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MAJOR ARTICLE

Persistent High Burden and Mortality Associated With Advanced HIV Disease in Rural Tanzania Despite Uptake of World Health Organization "Test and Treat" Guidelines

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Background. Information about burden, characteristics, predictors, and outcomes of advanced human immunodeficiency virus disease (AHD) is scarce in rural settings of sub-Saharan Africa. Human immunodeficiency virus (HIV) infections and associated deaths remain high despite specific guidelines issued by the World Health Organization (WHO).

Methods. Burden of AHD and 6-month death/loss to follow-up (LTFU) were described among 2498 antiretroviral therapy (ART)–naive nonpregnant people with HIV (PWH) aged >15 years enrolled in the Kilombero Ulanga Antiretroviral Cohort in rural Tanzania between 2013 and 2019. Baseline characteristics associated with AHD and predictors of death/LTFU among those with AHD were analyzed using multivariate logistic and Cox regression, respectively.

Results. Of the PWH, 62.2% had AHD at diagnosis (66.8% before vs 55.7% after national uptake of WHO "test and treat" guidelines in 2016). At baseline, older age, male sex, lower body mass index, elevated aminotransferase aspartate levels, severe anemia, tachycardia, decreased glomerular filtration rate, clinical complaints, impaired functional status, and enrollment into care before 2018 were independently associated with AHD. Among people with AHD, incidence of mortality, and LTFU were 16 and 34 per 100 person-years, respectively. WHO clinical stage 3 or 4, CD4 counts <100 cells/μL, severe anemia, tachypnea, and liver disease were associated with death/LTFU.

Conclusions. More than 50% of PWH enrolled in our cohort after test and treat implementation still had AHD at diagnosis. Increasing HIV testing and uptake and implementation of the WHO-specific guidelines on AHD for prevention, diagnosis, treatment of opportunistic infections, and reducing the risks of LTFU are urgently needed to reduce morbidity and mortality.

Keywords. advanced HIV disease; death and loss to follow-up; opportunistic infections; sub-Saharan Africa; test and treat.

Advanced human immunodeficiency virus (HIV) disease (AHD)—defined by the World Health Organization (WHO) as having a CD4 cell count <200 cells/μL or clinical stage 3 or 4 at presentation to care [1]—constitutes a major obstacle to the Joint United Nations Programme on HIV/AIDS' (UNAIDS) goal of ending AIDS by 2030 [2]. AHD is associated with high morbidity and mortality [3, 4], high costs for health system [5], and increased risk of severe opportunistic infections (OIs), which—without timely diagnosis and treatment—are often lethal [6–8].

The declining trend of AHD at diagnosis seems to have plateaued in recent years, still accounting for 30% of people with HIV (PWH) in high-income countries and up to 50% in low- to middle-income countries [1]. Studies on temporal trends in sub-Saharan Africa (SSA) reveal persistent high proportions of AHD among PWH [9–11]. Siedner et al found no significant increase in CD4 cell counts at presentation to care across SSA between 2002 and 2013, a time when antiretroviral therapy (ART) was scaled up in resource-limited settings but initiation was still subject to drug availability and CD4 cell count thresholds [9]. In Tanzania, with an HIV prevalence of 4.7% in 2018 [2], data from cohorts in Tanzania up to 2015 reported varying proportions of AHD ranging from 35% to 61% [12–14].

Recent WHO guidelines need to be evaluated for their effectiveness of reducing the burden of AHD and AIDS-related mortality in SSA.

In October 2016, the Tanzanian National AIDS Control Programme took up the WHO "test and treat" guidelines

Received 02 September 2022; editorial decision 27 October 2022; accepted 11 November 2022

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https://doi.org/10.1093/ofid/ofac611

[15–17] from 2015 recommending ART for all PWH regardless of their CD4 cell count. Results of 2 clinical trials informing these guidelines showed that early versus deferred initiation of ART was beneficial, leading to a reduction in AIDS-related morbidity and mortality [18, 19].

This study of a Tanzanian cohort of PWH enrolled between 2013 and 2019 aims to describe burden, characteristics, and predictors of AHD and the potential impact of test and treat guidelines and to identify predictors of unfavorable outcomes among ART-naive PWH diagnosed with AHD.

METHODS

Study Site and Population

This is a prospective observational nested study of PWH enrolled between 1 January 2013 and 16 August 2019 at the Kilombero Ulanga Antiretroviral Cohort (KIULARCO; see Appendix). KIULARCO was implemented in 2005 as a single-site, prospective cohort of PWH. It is based at the Chronic Diseases Clinic of Ifakara (CDCI), within the Saint Francis Referral Hospital (SFRH) in Ifakara, the main town of the rural district of Kilombero in southeast Tanzania. The SFRH serves as referral hospital of primary health care clinics and HIV care and treatment centers, covering the area of the Kilombero valley in the Morogoro region. The population comprised around 700 000 people and an estimated 40 000 PWH in 2016, with recent numbers expected to be higher [20, 21].

Procedures within the cohort are described elsewhere [20, 21]. In brief, following HIV diagnosis, patients are invited to join the KIULARCO cohort, where sociodemographic data are collected, blood samples are taken, and a clinical evaluation is done at baseline. ART eligibility is assessed and further visits scheduled. Patients are seen every 3 months: twice per year by a nurse and twice per year by a clinician.

For this study we included 2498 ART-naive nonpregnant people diagnosed with HIV-1 aged ≥15 years and enrolled between 1 January 2013 and 16 August 2019.

Ethical Considerations

Written informed consent of patients willing to participate in KIULARCO are obtained at registration. Yearly ethical approval for data and sample collection as well as analysis are sought from the Ifakara Health Institute institutional review board (IHI/IRB/No16-2006) and the Health Review Committee of the National Institute for Medical Research of Tanzania (NIMR/HQ/R.8a/Vol.IX/620).

Definitions

AHD at diagnosis was defined as having a CD4 cell count <200 cells/μL or WHO clinical stage 3 or 4, and "very AHD" as CD4 cell count <100 cells/μL. Six-month outcomes postenrollment included the primary composite outcome of death/loss to follow-up (LTFU). A composite outcome was chosen since in SSA, LTFU is often associated with death [22, 23]. In a previous cohort study from KIULARCO, 5-year mortality estimates among patients LTFU were approximately doubled when adjusted for unseen deaths [24]. Secondary outcomes were being under active follow-up, LTFU, transferred, or death. LTFU was defined as missing a scheduled visit for at least 60 days.

Statistical Analysis

Data were collected from 1 January 2013 until 16 August 2019. We used descriptive statistics to show baseline characteristics, prevalence of AHD, and outcomes at 6 months.

Associations between AHD and baseline variables of PWH were explored through logistic regression. Confounders included in the final model were age, sex, body mass index (BMI), education, marital status, smoking status, and calendar year.

Six months of follow-up of participants was chosen for analysis of death and LTFU, since in people presenting with AHD, these events mostly occur within the first 6 months after enrollment into care [3, 25]. Associations between the 6-month composite outcome of death/LTFU and baseline variables of people diagnosed with AHD (excluding those who transferred out within the first 6 months) were explored through Cox regression. Confounders included were age, sex, CD4 cell count, BMI, education, marital status, smoking status, and calendar year. The fit of the final model was assessed through Schoenfeld residuals ($P = .220$). Calendar year was included as potential confounder to take into consideration national guidelines published between 2013 and 2019 possibly impacting associations of independent variables including voluntary counseling and testing, functional status, or past OIs reflecting testing for opportunistic infections. Statistical analysis was performed using Stata version 16 (StataCorp LLC, College Station, Texas).

RESULTS

Study Population and Baseline Characteristics

Of 8274 patients enrolled at the CDCI between 1 January 2013 and 16 August 2019, 2498 (30.2%) patients were included in the final study population, 3575 (43.2%) being excluded due to lack of informed consent (Figure 1).

While most PWH were female (60.1%), more men than women presented to care with AHD (44.4% vs 55.6%) (Table 1). Median age at diagnosis was 39 years (interquartile range [IQR], 32–47 years), people with AHD being older (40 vs 37 years) than those without AHD. Median time to ART initiation was 5 days overall (IQR, 0–16 days)—1 day among people without AHD and 7 days among those with AHD, with similar proportions of ART initiation among both groups (90.8% and 88.6%).

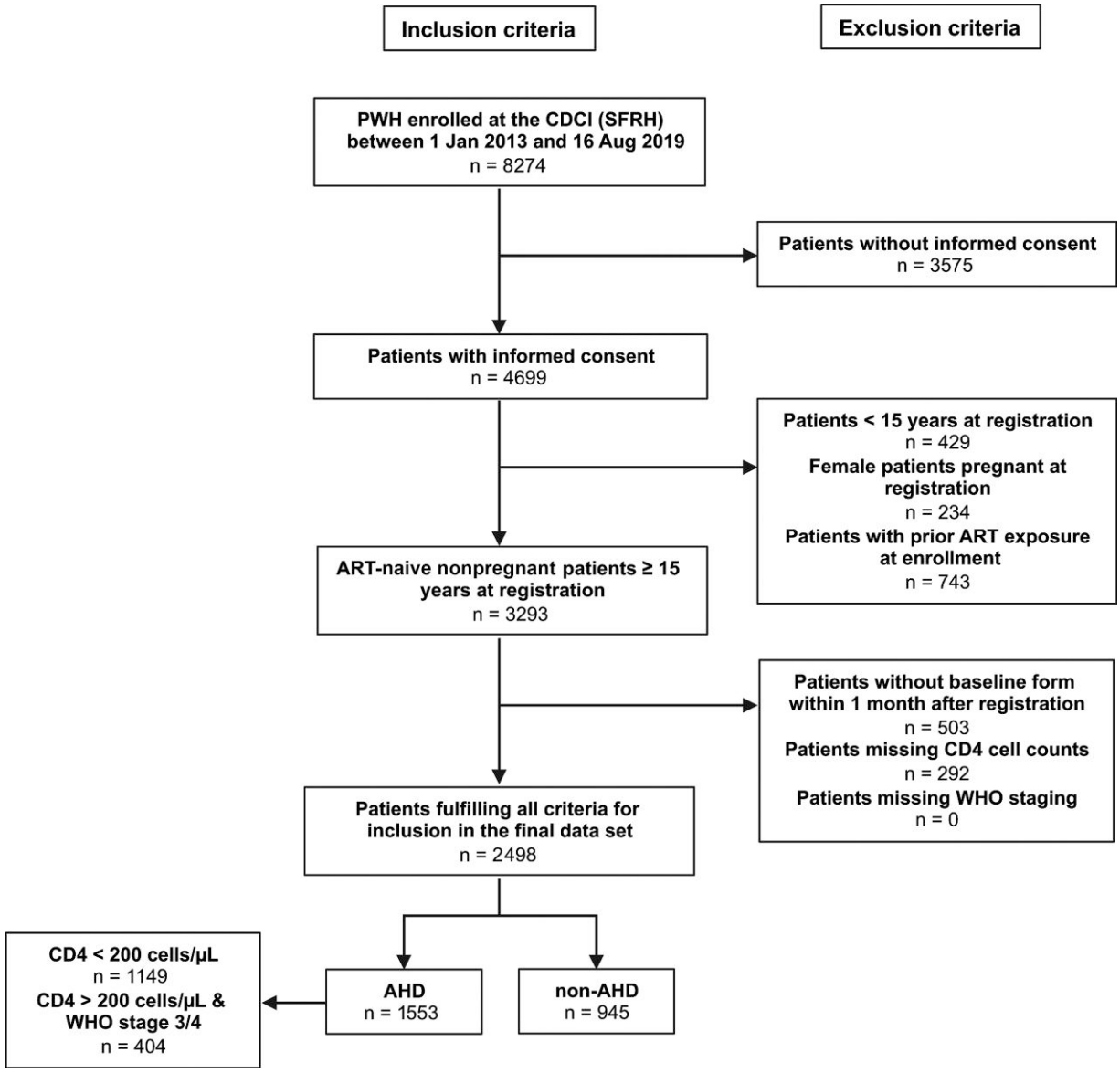


Figure 1. Flowchart of the study cohort. Overview of inclusion and exclusion criteria of people with human immunodeficiency virus enrolled in the Kilombero Ulanga Antiretroviral Cohort between 1 January 2013 and 16 August 2019. Abbreviations: AHD, advanced human immunodeficiency virus disease; ART, antiretroviral therapy; CDCI, Chronic Diseases Clinic of Ifakara; PWH, people with human immunodeficiency virus; SFRH, Saint Francis Referral Hospital; WHO, World Health Organization.

Median CD4 cell count at baseline was 221 cells/μL (IQR 87–394), with 119 cells/μL among people with AHD and 406 cells/μL among those without AHD (Table 2).

Overall, 69.7%, 46%, and 27.1% of PWH had a CD4 count below 350 cells/μL, 200 cells/μL, and 100 cells/μL, respectively. Clinically, 44.6% of PWH were diagnosed with WHO clinical stage 3 or 4 regardless of CD4 count, accounting for 71.7% among people with AHD.

At baseline, the most common AIDS-related diseases among people with AHD—as defined by the clinician in charge using the *International Classification of Diseases, Tenth Revision* coding—were tuberculosis (11.4%) with a median CD4 count of 116 cells/μL (IQR, 53–240); cryptococcosis (3.9%), with a median CD4 count 45 cells/μL (IQR, 22–73); bacterial pneumonia (6.8%), with a median CD4 count 145.5 cells/μL (IQR, 37–305); and candidiasis (6.8%), with a median CD4 count 51 cells/μL (IQR, 18–119) (Supplementary Table 1).

Burden of AHD and Impact of Test and Treat Guidelines

Among 2498 PWH, 1553 (62.2%) were diagnosed with AHD (46.0% with CD4 count <200 cells/μL and 44.6% with WHO clinical stage 3 or 4), and 678 (27.1%) with very AHD (Figure 2). Proportions of AHD and very AHD declined after national uptake of test and treat guidelines (1 October 2016)

Table 1. Summary of Baseline Characteristics of People With HIV at Enrollment Into the Kilombero Ulanga Antiretroviral Cohort

Characteristic	Overall (N = 2498)	AHD (n = 1553)	Non-AHD (n = 945)
Sociodemographic characteristics			
Age at registration, y	39 (32–47)	40 (33–48)	37 (30–45)
Sex			
Male	996 (39.9)	690 (44.4)	306 (32.4)
Female	1502 (60.1)	863 (55.6)	639 (67.6)
Education			
None	265 (10.6)	166 (10.7)	99 (10.5)
Primary school	2060 (82.5)	1305 (84.0)	755 (79.9)
Secondary school	140 (5.6)	60 (3.9)	80 (8.5)
College/university/polytechnic	29 (1.2)	21 (1.4)	8 (0.8)
Other	4 (0.2)	1 (0.1)	3 (0.3)
Marital status			
Married/living with partner	1499 (60.6)	900 (58.5)	599 (64.1)
Other[a]	975 (39.4)	639 (41.5)	336 (35.9)
District of origin			
Kilombero	2146 (85.9)	1325 (85.3)	821 (86.9)
Ulanga	327 (13.1)	214 (13.8)	113 (12.0)
Kilosa	5 (0.2)	2 (0.1)	3 (0.1)
Other	20 (0.8)	12 (0.4)	8 (0.3)
Occupation			
Farmer	2126 (85.1)	1337 (86.1)	789 (83.5)
Other[b]	372 (14.9)	216 (13.9)	156 (16.5)
Patient referral site			
Outpatient service	612 (24.5)	355 (22.9)	257 (27.2)
Inpatient care	399 (16.0)	304 (19.6)	95 (10.1)
RCH/PMTCT/EID	38 (1.5)	12 (0.8)	26 (2.8)
VCT or self-referral	1263 (50.6)	769 (49.5)	494 (52.3)
Disclosure of HIV status	1898 (76.0)	1203 (77.5)	695 (73.5)
Smoking status			
Never/stopped	2344 (93.8)	1435 (92.4)	909 (96.2)
Current	154 (6.2)	118 (7.6)	36 (3.8)
Linkage to care and ART			
Days between HIV diagnosis and enrollment into care	1 (1–3)	1 (1–3)	2 (1–4)
Days between enrollment into care and ART initiation	5 (0–16)	7 (1–17)	1 (0–14)
ART initiation	2234 (89.4)	1376 (88.6)	858 (90.8)
ART regimen[c]			
First-line	2104 (99.1)	1307 (98.5)	797 (100.0)
NNRTI	2087 (83.5)	1298 (83.6)	789 (83.5)
INSTI	110 (4.4)	49 (3.2)	61 (6.5)
Other first-line	17 (0.7)	9 (0.6)	8 (0.8)
Second-line			
PI	20 (0.8)	20 (1.3)	0 (0.0)
None	264 (10.6)	177 (11.4)	87 (9.2)

Data are presented as No. (%) or median (interquartile range).

Abbreviations: AHD, advanced human immunodeficiency virus disease; ART, antiretroviral therapy; EID, early infant diagnosis; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PMTCT, prevention of mother-to-child transmission; RCH, reproductive and child health; VCT, voluntary counseling and testing.

[a]Never married, separated, divorced, widowed, other (not specified).

[b]Student, employee, self-employed, unemployed, housewife, retired, other (not specified).

[c]First-line ART regimens include NNRTI-based regimens: 1 NNRTI + 2 nucleoside reverse transcriptase inhibitors (NRTIs); INSTI-based regimens: 1 INSTI (dolutegravir) + 2 NRTIs or other first-line (not further defined). Second-line ART regimens include PI-based regimens: 1 PI + 2 NRTIs.

from 66.8% (n = 970) and 29.1% (n = 423) to 55.7% (n = 583) and 24.4% (n = 255), respectively. Median CD4 cell count increased from 204.5 cells/μL to 253 cells/μL (Figure 2).

Unfavorable Outcomes Among People Presenting to Care With Advanced HIV Disease

A total of 1461 PWH were diagnosed with AHD between 1 January 2013 and 31 December 2018 with follow-up until June 2019 for analysis of 6-month outcomes. Among these, between January 2013 and December 2018, 297 (20.3%) died or were LTFU within 6 months after enrollment (Figure 3). Within a total of 601 person-years of observation, this corresponds to incidence rates of 16 deaths and 34 LTFU per 100 person-years. Among 419 people who died or were lost to follow-up 6 months after enrollment, 297 (70.9%) had advanced disease. Median time to death was 26.5 days (IQR, 10–62 days) (Supplementary Figure 1).

Factors Associated With AHD at Presentation to Care

In the final adjusted model of the multivariate logistic regression analysis (Supplementary Table 2), variables significantly associated with AHD were older age (34–47 years: adjusted odds ratio [aOR], 1.74 [95% confidence interval {CI}, 1.34–2.27]; >47 years: aOR, 1.61 [95% CI, 1.18–2.19]), male sex (aOR, 1.31 [95% CI, 1.04–1.66]), lower BMI (<18.5 kg/m^2; aOR, 2.87 [95% CI, 2.06–4.01]; >25 kg/m^2: aOR, 0.58 [95% CI, .45–.77]), elevated aminotransferase aspartate (AST) level (aOR, 7.93 [95% CI, 2.69–23.42]), severe anemia (aOR, 5.47 [95% CI, 3.08–9.73]), tachycardia (aOR, 2.73 [95% CI, 1.82–4.08]), actual complaints (aOR, 2.91 [95% CI, 2.35–3.60]), previous diagnosis of OIs (aOR, 1.51 [95% CI, 1.09–2.09]), chronic kidney disease stage 3 to 5, as defined by an estimated glomerular filtration rate below 60 mL/minute/1.73 m^2 (aOR, 1.75 [95% CI, 1.05–2.93]) and having enrolled into care before 2018 (aOR, 1.48 [95% CI, 1.15–1.90]).

A sensitivity analysis for factors associated with AHD as defined by CD4 counts of <200 cells/μL regardless of WHO clinical stage was performed after obtaining the final logistic regression model (Supplementary Table 3), and all associations remained, except for older age and past OIs.

Predictors of 6-Month Death/LTFU Among People Presenting to Care With Advanced HIV Disease

In the final multivariate Cox regression model, lower CD4 count (CD4 <100 cells/μL: adjusted hazard ratio [aHR], 1.60 [95% CI, 1.15–2.23]), WHO clinical stage 3 or 4 (aHR, 1.96 [95% CI, 1.31–2.94]), liver disease (aHR, 1.62 [95% CI, 1.06–2.47]), severe anemia (aHR, 2.49 [95% CI, 1.85–3.35]), and tachypnea (aHR, 3.03 [95% CI, 1.46–6.29]) were predictors of death and LTFU. Age <34 years was marginally associated with death/LTFU (aHR, 1.37 [95% CI, 1.00–1.88]; $P = 0.047$) (Supplementary Table 4).

Table 2. Summary of Laboratory Characteristics From Blood Sample Analysis and Clinical Presentation at Baseline

Characteristic	Overall (N = 2498)	AHD (n = 1553)	Non-AHD (n = 945)
Laboratory characteristics			
CD4 lymphocyte count, cells/μL	221 (87–394)	119 (49–208)	406 (295–591)
<100	678 (27.1)	678 (43.7)	0 (0.0)
100–199	471 (18.9)	471 (30.3)	0 (0.0)
200–349	592 (23.7)	227 (14.6)	365 (38.6)
≥350	757 (30.3)	177 (11.4)	580 (61.4)
AST level, U/L	26.7 (20.3–40.7)	29.9 (21.6–46.7)	23.6 (18.7–30.7)
eGFR, mL/min/1.73 m^2	125.2 (103.6–139.6)	122.6 (96.5–137.8)	129.6 (112.7–142.4)
Hemoglobin level, g/dL	10.9 (9.3–12.5)	10.2 (8.6–11.7)	12.1 (10.7–13.3)
Platelet count, 1000/μL	251 (190–331)	256 (183–349)	247 (198–305)
Clinical presentation			
WHO clinical staging			
Stage 1 or 2	1385 (55.4)	440 (28.3)	945 (100.0)
Stage 3 or 4	1113 (44.6)	1113 (71.7)	0 (0.0)
Past medical history			
Opportunistic infection	311 (12.5)	231 (14.9)	80 (8.5)
Actual complaints			
Any complaints[a]	1535 (61.5)	1136 (73.2)	399 (42.2)
Functional status			
Working	1875 (75.1)	1016 (65.4)	859 (90.9)
Ambulatory/bedridden	623 (24.9)	537 (34.6)	86 (9.1)
Anthropometric values and vitals			
BMI, kg/m^2	21.2 (19.2–23.6)	20.4 (18.3–22.4)	22.4 (20.5–25.6)
<18.5	478 (19.1)	414 (26.7)	64 (6.8)
18.5–24.9	1552 (62.1)	947 (61.0)	605 (64.0)
≥25	468 (18.7)	192 (12.4)	276 (29.2)
Any abnormal vital sign[b]	579 (23.2)	482 (31.0)	97 (10.3)
Tachycardia	305 (12.4)	265 (17.4)	40 (4.3)
Hypoxia	25 (1.0)	18 (1.2)	7 (0.8)
Tachypnea	23 (0.9)	22 (1.4)	1 (0.1)
Hypotension	288 (11.9)	242 (16.1)	46 (5.0)
Non-AIDS-related diseases			
Liver disease[c]	123 (5.6)	107 (7.7)	16 (1.9)
CKD (stage 3–5)	179 (7.7)	150 (10.3)	29 (3.3)
Arterial hypertension[d]	221 (9.1)	109 (7.2)	112 (12.2)
Severe anemia[e]	279 (11.6)	257 (17.2)	22 (2.4)

Data are presented as No. (%) or median (interquartile range).

Abbreviations: AHD, advanced human immunodeficiency virus disease; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; WHO, World Health Organization.

[a]Any complaints include ocular, ear-nose-throat, respiratory, cardiovascular, gastrointestinal/liver, genitourinary, sexually transmitted disease, neurological, joint-bone, and skin complaints.

[b]Any abnormal vital sign includes 1 or more of the following: tachycardia (heart rate >120 beats per minute), hypoxia (oxygen saturation <90%), tachypnea (respiratory rate >30 breaths per minute), hypotension (systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg).

[c]AST to platelet ratio index score >1.5.

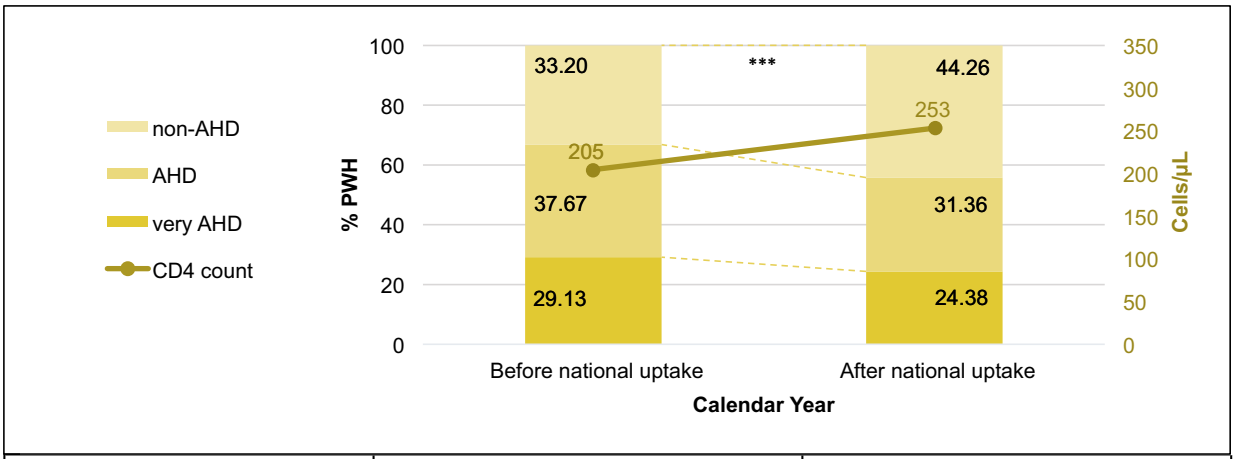
[d]Arterial hypertension: systolic blood pressure measurements ≥140 mm Hg and/or diastolic blood pressure measurements ≥90 mm Hg.

[e]Severe anemia: hemoglobin <8.0 g/dL.

A sensitivity analysis for predictors of documented death and LTFU as separate outcomes is shown in Supplementary Table 5. In addition to the predictors of death/LTFU, death was associated with age <34 years (aHR, 2.73 [95% CI, 1.52–4.88]) and >47 years (aHR, 2.46 [95% CI, 1.33–4.55]), being a current smoker (aHR, 2.60 [95% CI, 1.19–5.65]), and BMI between 18.5 kg/m^2 and 24.9 kg/m^2 (aHR, 1.86 [95% CI, 1.06–3.29] vs BMI <18.5 kg/m^2) (Supplementary Table 5). Outcome LTFU among people with AHD was additionally associated with lack of formal education (aHR, 1.67 [95% CI, 1.09–2.56]) and having no AIDS-related working diagnoses (aHR, 1.49 [95% CI, 1.05–2.12]), while associations with lower CD4 count and liver disease were lost (Supplementary Table 5).

DISCUSSION

Our study characterizes AHD and its outcomes in a cohort of PWH in rural Tanzania between 2013 and 2019. Key findings



	Before national uptake (1 October 2016)	After national uptake (1 October 2016)
Non-AHD - No. (%)	482 (33.2)	463 (44.26)
AHD (excl. CD4 count < 100 cells/µL) - No. (%)	547 (37.67)	328 (31.36)
very AHD - No. (%)	423 (29.13)	255 (24.38)
CD4 cell counts - median (IQR)	205 (79–377)	253 (103–426)

Figure 2. Proportions of people presenting to care with advanced or very advanced human immunodeficiency virus disease (AHD and very AHD, respectively) before and after uptake of World Health Organization test and treat guidelines (1 October 2016). Displayed CD4 counts were obtained at baseline visits. Patients enrolled in Kilombero Ulanga Antiretroviral Cohort until 16 August 2019. ***Significant change of proportions of AHD, very AHD, and CD4 cell counts after national uptake of test and treat guidelines; $P = .000$. Abbreviations: AHD, advanced human immunodeficiency virus disease; IQR, interquartile range; PWH, people with human immunodeficiency virus.

are (1) a high burden of AHD; (2) a decrease in the proportion of PWH presenting with AHD after the implementation of the test and treat guidelines; (3) a high contribution of AHD to mortality and LTFU; (4) identification of risk factors associated with AHD, and predictors of death/LTFU among people with AHD including readily available clinical and laboratory characteristics in rural SSA.

We found a high burden of AHD of 62%. Among people with CD4 cell counts <200 cells/µL, 72% had WHO clinical stage 3 or 4, highlighting the deviance between often inaccurate clinical staging [26] and CD4 cell counting, a more objective indicator of disease progression and risk for OIs [27]. Forty-six percent of PWH had CD4 counts <200 cells/µL at baseline, which is higher than the estimated proportion globally [28] and findings from other studies in SSA [29, 30]. However, some studies in SSA show even higher proportions of AHD at diagnosis, up to 71% in Ethiopia [31, 32].

The decrease in proportions of AHD and increase in CD4 cell counts observed after 2016 was likely attributable to the national adoption of the WHO test and treat guidelines. Additionally, national promotion of provider-initiated testing and counseling (PITC) from 2017 onward [33] may have facilitated the progression to earlier diagnosis. Conclusions on absolute numbers of people diagnosed with AHD affected by the test and treat guidelines are limited since PWH with AHD without informed consent are not captured and the time periods before and after uptake are of different length. Remarkably, despite an increase of the median CD4 count to 253 cells/µL in 2018 and 2019, it remained below the threshold of late presentation—350 cells/µL—throughout the study. Other studies in SSA confirm our findings: in rural Mozambique an increase by 68 cells/µL was observed after adoption of test and treat guidelines [34]. Interestingly, a study in Eswatini showed that despite an increase of the median CD4 cell count by 37 cells/µL retention in care remained similar under treat-all versus previous standard of care [35], which implies that HIV care goes beyond ART and should integrate early diagnosis, prophylaxis, and treatment of OIs as well as intensified adherence support.

One in 5 patients who enrolled into care with AHD experienced death or LTFU within 6 months. Similarly high proportions were described in studies from previous years in urban and semi-urban settings in health facilities in Ethiopia, Kenya, Mozambique, Tanzania, and Zimbabwe [13, 36]. Improved linkage to care and targeted adherence support are needed in order to reduce the persistently high proportion of unfavorable outcomes.

Six-month mortality was high among people with AHD and most deaths occurred within the first month of enrollment. In another study of the KIULARCO cohort, approximately half of deaths among PWH were attributable to infectious diseases, with tuberculosis accounting for 25% of reported death causes [37]. A recent postmortem study conducted in Brazil

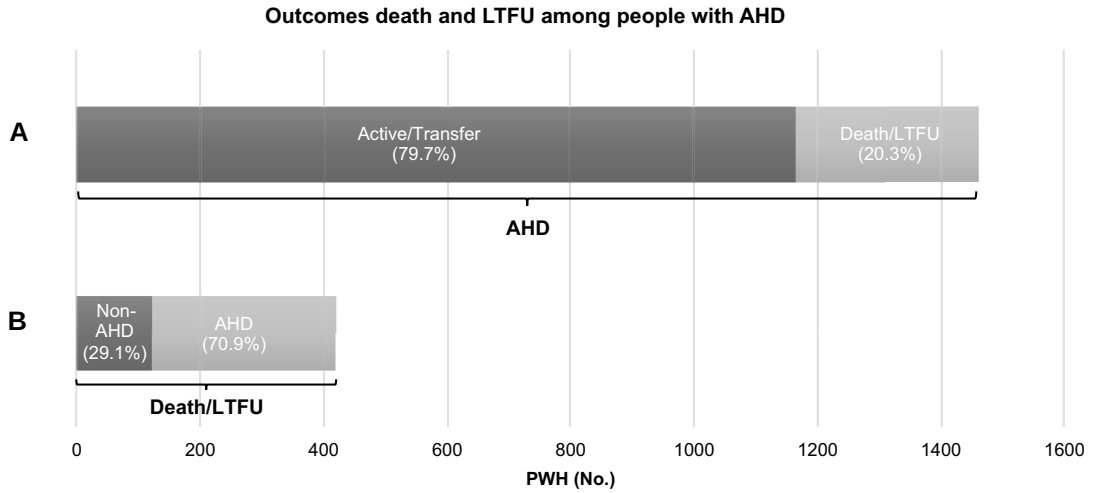


Figure 3. Contribution of advanced human immunodeficiency virus (HIV) disease (AHD) to death and loss to follow-up (LTFU). People with HIV (PWH) enrolled between January 2013 and December 2018. *A*, Six-month death and LTFU among people with AHD. *B*, Proportion of AHD among people with 6-month outcome death or LTFU. Outcomes after 6 months: "Active" indicates under active follow-up; "Transfer" indicates transferred to other clinics.

and Mozambique highlights that 40% of deaths due to infectious diseases could have been prevented through the implementation of the 2017 WHO package of care interventions for AHD [38]. The worldwide uptake of these guidelines was low in 2019 [39] and, despite efforts of governments to adopt them nationally, comprehensive implementation on health facility level is critical and remains a challenge in resource-limited settings in SSA including Tanzania. The delivery of the 2017 package of care interventions could significantly reduce mortality among PWH through isoniazid preventive therapy against tuberculosis, cryptococcal antigen lateral flow assays plus preemptive treatment against cryptococcosis, and cotrimoxazole against *Pneumocystis* pneumonia and toxoplasmosis [1].

Factors independently associated with AHD at presentation to care were older age, male sex, elevated AST levels, severe anemia, impaired functional status, lower BMI, tachycardia, and kidney disease. People with AHD were diagnosed when they were already very sick, as seen in other studies in SSA [31,40–42]. We found a strong association with severe anemia, consistent with results from a study in urban Tanzania [43], and identified tachycardia—which importantly is one of the danger signs used by the WHO to define a seriously ill person and criterion for screening and prophylaxis of OIs in the WHO guidelines for managing AHD [1].

Reduced odds of AHD after 2017 possibly resulted from an intensification of PITC [33]. However, to advance the decline of AHD and morbidity among PWH in resource-limited settings, it is imperative to further promote universal HIV testing and counseling as well as prompt linkage to care, especially among older men who were found at high risk of AHD previously [28, 29, 31–33].

Among people diagnosed with AHD, lower CD4 count, WHO clinical stage, low hemoglobin levels, liver disease, impaired functional status, and tachypnea were independent predictors of death and LTFU. CD4 counts <100 cells/μL and WHO clinical stages 3 and 4 at clinical presentation have been described as predictors of AIDS-related morbidity and mortality in studies across SSA [3, 13, 36, 44]. Lower hemoglobin levels frequently originating from severe OIs [45] have been associated with higher mortality previously [3, 46]. We further identified liver disease, possibly indicating OIs, and tachypnea associated with death/LTFU. The latter is easily assessed at the outpatient setting, suggestive of severe pulmonary disease, and one of the danger signs included by the WHO as a criterion for screening and prophylaxis of OIs among people with AHD [1]. Sensitivity analyses showed similar associations for outcomes death and LTFU alone. Death was additionally associated with being older and smoking, a well-known risk factor of AIDS-defining illnesses [47]. The outcome LTFU included an association with lack of education. While CD4 counts were not associated with LTFU, people LTFU were more likely to have no AIDS-related diagnoses. People with AIDS-related diagnoses are expected to receive closer follow-up during treatment of OIs and thus are less likely to be LTFU.

Reasons for higher hazards of death/LTFU at enrollment into care from 2015 onward possibly include different factors making clinic attendance difficult for patients, such as stigmatization and transport costs. We excluded patients who were transferred to other clinics to avoid misclassification as transfer reasons are unknown. A sensitivity analysis, however, did not show noticeable differences in baseline characteristics among the group of transferred patients (Supplementary Table 6).

Our study had limitations: HIV viral loads, which could have added important information to our analysis, were not included. However, viral load testing is not yet widely available in SSA and

many rural clinics rely on CD4 counting and clinical criteria, as reflected in our study. The proportion of AHD is possibly underestimated since a high proportion of PWH enrolled into care did not provide written informed consent, some of them incapable to sign it due to severe illness, and were therefore not included in our analysis. Since data collection stopped in 2019, our study does not capture the impact of the coronavirus disease 2019 (COVID-19) pandemic on the proportions of AHD. However, the latest UNAIDS report implies a step backwards in the global response to the HIV pandemic [48]. Further analyses are needed to assess the impact of COVID-19 on our cohort.

This study comprehensively describes the burden, characteristics, and outcomes of AHD in rural Tanzania and is representative for resource-limited settings in SSA. The magnitude of information collected in this cohort allowed us to thoroughly characterize people diagnosed with AHD in regard to clinical and laboratory parameters. Further elaboration on the identified predictors of death/LTFU harbors the potential to guide clinical decision making in resource-limited settings in order to reduce morbidity and mortality among people at risk of death and LTFU.

CONCLUSIONS

In our cohort, two-thirds of people presented to care with AHD, of which almost half were very severely immunosuppressed. Despite increasing CD4 counts over time, at the end of the study still half of PWH were diagnosed with AHD.

The distressingly high burden of AHD in this rural Tanzanian cohort, which remained high despite the treat-all guidelines, is representative for resource-limited settings throughout SSA. Addressing AHD from a public health approach through providing access to the right diagnostic tools and treatment regimens and implementation of differentiated care interventions such as the existing WHO guidelines for AHD could significantly reduce the still unacceptably high AIDS-related morbidity and mortality and pave the way to end AIDS by 2030.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. L., L. S., T. K., H. M., A. K., and M. W. designed the study. L. S. and E. L., with data management support from A. V. K., performed the statistical analyses. A. K., H. M., A. V. K., L. E., E. L., and M. W. contributed to data collection at the clinic. L. S. wrote the first draft, which was critically revised by E. L., M. W., M. B., T. K., A. V. K., A. K., and H. M.. All authors contributed to and approved the final version of the manuscript.

Acknowledgments. We are thankful to all the participants of the KIULARCO cohort. We thank the staff of the Chronic Diseases Clinic of St Francis Referral Hospital in Ifakara for making this study possible.

Patient consent. Written informed consent of patients willing to participate in KIULARCO were obtained at registration. Yearly ethical approval for data and sample collection as well as analysis were sought from the Ifakara Health Institute institutional review board (IHI/IRB/No16-2006) and the Health Review Committee of the National Institute for Medical Research of Tanzania (NIMR/HQ/R.8a/Vol.IX/620).

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Financial support. This work was supported by the Ministry of Health and Social Welfare of the Government of Tanzania; the Government of the Canton of Basel, Switzerland; the Swiss Tropical and Public Health Institute, Basel, Switzerland; Ifakara Health Institute, Tanzania; the University Hospital Basel, Basel, Switzerland; and United States Agency for International Development (USAID) Boresha Afya (service and drug support with funding through the USAID from the President's Emergency Plan for AIDS Relief). A. V. K. was supported by the Consortium for Advanced Research Training in Africa (CARTA). CARTA is jointly led by the African Population and Health Research Center and the University of the Witwatersrand and funded by the Carnegie Corporation of New York (grant number G-19-57145), Sida (grant number 54100113), Uppsala Monitoring Center, Norwegian Agency for Development Cooperation (Norad), Wellcome Trust (reference number 107768/Z/15/Z), and the UK Foreign, Commonwealth and Development Office, with support from the Developing Excellence in Leadership, Training and Science in Africa (DELTAS Africa) program.

Potential conflicts of interest. Since May 2021, E. L. has been a full-time employee at ViiV Healthcare. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

APPENDIX

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