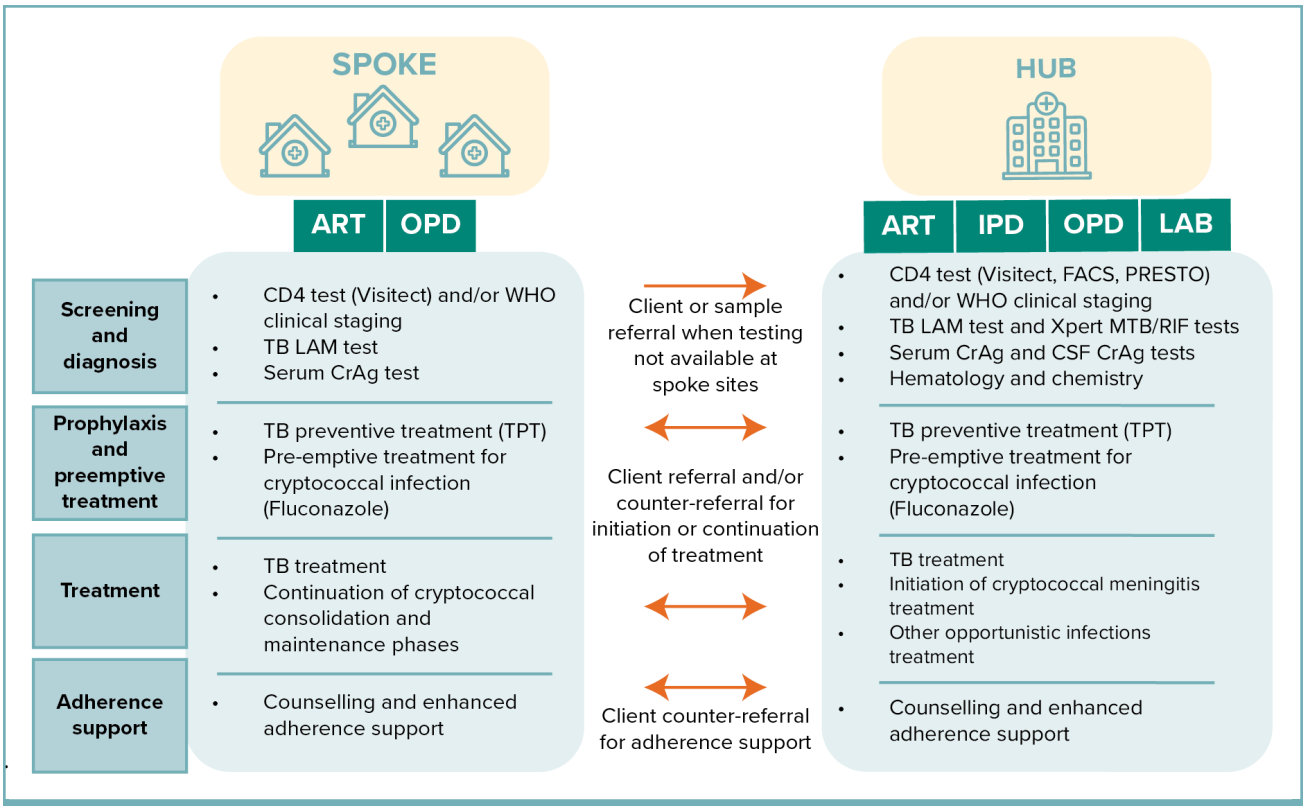

Figure 2: AHD Services Available at Hub and Spoke Sites

At primary-level facilities (spokes), EGPAF successfully advocated for decentralization and task shifting of VISITECT CD4, Serum CrAg, and TB LAM testing from laboratory workers to nurses and primary counsellors. As health facilities gained experience with the hub-and-spoke model, there were improvements in referral and counter-referral of clients as well as in the documentation of treatment outcomes.

2.4 Securing access to AHD commodities

To facilitate early uptake of the AHD package of care, EGPAF procured select AHD commodities and distributed them to project sites. EGPAF procured CrAg test kits, 5- Flucytosine tablets, Amphotericin B, and Fluconazole, while TB LAM test kits were procured from local suppliers. In November 2020, EGPAF collaborated with the MOHCC to secure 4,500 Omega VISTECT CD4 test kits through the CHAI Early Market Access Vehicle (EMAV) mechanism. Before the EGPAF AHD project, CD4 testing was done on a conventional platform in the laboratory only. The introduction of VISITECT decentralized CD4 testing to the primary care level and catalyzed task shifting to non-laboratory staff, who were trained to use VISITECT and CrAg LFA, with support from the MOH. Table 2 shows the commodities that the project supplied to project sites.

Table 2: Commodities Supplied to Project Sites to Support Access to the AHD Package of Care

Commodity	Unit size	Quantity	Time period
VISTECT CD4 test kits	25 per box	180	March 2021 to March 2022
CrAg Kits	50 per box	52	February 2021 to October 2021
TB LAM Kits	100 per box	29	February 2021 to October 2021
Fluconazole 200mg Tablets	100 tablets per box	869	February 2021 to May 2021

Flucytosine (5-FC) 500mg tablets	100 tablets per box	101	February 2021 to March 2022
Amphotericin B deoxycholate 50mg/Vial	50 mg vial	550	February 2021 to August 2021

After supplying the initial batch of AHD commodities to project sites, EGPAF worked with partners to quantify and plan for a sustainable supply of these commodities. The Global Fund procured CrAg and TB LAM, which were distributed to project sites through the national distribution system, the Zimbabwe Laboratory Commodities Distribution System (ZiLaCoDS). EGPAF participated in national quantification and procurement meetings to advocate for the procurement of adequate AHD commodities and the incorporation of new commodities, such as VISITECT CD4, into the national procurement system.

2.5 Building and sustaining capacity to deliver the AHD package of care

EGPAF supported the MOHCC and National Microbiology Reference Laboratory (NMRL) to develop and roll out a training curriculum for AHD. Between November 2020 and February 2021, EGPAF supported the MOHCC and other implementing partners (e.g. OPHID, AHF) to train more than 145 HCWs on the AHD package of care. The training had both theoretical and practical components and was conducted over three days. Participants were drawn from HIV clinics, medical wards, pharmacies, and laboratory departments to create well-trained, multi-disciplinary teams to identify and manage AHD. Laboratory scientists from the National Microbiology Reference Laboratory (NMRL) facilitated training on diagnostics, such as CrAG and TB-LAM.

In April 2021, four laboratory scientists from the NMRL were trained as trainers for VISITECT CD4 testing by the local distributors of the product. The four trainers subsequently cascaded the training to medical officers, nurses, and primary care counselors at the 10 project sites. High staff attrition was noted at the sites through the post-training mentorship visits and another training was conducted in August 2021 with support from PEPFAR implementing partners. Training on the AHD package of care and diagnostics also was offered to staff from non-project sites as part of the national roll-out of the AHD package of care.

EGPAF also supported clinical mentorship sessions and conducted quarterly post-training visits to the 10 pilot sites. Participants in the clinical mentorship sessions included physicians, pediatricians, medical officers, and nursing staff. During the post-training site visits, the EGPAF team applied a quality improvement approach to help staff at the sites identify challenges and develop and implement mitigating actions, which are described in the section below.

2.6 Improving the collection and reporting of AHD data

From January-December 2021, routine monitoring data were collected monthly and aggregated and reported quarterly. The national health information system did not have standalone data collection tools for advanced HIV disease. However, all data were available in generic HIV data collection tools. This presented challenges in collating data as patient information was being tracked across several tools in the continuum of care. EGPAF advocated for the revision of data collection and reporting tools to include data points for adequate AHD data reporting. Alternatively, data for AHD patients could be abstracted from the electronic patient-level monitoring system. However, only a third of facilities in the country were using the system, which limited the use of this tool for AHD reporting.

3. Challenges and solutions

Key challenges and solutions faced during the project are described in the table below.

Challenges	Solutions
Accurate diagnosis of AHD due to poor access to CD4 testing. All 10 facilities had access to CD4 testing, but spoke sites referred clients or sent samples to hub sites, which delayed the management of clients.	• Placed VISITECT CD4 tests at lower-level facilities.
Reluctance by clinicians to adopt the semi-quantitative VISTECT CD4 test: Clinicians expressed a preference for quantitative CD4 count testing over the semi-quantitative Omega VISITECT CD4 testing, which affected the early uptake of VISITECT CD4 cell count testing.	• Conducted clinical mentorship sessions with clinicians to increase the uptake of VISITECT CD4 testing.
AHD commodity challenges: Overstocks, stock outs, and the expiration of diagnostic tests and therapeutics due to inaccurate quantification and poor supply planning for new products (i.e., evolving demand requires the frequent review of assumptions and epidemiological data). For example, hub sites had overstocks of reagents for the quantitative FACS Presto CD4 machines because quantification was based on data on CD4 testing for monitoring and not on the estimated number of clients in need of screening for AHD.	• Supported quantification, supply planning, and distribution.
Heavy workload and turnover of healthcare staff: The AHD algorithm was not followed and/or diagnostic tests and treatments were delayed due to high turnover of staff and/or heavy workloads. Some HCWs reported limited time to conduct VISITECT CD4 and other diagnostic tests at spoke facilities.	• Trained more staff, both lab and non-lab, to perform VISITECT CD4 tests. • Conducted training and onsite mentorship on the AHD package care to address some of the identified service gaps identified through performance data. • Trained district-level lab technicians who can retrain new staff when there is turnover at healthcare facilities. • MOHCC updated the integrated training curriculum for HIV and conducted a training of trainers in the southern and northern regions of the country.
Slow uptake by clinical staff of low-volume, specialized therapeutics such as Amphotericin B for CM. Clinicians were not always prescribing dual therapy of Amphotericin B and 5-Flucytosine for the treatment of cryptococcal meningitis. Reasons given were: not aware 5-Flucytoscine was available, and not prescribing amphotericin B because reagents for chemistry were stocked out or the chemistry machines broke down thus, they could not monitor electrolytes and urea in patients on CM treatment.	• Retrained clinicians in the use of therapeutics (senior clinicians mentoring others to use the new therapeutics). • Conducted clinical mentorship sessions on the management of CM. • Encouraged the pharmacy department to share a list of available medicines with clinicians weekly.

Poor documentation of the AHD cascade in patient registers and lack of routine AHD data to estimate the burden and track progress towards national goals: Data collection tools and reporting system could not capture critical data points such as patients initiating ART with a CD4 count of <200cell/mm3, routine cryptococcal antigen (CrAg) screening volume, TB-LAM testing volume, and treatment outcomes for clients. Sites used improvised registers to capture VISITECT CD4 tests, CrAg, and TB Lam tests, because the M&E department under the Ministry of Health was moving to electronic tools thus there were no plans to develop paper-based registers.	• Developed improvised registers to capture laboratory testing services. • Conducted training for healthcare workers to enhance their understanding of AHD data collection and reporting. • Advocated for incorporation of all AHD indicators in the electronic tools. • Provided technical assistance on the revision of HIV tools to capture AHD data points.
Challenges in distributing commodities to peripheral healthcare facilities: The Zimbabwe Laboratory Commodities Distribution System (ZiLaCoDs) does not service primary healthcare facilities. Thus, commodities were not delivered to these facilities.	• Primary health facilities placed their orders through the hub facilities.

4. Results

Between January-December 2021, the number of AHD patients identified, in both inpatient and outpatient services, increased with each quarter. AHD patients were screened for TB and cryptococcal infection. Sputum samples were sent from spoke to hub sites for Xpert MTB/RIF assay, which is the gold standard for the diagnosis of TB in Zimbabwe. TB prophylaxis/treatment was offered at spoke facilities. Patients who tested positive for serum CrAg were given preemptive treatment with fluconazole and referred from spokes to hubs for lumbar puncture and CSF CrAg testing. Some missed opportunities were observed along the cascade of care due to incomplete referrals and deaths before clients commenced treatment.

4.1 CD4 testing amongst newly diagnosed PLHIV

There was a general increase in the number of PLHIV diagnosed with AHD from 177 in Q1 of 2021 to 408 in Q4 of 2021. For clients newly-diagnosed with HIV, access to CD4 testing and diagnosis of AHD increased over time, from 6% in the first quarter of 2021 to 93% in the last quarter of 2021. This increase can be attributed to the introduction of VISITECT CD4 test kits, the decentralization of CD4 testing to primary health facilities, training of HCWs on the AHD package of care, and ongoing mentorship and support supervision.

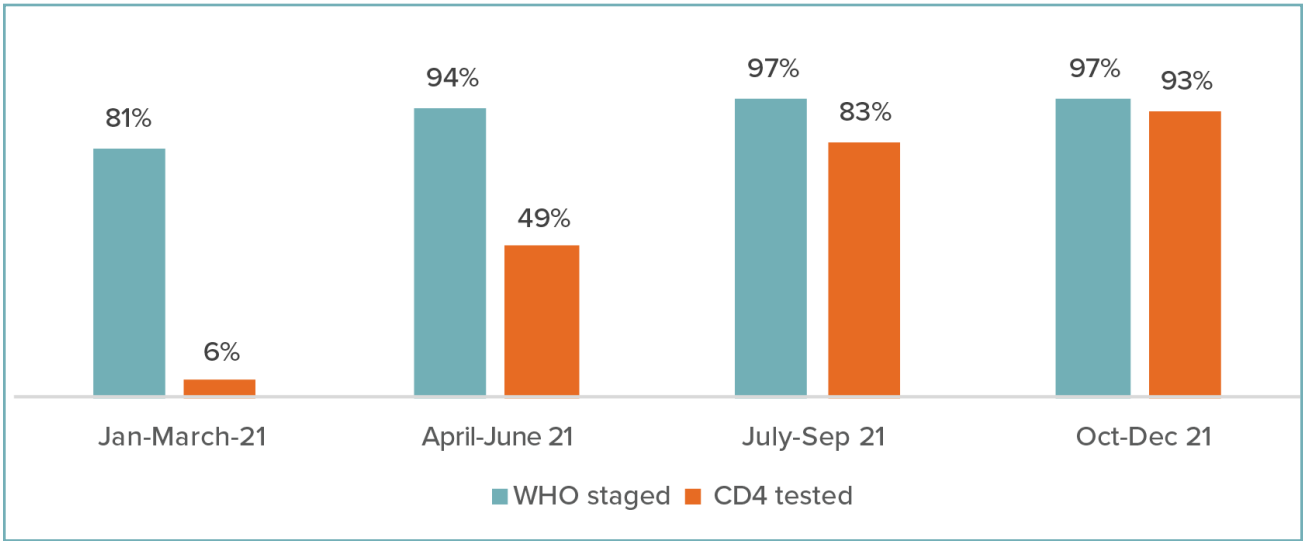

Figure 3: Percentage of patients newly diagnosed HIV+ who received WHO staging and CD4 testing from January through December 2021

4.2 TB diagnosis and treatment for AHD clients

Figure 4 illustrates an increase in the proportion of AHD patients tested for TB from 73% in Q1 of 2021 to 96% in Q3 of 2021. In Q4 of 2021, the proportion of AHD patients tested for TB declined to 54%. This is partly due to a stock out of urinary TB-LAM testing kits during the quarter. The proportion of AHD patients diagnosed with TB also increased from 12% in Q1 of 2021 to 22% in Q3 of 2021, with a decline to 17 % in Q4 of 2021. The absolute number of AHD patients who were diagnosed with TB and initiated TB treatment steadily increased from Q1 of 2021 to Q3 of 2021. However, documentation of linkage to treatment for clients diagnosed with TB remains suboptimal. Some hub facilities referred clients back to spoke sites for TB treatment initiation and it could not be ascertained if the patients were initiated on TB treatment as some spoke sites were not supported by the project.

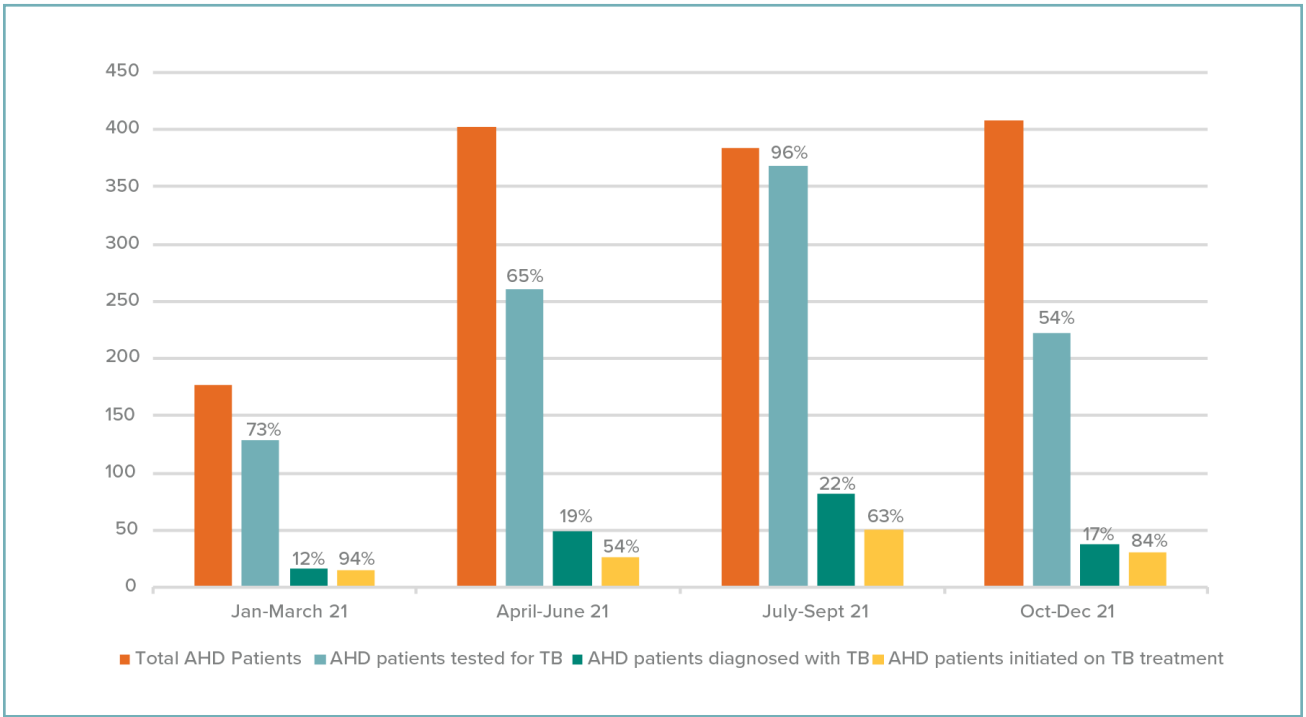

Figure 4: Number and proportion of AHD patients tested, diagnosed, and treated for TB from January through December 2021

4.3 CI/CM diagnosis and treatment for AHD clients

The proportion of AHD clients who were screened for cryptococcal infection increased from 58% in Q1 of 2021 to 89% in Q4 of 2021. There was a decline in the proportion of AHD patients that screened positive for cryptococcal infection from 15% in Q2 of 2021 to 7% in Q4 of 2021. In Q1 2021, there were no medicines available at pilot sites to treat CM. Linkage to care and treatment was poor, particularly in Q2 2021, when 26 patients were diagnosed with CM, but only 16 (61%) were documented as having initiated treatment. Some patients died before they were initiated on CM treatment. However, poor documentation also contributed to the ability to confirm the number of patients initiated on treatment. During Q4 2021, fewer clients were documented as diagnosed with cryptococcal infection using CrAg than with CM. This is partly due to patients presenting at hub sites with CrAg results from spoke sites that were not supported and tracked by the project.

Following mentorship sessions with clinicians, there was an increase in the number of patients initiated on the preferred treatment (Amphotericin B and Flucytosine) for CM from six in Q2 of 2021 to 21 in Q4 of 2021. However, gaps were still seen at some hub facilities, where clinicians did not initiate CM patients on the preferred regimen due to a lack of treatment-monitoring commodities, such as kidney function tests. The test is expensive in the private sector and beyond the reach of many patients requiring it.

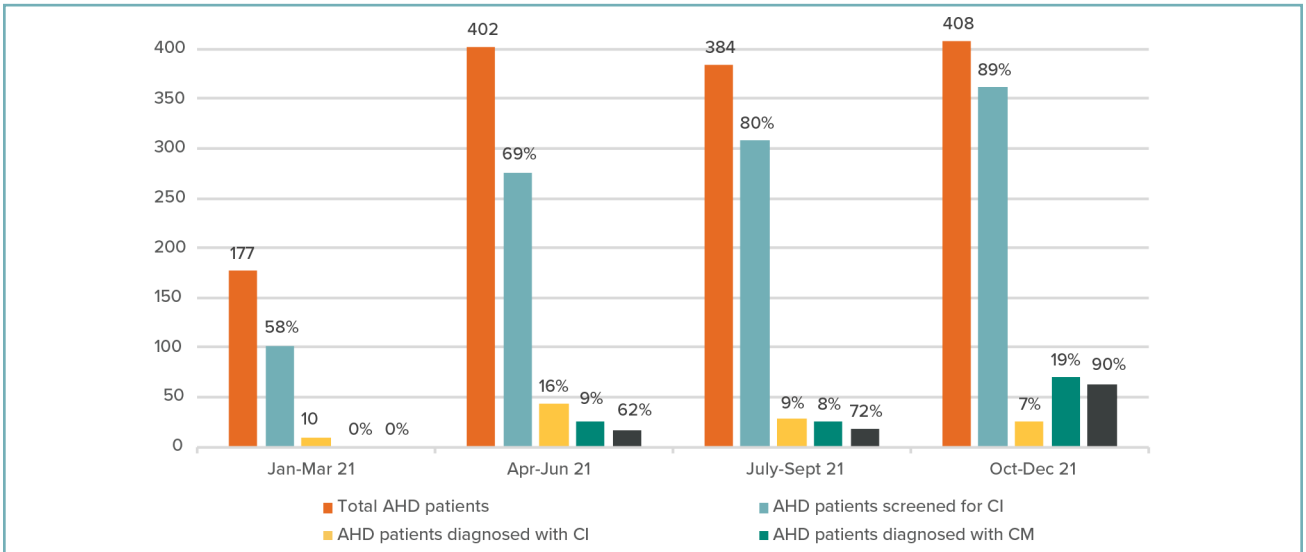

Figure 5: Number and percent of AHD patients tested, diagnosed, and treated for cryptococcal infection/meningitis from January through December 2021

5. Lessons Learned and Recommendations

HCWs across project sites were motivated to offer the AHD package of care. One said, *"Patients are initiated early on ART, especially at the primary health facilities, because we no longer wait for CrAg and TB results from the lab. Once we screen our patients, we then provide necessary treatment there and then."* A nurse from Bulawayo also said, *"This program opened my eyes, especially on the importance of screening for CM and management of serum CrAg-positive patients. I had no clue on how to handle such cases. I personally believe that implementation should continue so that we save people's lives."*

Experiences from the project informed policy changes at the national level and practices at the facility level. At the end of the project, there were plans to roll out AHD services to all the facilities once resources permit. During the pilot, we also observed some gaps in the cascade of AHD care, which were primarily due to poor access to AHD commodities, especially at the primary facility level; as well as high turnover of staff; lack of clear guidance to address AHD in children; and weak linkages between different levels of healthcare facilities.

The following recommendations can be made based on the project implementation and results.

National coordination, policies, guidelines, and plans:

- EGPAF already began discussions with MOHCC managers at national and provincial levels on how to transition management of AHD-related work to the MOHCC and other partners, including advocacy for AHD commodity security and continuous capacity building of clinicians. A more comprehensive national coordinating mechanism is needed to bring together all relevant MOHCC units and all national partners and donors to support a baseline analysis of the AHD introduction and develop and implement a national plan for rolling out the AHD package of care.

- A greater focus is needed on children with AHD. Diagnosis and management of AHD in children differ from adolescents and adults due to the associated disease conditions and require specific interventions, commodities, and supplies, such as vaccination and nutritional support. The next phase of the AHD program rollout should include a greater focus on AHD in children.

Commodity security for the "package of commodities" needed for AHD service delivery

- CD4 testing is superior to WHO staging for diagnosing AHD. It is estimated that WHO staging alone misses a significant proportion of clients with AHD. Both laboratory-based and point-of-care CD4 testing should be used to expand access to CD4 testing and ensure rapid return of test results at all levels of healthcare facilities. The MOHCC should consider making VISITECT CD4 testing available at all primary healthcare facilities.

- A more systematic, holistic, and coordinated approach to the quantification and procurement of AHD commodities is needed. This will require greater investments not only to diagnose, but also treat clients with AHD. EGPAF developed a guidance document on quantification and supply planning for AHD commodities and will continue working with the Zimbabwe supply chain department to ensure proper quantification and delivery of commodities to facilities.[7]

- Continuous engagement with national pharmacy and laboratory managers, and with provincial focal persons, is needed to ensure timely procurement and sustained delivery of AHD commodities to facilities and avert service interruptions.

Training and supervision

- Task shifting and decentralization of AHD diagnostics (e.g., VISITECT testing, CrAg, and TB-LAM) to non-laboratory staff at primary-level spoke facilities improved case identification and linkage to care. This should be considered a new standard of practice in decentralizing and scaling up AHD services.

- Provincial laboratory scientists were trained to provide training and mentoring support to project sites, which enabled a sustained capacity for training and mentorship. Trained district laboratory technicians supervise and train additional staff when there is turnover at healthcare facilities.

- Post-training support proved vital in identifying gaps and developing strategies to address them. A national plan is needed for post-training support, including mentorship to ensure the implementation of the AHD package of care with fidelity.

- To meet PEPFAR targets, implementing partners should include training and supervision for AHD service delivery within their standard package of HIV program activities.

Hub-and-spoke model

- Some services, such as CM diagnosis and treatment, are only available at higher-level facilities. For this reason, effective referral and counter-referral between lower- and higher-level facilities is needed to ensure treatment initiation at hub sites as well as treatment continuation and follow-up care at spoke sites.

- Access to some elements of the AHD package can be decentralized to lower-level facilities. But this requires training of a range of HCWs. For example, VISITECT was too time-consuming for nurses at peripheral facilities and there was a need to train primary care counselors to conduct the test.

Updating national information systems for AHD M&E

- Limited and disbursed tracking of patient-level data made it difficult to monitor patient progress through the AHD cascade of care, including treatment outcomes of AHD clients. AHD indicators for children, adolescents and adults should be integrated into national M&E systems and PEPFAR should include key AHD indicators in monitoring, evaluation and research (MER) guidelines.

AHD in children and adolescents from 0-19 years of age

- The major causes of morbidity and mortality among children living with HIV in low- and middle-income countries are pneumonia (including P. jirovecii pneumonia), TB, bloodstream infections, diarrheal disease, and severe acute malnutrition. The STOP-AIDS toolkit provides guidance and an algorithm to identify and manage AHD in children and adolescents. A stronger focus on the specific needs of children and adolescents is needed as the country moves forward with planning the national rollout of the AHD package of care.[2]

Photo: Eric Bond/EGPAF, 2022

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