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Implementation of the advanced HIV disease package of care using a public health approach: lessons from Nigeria

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Abstract

Background Nigeria adapted the WHO package of care for Advanced HIV Disease (AHD) in 2020. The package includes CD4 + cell count testing to identify People Living with HIV (PLHIV) with AHD, screening and treatment of opportunistic infections, rapid antiretrovirals (ART) initiation, and intensive adherence follow-up. The national program adopted a phased approach in the rollout of the AHD package of care to learn lessons from a few representative health facilities before scaling up across the country. This study describes the process and lessons learned from the first phase of implementation.

Methods This was a prospective observational study, and participants were enrolled between February and September 2021. Healthcare-worker (HCW) capacity was built to implement the AHD package of care. The study population included newly diagnosed PLHIV ≥ 10 years presenting to care in 28 selected facilities across 4 states in Nigeria. Eligible participants received CD4 + cell testing at baseline. Those with CD4 + cell count < 200 cells/mm^3 were subjected to a blood cryptococcal antigen (CrAg) test and urine TB lateral flow lipoarabinomannan (LF-LAM). Those with positive CrAg tests had a cerebrospinal fluid (CSF) test to confirm cryptococcal meningitis. Those negative for both blood CrAg and TB LF-LAM were rapidly initiated on ART and underwent intensive follow-up. Participants were followed up for 12 months.

Results A total of 6,781 patients were enrolled; 71% (4,812) received CD4 + cell count test, of which 41% (1,969 of 4812) had a CD4 + count < 200 cells/mm^3. Approximately 81% (1,492 of 1,850) of those with CD4 + count < 200 cells/mm^3 had TB LF-LAM test results documented; 25% were positive, of which 47% started TB treatment. Blood CrAg screening coverage among those with CD4 + count < 200 cells/mm^3 was 88% (1,634 of 1,850), of which 5% (85 of 1,634) were positive. Cotrimoxazole preventive therapy was initiated for 65% (1,198 of 1,850) of the participants with CD4 + count < 200 cells/mm^3, and 70% (966 of 1,375) of AHD patients with a negative TB LF-LAM and blood CrAg results were initiated on ART on the day of enrolment. Approximately 91% (421 of 461) of those who received viral

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load results at month 12 post-enrollment were virally suppressed. The retention rate and the Kaplan Meier survival probability estimate at month 12 were 65% (1,204 of 1,850) and 0.93 (CI, 0.91–0.94), respectively, for the enrolled participants.

Conclusion Implementation of the AHD package of care in Nigeria has improved the diagnosis of TB and CM, and will potentially enhance the quality of care for PLHIV if sustained. Findings from this implementation were used to guide national scale-up.

Keywords Advanced HIV Disease (AHD), People Living with HIV (PLHIV), CD4+, Cryptococcal meningitis, Tuberculosis, Antiretroviral Therapy (ART)

Background

The morbidity and mortality associated with HIV infection have decreased over the past decade due to increased access to antiretroviral therapy (ART) [1]. Worldwide, the number of AIDS-related deaths markedly declined from 1.7 million in 2004 to approximately 920,000 in 2014 [1]. However, since 2014, there has been a stagnation in the decline in HIV-related deaths globally, which was estimated to be 730,000 in 2020 [2]. The plateau in HIV-related deaths in recent years has mostly been due to the persistent challenge of advanced HIV disease (AHD) [1, 3–8]. The trend in HIV-related deaths in Nigeria is similar to that in the global picture, as deaths declined significantly from 93,000 in 2004 to 55,000 in 2014 but have remained relatively static, with AIDS-related deaths estimated at 56,000 as of 2020 [2]. From HIV programming experience, some of the reasons why AHD cases has remained high despite increased access to ART include late presentation of patients to care, insufficient access to diagnostic [9], prevention, and treatment tools, limited implementation of the STOP AIDS guidance for children with AHD, and the challenge with leaving some populations and geographies behind.

The deaths from AHD are caused mainly by opportunistic infections (OIs), the major of which are tuberculosis (TB), cryptococcal meningitis (CM), histoplasmosis, toxoplasmosis, and severe bacterial infections [1]. Nigeria has the 7th highest burden of tuberculosis globally [10] and is estimated to have more than 25,000 cases of cryptococcosis per annum [11]. Although histoplasmosis was not listed as one of the major AHD killer diseases, reports from Nigeria and Uganda showed that histoplasmosis is not uncommon among severely immunocompromised persons with AHD, being 7% in symptomatic severely immunocompromised Nigerians [12] and 4% in Uganda with CD4+cell count<100 cells/mm^3 [13]. These infections account for significant morbidity and mortality in the AHD population in the country.

The 2017 World Health Organization (WHO) guidelines on the management of AHD recommend that a package of care for screening, diagnosis, prophylaxis and treatment of OIs; rapid ART initiation; and intensified adherence support be offered to everyone living with HIV presenting with AHD [1]. The guidelines include an algorithm to support decision making for providing care for people with AHD. The current Nigeria HIV treatment guidelines highlighted the need to provide a differentiated package of care for OIs and AHD. In 2019, the Government of Nigeria (GON) established the AHD Technical Working Group (TWG) to adapt the WHO AHD package of care for Nigeria and oversee its implementation. The Nigerian HIV programme adopted a phased approach to introduce the AHD package of care to learn lessons from a few representative health facilities before scaling up across the country. This is because the AHD package of care requires a significant review of the existing HIV services, client flows, legacy strategies that have been used to maintain a high linkage rate, and the reintroduction of CD4+cell count testing that was deprioritized with the commencement of the "test and start" strategy.

The purpose of this study was to evaluate the first phase of the AHD package of care implementation, which included the use of the CD4+Lateral Flow Assay (LFA - VISITECT) and WHO stage 3 or 4 clinical disease to identify HIV infected people with AHD. We screened for TB using urine TB LF-LAM, screened for cryptococcaemia using CrAg LFA, and performed lumbar puncture when indicated to (i) detect cryptococcal antigen and (ii) measure raised intracranial pressure. The study aimed to assess the feasibility of implementing the package of care using a public health approach and to document outcomes and key lessons. The study also assessed healthcare worker (HCW) knowledge, practice, and level of confidence in managing PLHIV with AHD.

Materials and methods

This was a prospective descriptive observational study that enrolled participants over a period of 8 months with a follow-up period of 12 months.

Study setting

The study was conducted at 28 high-volume ART sites across 4 high-HIV burden states according to the NAIIS 2018 preliminary report: Akwa-Ibom, Anambra, Lagos, and Rivers states. Other site selection criteria were high

patient enrolment in 2018, availability of onsite CD4+cell count equipment and comprehensive laboratory services, and availability of requisite clinical expertise (doctors, nurses, pharmacists, and laboratory scientists). There was a total of 21 sites with a functional flow cytometry device, and this was spread across all the 4 states (4 in Anambra, 4 in Akwa Ibom, 4 in Rivers, 9 in Lagos).

Study population

The target population included all PLHIV aged ≥ 10 years newly diagnosed and presenting with a CD4+cell count < 200 cells/mm^3 and/or WHO clinical stage 3 or 4 disease at the 28 sites.

Sample size calculation

Although the study enrolled all clients that presented at the participating facility during the period of study, the sample size formula shown below revealed that the facility chosen can contribute desired sample size to demonstrate 90% likelihood that a client will receive same day CD4+cell count service. The study was designed to observe the first phase of implementation of the AHD package of care in Nigeria. One of the most critical services that the AHD package of care hoped to deliver was same-day return of CD4+cell count results for clinical decision making. An important assumption around this service was that at least 90% of newly enrolled patients should be able to receive same-day CD4+cell count results. To determine the sample size per facility needed to demonstrate that 90% of the enrollees would receive the same-day CD4+cell count result, assuming a 95% confidence interval (CI), 5% margin of error (MOE), and a finite sampling frame per facility of 200, we adopted the sample size formula for the population proportion given as outlined below:

$$\mathbf{Sample\ size}\ (\mathbf{n}) = \mathbf{N} * \mathbf{X} / (\mathbf{X} + \mathbf{N} - \mathbf{1})$$

where

$X = Z\alpha/2 * p * (1-p) / MOE2,$

$N = 200$

$P = 0.9\ (90\%)$

$MOE = margin\ of\ error = 0.05\ (5\%)$ and

Zα/2 = critical value of the normal distribution curve and this is equal to 1.96 when we assume 95% confidence interval and an MOE of 5%.

Thus, at least 83 subjects were required per site to demonstrate that 90% of patients could receive same-day CD4+count test results. However, this study enrolled all new PLHIV clients who presented at the sites.

Study procedures

Enrollment of participants in the study commenced in February 2021 and ended in September 2021. Each participant enrolled received the standard AHD package of care as outlined in Fig. 1.

Newly confirmed HIV-positive patients received CD4+cell count testing at baseline and WHO clinical staging. Those that had a CD4+cell count < 200 cells/mm^3 received blood cryptococcal antigen test (CrAg) to diagnose cryptococcal infection (CI) and urine TB lateral flow lipoarabinomannan (LF-LAM) for TB infection. Those positive for CI were subjected to lumbar puncture (LP), and cerebrospinal fluid (CSF) was collected for confirmatory diagnosis of CM using the CrAg test. CSF CrAg-positive patients received treatment for CM, while CSF CrAg-negative patients received pre-emptive therapy for CI. Patients who were positive for TB LF-LAM received an Xpert MTB/RIF test to assess rifampicin resistance and were subsequently placed on the appropriate treatment based on the national TB treatment guidelines. ART was rapidly initiated in patients who were negative for both blood CrAg and TB LF-LAM within 7 days. All patients with AHD received weekly follow-up phone calls for 4 weeks. To assess outcomes, patients were followed up for 12 months where their enrolment status, survival, and viral suppression were assessed. Viral load was conducted using plasma samples.

Prior to the commencement of the study, the HCWs were trained on the delivery of the AHD package of care. A pre/post-test was administered before and after the training respectively. At month 6 post commencement of the facility AHD implementation, a knowledge and competence assessment was conducted for the HCW using a structured questionnaire. Also, a self-rating assessment using a Likert scale to measure HCW confidence in administering the AHD package of care was conducted at month 6 post-commencement.

The study was conducted in 28 ART facilities across four states in the southern part of Nigeria: Rivers [6], Akwa Ibom [6], Lagos [11], and Anambra [5]. The data included in the cascade were for patients enrolled in HIV care from February 2021 to September 2021 in 26 of the 28 implementation health facilities. Two of the facilities were unable to submit cohesive cascade data due to operational issues.

Assessment measures

The study collected and analysed the following data to assess the implementation of the AHD package of care and patient outcomes at the facility.

1. AHD diagnosis cascade – proportion that presented with CD4 + cell count < 200 cell/mm^3 and WHO stage 3 or 4.
2. Operational suitability and performance of VISITECT – measure of agreement between VISITECT and flow cytometry results.

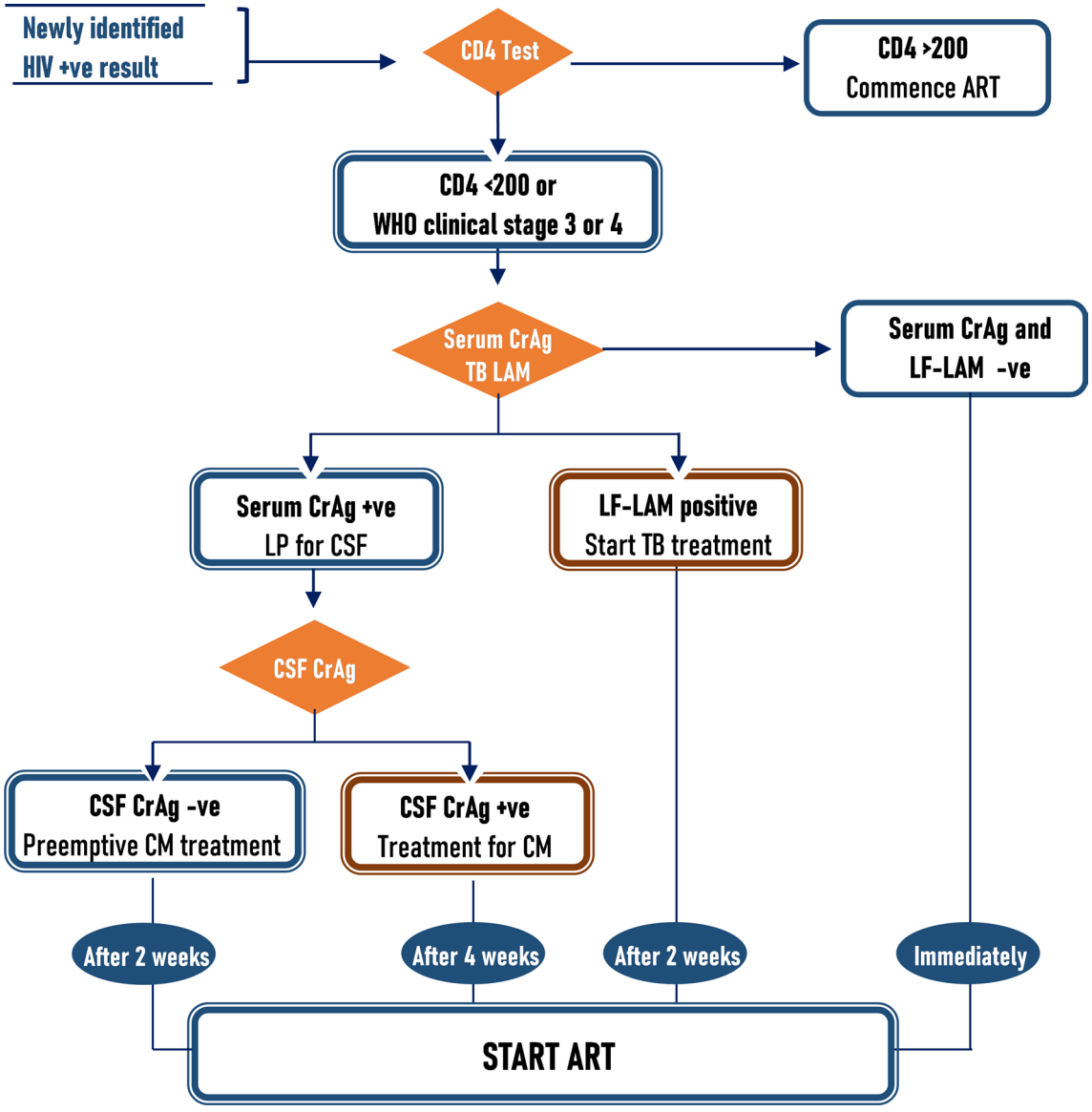


Fig. 1 Patient cascade for AHD package of care

3. AHD TB cascade – proportions of AHD patients who tested positive for TB LF-LAM and commenced TB treatment.
4. AHD CM cascade - proportions of AHD patients who tested positive for CrAg and commenced CM treatment.
5. Rapid initiation of ART within 7 days – the proportion of eligible patients who initiated ART within 7 days.
6. Cotrimoxazole preventive therapy (CPT) – proportion of AHD patients who received CPT.
7. Pre-& post-training HCW knowledge – test score performance of HCWs by various cadres.
8. HCW knowledge and competence – Performance test score for knowledge and weighted rating of competence by various cadres. Following healthcare workers' training on AHD management, the HCWs were assessed 6 months post-training on their knowledge of the AHD package of care.
9. Retention and mortality – survival analysis of AHD patients at 3, 6, and 12 months.
10. Viral load suppression rate - proportion that was virally suppressed at months 6 and 12.

The diagnostic and treatment commodities used for the study included the following: VISITECT CD4 advanced disease, CyFlow Counter and BD FACSPresto™ CD4 for CD4 assessment; Determine TB™ LAM Ag and Xpert® MTB/RIF for TB diagnosis in AHD; CrAg® LFA for diagnosis of cryptococcal infection and CM; liposomal

amphotericin B, flucytosine and fluconazole for the treatment of CM. VISITECT® is the world's first instrument-free, rapid, disposable CD4+cell count test that provides an affordable and simple solution for CD4+cell count testing [14]. VISITECT® accelerates clinical disease management, reduces the burden on HCWs, reduces costs, as it does not require investment in equipment or sample transport, and can be used anywhere, anytime, and read by eye [15]. TB LF-LAM is a point-of-care test that identifies the presence of lipoarabinomannan, a product of Mycobacterium cell wall breakdown, in urine within 25 min [16, 17].

Data management and statistical analysis

Patient data from the National HIV Monitoring & Evaluation Tools and from the HCWs' Knowledge and Competence Assessment Questionnaire were extracted into an MS Excel tool and analysed using Microsoft Excel and Stata/IC 16.0.

Ethical consideration

Approval for the study was secured from the National Health Research Ethics Committee of Nigeria with approval number NHREC/01/01/2007-27/01/2021 as part of the operations research for the first phase of implementation of the AHD package of care in Nigeria. Participants were not subjected to any additional risk beyond that involved in receiving HIV treatment in Nigeria.

Results

Patient enrolment

A total of 6,781 participants were enrolled in the study over the 8-month period, indicating an average monthly enrolment of 847 patients. The mean enrolment per facility was 260 over the 8-month enrolment period. There were 41% (2,834) males, and the median age of the participants was 35 years (IQR 28–43).

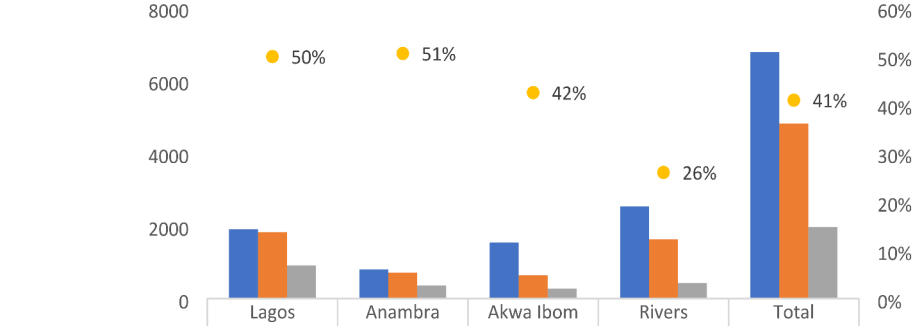
AHD diagnosis cascade

Among the 6,781 newly identified patients enrolled, 71% (4,812) had a baseline CD4+cell count, and 41% (1,969 of 4,812) had a CD4+cell count < 200 cells/mm^3, as shown in Fig. 2. Overall, the AHD prevalence in this study was 41%, and this ranged from 26% in Rivers State to 51% in Anambra State.

Of the 1,866 health facilities providing comprehensive ART services, only 322 (17%) had CD4+flow cytometry devices. VISITECT was introduced to bridge the CD4+testing gap in the country. Of the 4,812 CD4+cell count tests conducted, 51.6% were enumerated using VISITECT alone, 7.3% were enumerated using a flow cytometry device alone, while 41.1% were enumerated using both VISITECT and a flow cytometry device. Of the 26 facilities across the four states, 21 had flow cytometry devices. The total number of test done using VISITECT across these 21 facilities were 3435, and only 2,333 test were conducted using flow cytometry device. A high agreement (chance agreement was 51%; however, the actual agreement was 92.86%) with kappa of 0.854 and $P<0.01$ was found between values of VISITECT® and flow cytometry.

Among those with a valid flow cytometry result (2,335), the median CD4+cell count was 269 cells/mm^3 (IQR, 117, 459). Of the 2,335 CD4+cell count results, only 526 (22.5%) had a time stamp for sample collection and sample analysis. Based on these 526 samples, the median turnaround time (TAT), defined as time interval between sample collection and sample analysis, using flow cytometry device was 50 min (IQR, 40, 67.5). The report of TAT was based on the report of persons with a time stamp.

A review of the WHO clinical staging for all the new patients revealed that 6,541 (96%) of the 6,781 patients



	Lagos	Anambra	Akwa Ibom	Rivers	Total
No of PLHIV enrolled	1903	801	1542	2535	6781
No with CD4 test	1827	710	645	1630	4812
CD4 <200	912	359	274	424	1969
AHD prevalence	50%	51%	42%	26%	41%

Fig. 2 AHD identification cascade (February–September 2021)

had documented staging. Of these, 854 (13%) had stage 3 or 4 disease. Of the 854 patients with WHO clinical stage 3 or 4 disease, 821 (96%) had a documented CD4+cell count. One hundred and eighty-six (23%) of the 821 patients with clinical stage 3 or 4 disease had a CD4+cell count > 200 cells/mm^3. Also, of the 4,820 patients with WHO clinical stages 1 or 2 diseases, a total of 1,254 (26%) had a CD4+cell count < 200 cells/mm^3.

Of the 2,155 confirmed AHD patients (including patients with a CD4+cell count < 200 cells/mm^3 [1,969] and WHO stage 3 or 4 disease [186]), only 1,850 (85.84%) had complete documentation for the subsequent cascade.

AHD – TB cascade

As shown in Fig. 3, about 81% (1,492 of 1,850) of the newly enrolled PLHIV with a CD4+cell count < 200 cells/mm^3 had TB LF-LAM test results. TB LF-LAM positivity was 25% (373) among the 1,492 patients. Among the TB LF-LAM-positive patients, 49% (181 of 373) were tested using sputum samples on GeneXpert, and 33% (60 of 181) were positive. Of all the TB-LAM-positive patients, 47% commenced TB treatment.

TB-LAM positivity varied by state, with Lagos, Anambra, Akwa Ibom and Rivers recording 27%, 30%, 25% and 15%, respectively. Of the 1,850 individuals with complete documentation, 1,276 had documented TB screening using the WHO four symptom screening. Of the 1,276 individuals, 52% (667) were presumptive for TB. We analysed presumptive TB and TB LF-LAM results. Of the 373 participants that were urine TB LF-LAM-positive, 54 (14.5%) were not presumptive for TB on screening. On the other hand, there were 1,118 participants that were urine TB-LAM-negative. Of these, 318 (28%) were presumptive for TB on screening.

AHD-CM cascade

Over the implementation period, 88% (1,634 of 1,850) of patients with complete documentation received the serum CrAg test, 5% (85 of 1,634) of whom were positive for cryptococcosis. However, only 4% (3 of 85) of the patients who were positive for serum CrAg received a lumbar puncture for CSF CrAg test to confirm CM. Of the 3 patients who received a CSF CrAg test, 1 was positive, but there was no evidence of treatment, as shown in Fig. 4.

The serum CrAg positivity rate was similar across Lagos, Akwa Ibom and Rivers states, at 3% (27 of 801), 4% (7 of 194) and 3% (10 of 347), respectively; however, it was higher in Anambra (14% (41 of 259)). Available data from 30 blood CrAg-positive patients indicated the following factors as the major contributors to low uptake of lumbar puncture (LP): withheld patient consent (30%), lack of LP kits (27%), inability of patients to pay for LP (23%), pre-LP mortality (10%), lack of HCW competence (7%), and loss to follow-up (3%). It is surprising that only 6 of the 85 individuals with serum CrAg positive were documented to have received fluconazole pre-emptive therapy.

Further data analysis revealed that 61% (52 of 85) of the serum CrAg-positive patients were also positive for TB LF-LAM.

Rapid ART initiation

One of the components of the AHD package of care implemented in the selected health facilities is rapid ART initiation. Of the 1,850 clients with AHD, 94.1% (1,741) had valid enrollment and ART start dates. Of these, 366 were positive for blood CrAg, TB LF-LAM or both and were ineligible for immediate ART initiation. Of the 1,375 individuals eligible for same-day initiation, 70% (966) were initiated the same day, while 83% (1,141) were initiated within 7 days. The median time in days from identification to ART initiation was 0 (IQR 0,1).

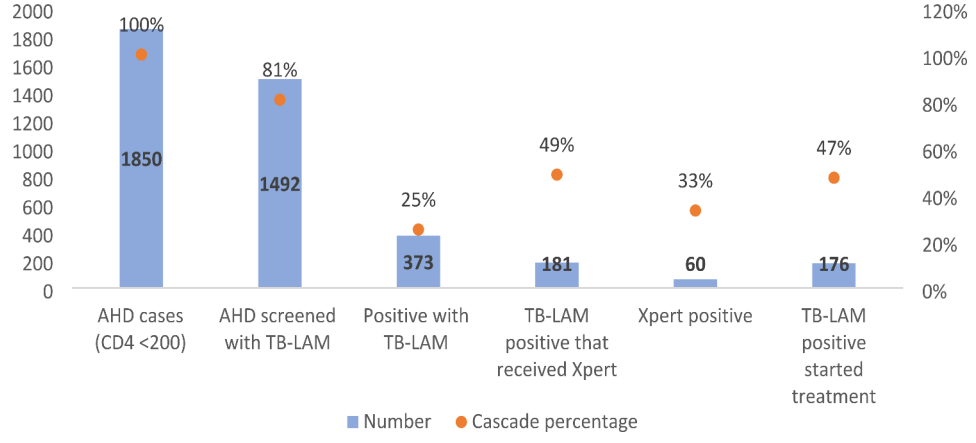


Fig. 3 AHD-TB cascade

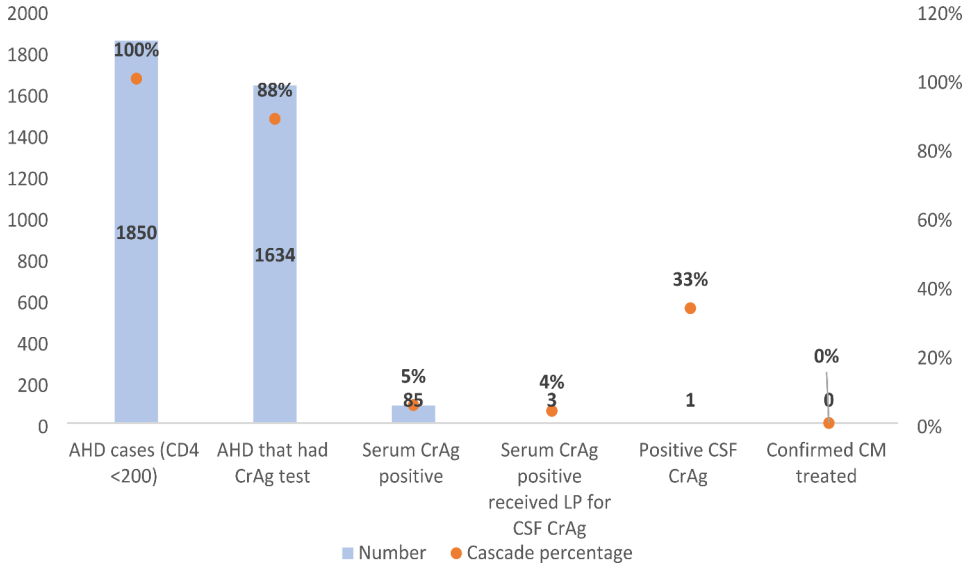


Fig. 4 AHD–CM cascade

Table 1 Mean percentage scores of pre & post test of healthcare workers by work category

Category of HCW	Pre-test mean score, % (SD)	Post-test mean score, % (SD)	Difference in pre- and post-test mean scores %	% Increase in mean score	*p*-value
Clinicians (*n* = 29)	66 (15.2)	79 (11.0)	13	19.8	< 0.001
Lab scientist (*n* = 25)	59 (11.3)	76 (11.6)	17	28.8	< 0.001
Monitoring & Evaluation officer (*n* = 18)	55 (10.6)	74 (13.0)	19	34.5	< 0.001
Pharmacist (*n* = 23)	63 (8.9)	80 (9.9)	17	30.6	< 0.001
Adherence nurse (*n* = 24)	55 (11.7)	77 (11.6)	22	40.0	< 0.001

Cotrimoxazole preventive therapy

Of the total AHD patients, 65% (1,198 of 1,850) received Cotrimoxazole Preventive Therapy (CPT). The CPT coverage among AHD patients varied by state, with Lagos, Anambra, Akwa Ibom and Rivers recording 60% (515 of 860), 78% (270 of 348), 58% (162 of 280) and 69% (251 of 362), respectively.

Pre- & post-training healthcare worker knowledge

Before the implementation, 119 HCWs were trained on the AHD package of care using the AHD training tool kit and slides developed by the AHD TWG. Knowledge of AHD among HCWs was assessed pre- and post-training to determine the training outcomes. The pre- and post-test scores disaggregated by healthcare cadre are presented in Table 1. Across all the cadres, there was a significant increase in knowledge of AHD and its package of care after the training.

As shown in Table 1, adherence nurses and M&E officers had the most knowledge gained compared to clinicians and others. The highest post-test score was 95%, while the least was 39%, and the average increase in test score for all HCWs was 18%.

At 6 months post-commencement of AHD implementation, 135 HCWs (including those trained prior to commencement of implementation and those who received step-down training) across various cadres at the 28 sites responded to the questionnaire on knowledge and competence assessment. The median age of the respondents was 42 (IQR 34–48), the median duration at the facility was 5 years (IQR 2–11), and the median duration of HIV service delivery was 7 years (IQR 4–11).

The average score for all the healthcare workers' knowledge of AHD identification was 85%, while the average score for questions about the management of AHD-associated OIs was 73%. Counsellors had the highest (82%) knowledge at 6 months post-training and commencement of the AHD package of care implementation across the facilities, while doctors had the least (65%) knowledge (see Fig. 5).

The self-assessment results obtained using a 10-point Likert scale (1 least, 10 highest confidence) indicating the confidence of HCWs in the delivery of the AHD package of care are presented in Fig. 6.

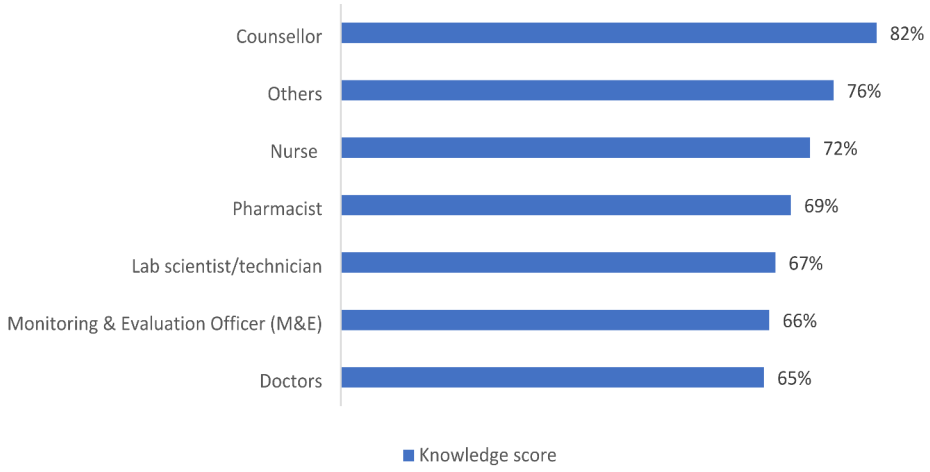


Fig. 5 Knowledge of the AHD package of care by HCW cadres after 6 months of AHD implementation

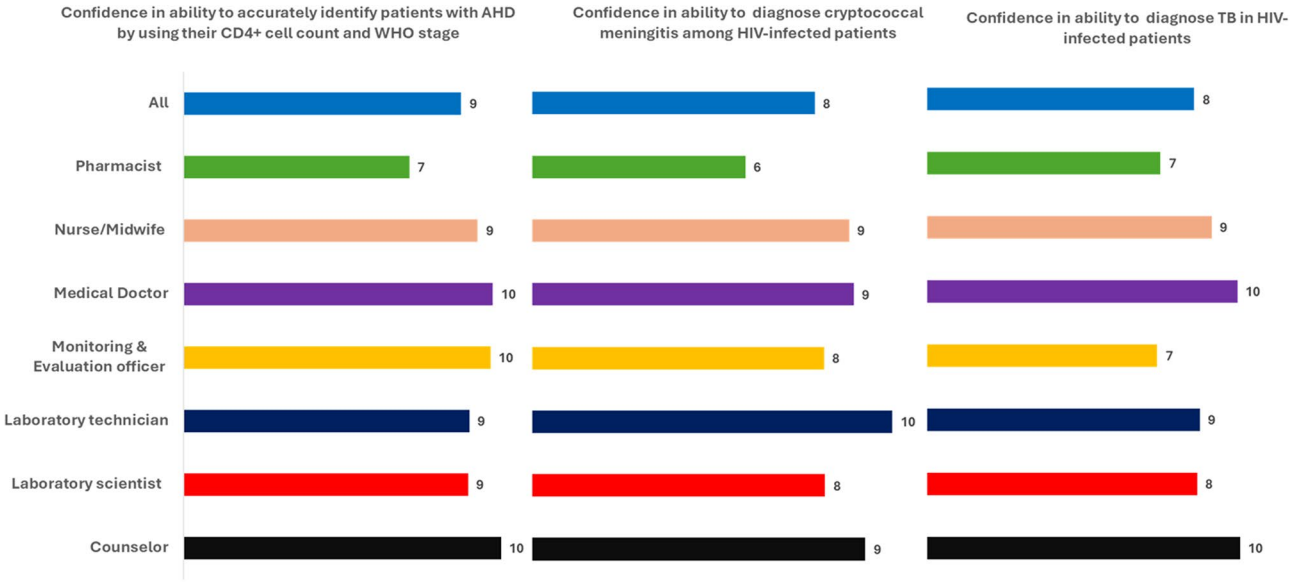


Fig. 6 Self-assessment of HCWs on their confidence in delivering the AHD package of care

AHD patient outcomes – retention and mortality

From available data, of the 1,850 AHD patients in care at month zero, only 86.4% (1,599), 76.8% (1,421), and 65.1% (1,204) were retained in care at month three, six and twelve respectively. Of the 1,850 AHD patients, mortality data was available for 90.6% (1,676). From the available data, the numbers of confirmed deaths at months 3, 6 and 12 were 77, 115, and 128, translating to mortality rates of 4%, 6% and 7%, respectively. The Kaplan–Meier estimated survival probability for all AHD patients, regardless of opportunistic infection (OI) status at 12 months, was 0.93. CI (0.91–0.94).

Of the 1676 patients with mortality records, 361 had a positive TB-LF-LAM and/or blood CrAg test. Additionally, the Kaplan–Meier estimated survival probabilities at 12 months for TB LF-LAM-positive patients and patients with cryptococcal infection were 0.88 (CI, 0.84–0.90) and 0.82 (CI, 0.72–0.89), respectively. Figure 7 compares the Kaplan–Meier survival probability estimates among (i) patients with AHD, (ii) AHD patients with negative CrAg and TB LF-LAM results, (iii) AHD patients with cryptococcal infection, and (iv) AHD patients with positive TB LF-LAM results at various time points.

At month three, of the 77 patients who died, 30 (39%) had TB infection, 8 (10%) had cryptococcal infection, and 6 (8%) had both TB and cryptococcal infections. Additionally, we interrogated the risk of death among subjects who received positive urine TB LF-LAM who have record of starting treatment and those without record of starting treatment. Of the 176 with record of starting treatment, a total of 23 had died at 12 months, 58 unaccounted for (censored), the rest were alive. Whereas,

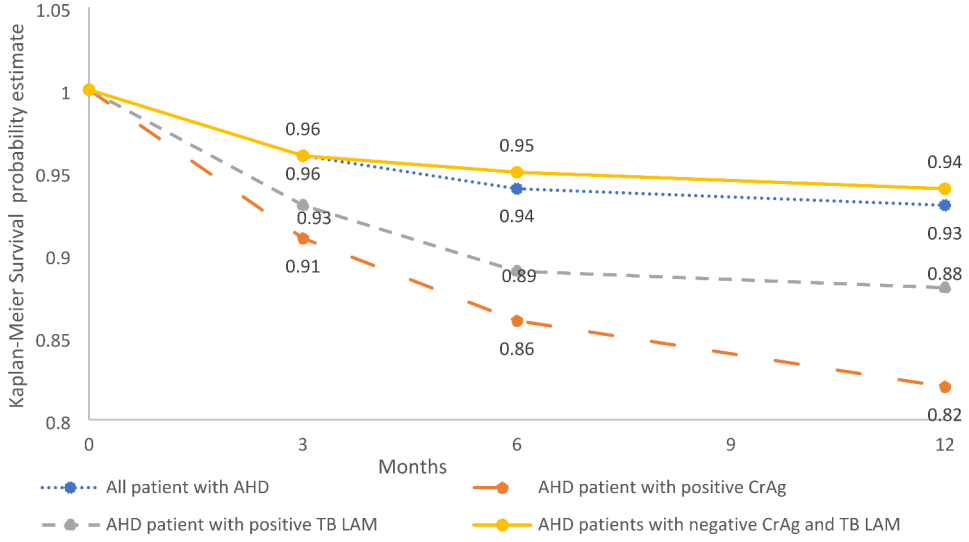


Fig. 7 Survival rate of patients with AHD, Cryptococcal infection (CI) and TB

Table 2 Viral load outcomes for enrolled AHD patients

	Month 6	Month 12
Number with viral load result	1,096	461
Number suppressed (suppression rate)	965 (88%)	421 (91%)
Number undetectable, i.e., < 20 copies/ml ("undetection rate")	509 (46%)	256 (55%)

among those without record of starting treatment, 20 died, 60 were censored, the rest were alive. No differences existed in risk of death or censorship in both groups ($c^2=1.35$, $p=0.50$). The number of CrAg positive patients with documented evidence of treatment are too few [6] for us to demonstrate differences in survival among those treated and untreated.

Patient outcomes – viral suppression

Table 2 presents the viral suppression rate (<1000 copies/ml) for AHD patients enrolled in the phased implementation.

The viral detection rate among AHD patients in month 12 was significantly lower than that at month 6 ($P<0.01$), and the suppression rate in month 12 was higher than in month 6, although this was not statistically significant ($P=0.07$).

Discussion

There was an increase in CD4+cell count testing from 16 to 71% after the implementation of the AHD package of care. Access to CD4+cell count has been poor since the commencement of the test and treat strategy in Nigeria and other LMICs. A study in Malawi reported more than half of new patients that started ART in 2021 did not receive CD4+test due to limited resources to support the expansion of point of care services for AHD [9]. The increased access to CD4+cell count from this implementation may be attributed to an improved supply of commodities for CD4+cell count and the increased capacity of staff to conduct CD4+cell count. This study noted a variation in CD4+cell count coverage by state, ranging from 42% in Akwa Ibom to 96% in Lagos. Akwa Ibom and Rivers had the lowest CD4+cell count coverage, and there was a missed opportunity to identify AHD among 1,790 newly enrolled PLHIV in the two states over the 8-month period. There is a need for national programmes to ensure equitable access to CD4+cell count testing for all eligible patients to improve AHD care.

One of the major gains of the phased implementation of the AHD package of care in Nigeria was the introduction of VISITECT® CD4 Advanced Disease Lateral Flow Assay. Prior to VISITECT introduction, CD4+cell testing device was not widely available in most ART sites in the country. A significant number of the ART sites are located in remote areas with unstable power supply. A previous attempt by the national HIV programme to utilize a hub and spoke model for CD4+cell count did not yield much result as the operational challenges associated with specimen transport do not support timely analysis. CD4+cell count enumeration must be conducted within 6 h of specimen collection before biodegradation of the CD4+molecules on the cell membrane [18]. Hence, we observed from our study that the introduction of VISITECT® and similar point of care CD4+testing techniques will bridge the gap in the CD4+testing in the country. The observed high agreement between VISITECT® and flow cytometry results in our study demonstrated that VISITECT can correctly identify patients with AHD and has the potential to improve access to CD4+cell count testing and linkage to care, especially in hard-to-reach settings. This corroborate other findings by Lechiile et al. and Ndlovu et al. that reported sensitivities of 94.1%

in Botswana and 95% across three countries respectively, noting a high agreement between VISITECT & flow cytometry [19–22]. Furthermore, even though the actual analysis time for BD FACSPresto, Partec Cyflow, and VISITECT were 25, 20, and 42 min, respectively, our study showed that the result turnaround time was lowest for VISITECT. This is due to the other operational steps required before actual analysis on the flow cytometry. Hence, a point-of-care test such as VISITECT has an operational advantage over flow cytometry in terms of turnaround time as it is user-friendly and acceptable to health care workers. This benefit of VISITECT was also documented by a profile review of the test by Pham et al. [23], however, they may be a need for a reader to aid result interpretation of the test in public health setting. In general, the CD4+cell count turnaround time was less than 24 h. This implies that same day CD4+cell count test result is feasible and implementable without prejudice to the "test and treat" policy.

The prevalence of AHD in this study (41%) is comparable to the prevalence reported by the WHO for low- and middle-income countries [24], and higher than that reported by Sakyi et al. (28.6%) in a study in Ghana [25]. Our findings revealed a poor correlation between immunological and clinical diagnosis of AHD, as 26% of patients with WHO stage 1 or 2 disease had a CD4+cell count < 200 cells/mm^3, which is similar to the findings of Hakim J et al. [26]. Hence, relying on clinical staging alone risks missing substantial numbers of PLHIV with severe immunosuppression. Our findings support the recommendation that all new PLHIV receive both WHO clinical staging and CD4+cell count to avoid missed opportunities for AHD identification.

An integral intervention in the AHD package of care is screening for OIs, the most common of which is TB [1]. A major finding on the TB cascade was that 67% of patients who tested positive with TB LF-LAM were negative according to GeneXpert. This large proportion of AHD patients could have been missed if the programme relied only on the GeneXpert test, and the findings suggest that TB LF-LAM is a tool that has utility for identifying TB pathogens that are extrapulmonary among AHD patients.

Our study also noted that 14.5% of patients who were not presumptive for TB on screening and may have been missed were diagnosed with TB LF-LAM. Prior to TB LF-LAM, only presumptive TB patients were eligible for GeneXpert and sputum acid-fast bacilli confirmatory tests. Thus, our findings support the report of other studies [27–30] that the use of both TB LF-LAM and GeneXpert MTB/RIF increases TB case finding among AHD patients with a shortened time-to-treatment.

Although the TB LF-LAM result is diagnostic and can be used to start treatment, patient assessment for rifampicin resistance with GeneXpert is still important for proper management as a report from Ethiopia by Diriba et al. revealed extrapulmonary TB patients could have greater rate of rifampicin resistance than pulmonary TB patients [31]. Hence, the national programme should encourage GeneXpert testing for all positive TB LF-LAM patients. Despite being a diagnostic test, TB treatment was not initiated for almost half of patients who were positive for TB LF-LAM during the implementation because of substantive guidance at the time from the national TB program recognizing GeneXpert and Acid-Fast Bacilli as the only confirmatory TB test. More HCW sensitization on the use of TB LF-LAM and patient management actions following the test results is required for prompt initiation of TB treatment. Other operational challenges that impacted the uptake of TB LF-LAM included the limited availability of urine sample cups for TB LF-LAM tests, hence only facilities that had access to sample cups from other sources performed the test at the initial stage of implementation. Furthermore, urine samples could not be readily obtained from some AHD patients at the time of enrolment, resulting in missed opportunities for TB diagnosis.

The blood CrAg positivity rate (5.2%) among AHD patients in this study was similar to that noted in other studies (4.4 – 12.7%) conducted in Nigeria [32–35]. This significant rate of cryptococcal infection calls for urgent public health action. A major barrier to CM management, as shown by this implementation, is poor access to LP procedures. Research has shown that CSF CrAg positivity among blood-positive CrAg patients is as high as 50% [32, 36]. This implies that close to 50% of potential CM cases were not identified among those enrolled in the implementation facilities. More disturbing however is the finding that only 6 of 85 participants that were serum CrAg positive received fluconazole pre-emptive therapy. We believe that a few of these individuals may have had CM and died. This probably will explain the lowest survival rate of 82% among those that were serum CrAg positive. Given the high mortality associated with CM, this treatment gap was a missed opportunity to reduce AIDS-related death in the national HIV programme. It is clear that training and retraining of health care staff at our facilities is required to diagnose, offer effective pre-emptive therapy for blood CrAg positive persons, and manage CM.

We noted that some of the factors that contributed to poor access to LP among AHD patients were HCW capacity gaps, patient hesitancy, poor availability of LP kits, and cost of procedure. This is consistent with the findings of Elafros et al. who classified them as either patients/caregivers or health providers related [37], and Zibusiso who noted that many ambulatory asymptomatic patients refuse lumbar puncture or do not go for

referral [38]. Urgent policy and programmatic interventions are needed to address poor access to LP, including training and retraining of HCWs, providing guidance for the management of symptomatic blood CrAg-positive patients, strengthening referral models within the hub and spoke mechanism, providing patient education and literacy for ready consent to LP procedure, providing LP kits and funding the procedure cost. This study revealed a high rate (61%) of cryptococcal and TB co-infection among AHD patients. The high rate of co-infection is not unexpected as both pathogens are associated with severe immunosuppression.

While the various point of care tests used for this implementation improved access to AHD diagnostics, there is a need to integrate these technologies into existing laboratory networks in a cost-effective and efficient manner as also noted by Stevens et al. [39]. It is also important to develop and establish effective internal and external quality assurance (EQA) systems for these tests to boost end user confidence. One limitation to note is that neither of the three point of care test used in this implementation had a standard EQA panel at the time the study was conducted.

Considering the gains from same-day ART initiation practice following the "test and treat" policy, it was desirable that implementing the AHD package of care should not compromise the national ART linkage rate. A report from Haiti in 2017 indicated significant benefits in care retention and viral suppression rates among patients that started ART the same day of diagnosis over those that delayed initiation [40]. In this study, except for patients who had OIs such as TB or CM that warranted a delay in ART commencement, most of the newly identified HIV patients were initiated on ART within 7 days, and 70% were initiated on the same day of enrolment. Hence, the AHD package of care can be rolled out with little or no impact on the linkage rate.

The coverage of CPT in this study was suboptimal (65%), despite guidance to provide CPT to all AHD patients. The therapy serves as prophylaxis against OIs, mainly *Pneumocystis jirovecii* pneumonia and toxoplasmosis. Our interest was mainly on CPT coverage and did not analyse association between CPT and mortality as it has been well established that CPT is associated with reduced mortality among AHD patients [41, 42]. A major reason for the poor coverage of CPT is commodity stockout, and this has also been documented by the WHO [43]. The national HIV programme needs to prioritize the supply of cotrimoxazole for AHD patients to prevent opportunistic infections.

This study found a retention rate of 65.1% at 12 months for AHD patients, which is lower than the average national retention rate of 76% in the general ART population [44], and 78% in a study conducted in the Democratic Republic of Congo [45]. This underscores the need for intensive follow-up for AHD patients, as recommended in the AHD package of care. In our study, the survival rate among AHD patients at month 12 was 93%, whereas, the national mean annual mortality among patients on ART from 2017 to 2021 was 13,446 (SD 3423), and the mortality rate among patients on ART was 0.6%, implying a survival rate of 99.4% [46]. A multi-country study by Kibuuka et al. documented a much lower rate of death among ART patients—0.47% between 2019 and 2021 [47]. The mortality rate among AHD patients in this study was highest in the first three months of care, which aligns with the findings of other studies [3, 48]. As expected and in line with other studies [3, 47, 49], survival rates were even lower for patients with cryptococcal infection and tuberculosis, the two commonest AIDS defining illnesses. We also found a greater probability of survival in AHD patients without TB or cryptococcal infection than in those with these diseases. This is expected, as OIs are the major drivers of mortality among AHD patients. Therefore, baseline CD4+cell count and assessment for OIs may be helpful prognostic factors in patients starting ART, as they are predictive of mortality. As such, the CD4+cell count should not be deprioritized [5]. Our study supports the implementation of differentiated care requiring intensive follow-up and enhanced prophylaxis for patients with AHD to improve their survival rate [26].

The observed viral suppression rate among AHD patients in this study was comparable to the national average for all ART patients during the same period (89% in 2021 and 96% in 2022) [46, 50]. This is not surprising, as most of the patients were rapidly started on DTG-containing regimens, these regimens have a demonstrated good suppression rate in the country [51].

Conclusion

The implementation of the AHD package of care in Nigeria has improved diagnosis of TB and CM among PLHIV with AHD. If sustained, the AHD package of care will enhance the quality of life of PLHIV. However, offering of prompt treatment for individuals that were TB LF-LAM positive and those that are serum CrAg positive was suboptimal resulting in failure to observe an expected reduction in AIDS-related mortality. The delivery of the AHD package of care requires a review of client flow in the facilities for an effective public health approach. The findings from this implementation indicate that same-day CD4+cell count testing is possible and does not compromise the "test and treat" policy.

The success recorded from this first phase of AHD implementation was aided by effective coordination of the AHD TWG, close monitoring of the delivery of the package of care, commodity security, the political will

of the government and buy-in from the donor partners. This should be sustained during the scale-up of the intervention across the country. Moreover, adequate funding for both commodity and ancillary services and reliable quality assurance systems for the point of care technologies are required to effectively implement the AHD package of care.

Abbreviations

AHD	Advanced HIV Disease
ART	Antiretrovirals
CSF	Cerebrospinal fluid
CrAg	Cryptococcal antigen
CM	Cryptococcal meningitis
CPT	Cotrimoxazole Preventive Therapy
GON	Government of Nigeria
HCW	Healthcare worker
HIV	Human immunodeficiency virus
LF-LAM	TB lateral flow lipoarabinomannan
LP	Lumbar Puncture
MOE	Margin of Error
OI	Opportunistic infection
PLHIV	People living with HIV
TAT	Turn-around-time
TB	Tuberculosis
TWG	Technical Working Group
WHO	World Health Organization

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Author contributions
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Data availability
The data sets used for the study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
Approval for the study was secured from the National Health Research Ethics Committee of Nigeria with approval number NHREC/01/01/2007-27/01/2021 as part of the operations research for the first phase of implementation of the AHD package of care in Nigeria. Participants were not subjected to any additional risk beyond that involved in receiving HIV treatment in Nigeria.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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