

ORIGINAL RESEARCH OPEN ACCESS

Prevalence, Predictors, and Outcomes of HIV Care in HIV-Positive Clients Entering HIV Care With Advanced HIV Disease in Sub-Saharan Africa 2010–2022: Systematic Review and Meta-Analysis

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Received: 7 November 2023 | **Revised:** 21 November 2024 | **Accepted:** 28 November 2024

Funding: The authors received no specific funding for this work.

Keywords: advanced HIV Disease | HIV testing | mortality | opportunistic infections | people living with HIV | prevalence

ABSTRACT

Background and Aims: Sub-Saharan Africa drives global HIV-related mortality, and patients continuously present with advanced HIV disease (AHD) at diagnosis. We describe prevalence, predictors, and treatment outcomes in HIV clients with AHD.

Methods: We systematically reviewed PUBMED, SCOPUS, Web of Science, JSTOR, and CINAHL for relevant studies conducted in Sub-Saharan Africa from 2010 to 2022. We used a narrative synthesis to describe included studies and a random effect meta-analysis to determine AHD pooled prevalence. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guided the reporting, while the Joanna Briggs Institute's quality assessment checklist assessed the quality of included articles. Cochrane's Q and the I^2 tests assessed heterogeneity between included studies.

Results: We included 24 studies with a sample size of 322,676. Prevalence of AHD ranged from 11.0% to 89.7% with an overall pooled prevalence of 58.7% (95% CI: 51.3%, 66.0%): 66.1% (95% CI: 58.8%, 73.4%) between 2010 and 2016, and 51.2% (95% CI: 37.7%, 64.6%) from 2017 to 2022. Predictors of AHD include male sex, older age (≥ 35), widowed or divorced, unemployment, gap in care of ≥ 12 months before antiretroviral therapy (ART) initiation, no history of HIV testing, and seeking care from a traditional healer before presenting for HIV care. Loss to follow-up ranged from 6.7%–58.3%, while the proportion of death ranged from 1.8%–13.1%. Predictors of death were being male, advanced age (≥ 50 years), advanced clinical stages, late ART initiation, higher mean log viral load, CD4+ cell count < 50 cells/mm³ and severe anaemia.

Conclusions: The high baseline prevalence of AHD suggests the need for targeted, people-centred HIV testing in Sub-Saharan Africa. Country HIV programs should accelerate the implementation of comprehensive HIV services that identify clients at risk of AHD for early enrolment with systems for monitoring the WHO care package for preventing, diagnosing, and treating AHD and associated comorbid conditions.

PROSPERO number: 2022 CRD42022336487.

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1 | Introduction

Sub-Saharan African countries, with nearly two-thirds of the global HIV burden, have made remarkable progress in responding to the HIV pandemic. In 2023, antiretroviral therapy (ART) coverage for the estimated 25.1 million people living with HIV (PLHIV) has reached 78%, while HIV-related mortality and incidence decreased by 57% and 56% respectively, compared to 2010 [1]. Reassuring, five countries in sub-Saharan Africa (SSA) had achieved the Joint United Nations Program on HIV/AIDS (UNAIDS) targets of 95% of all PLHIV identified, of which 95% are on ART and 95% are virally suppressed by 2023 [2].

Despite progress, HIV remains one of the leading causes of death in the region, with over 25% of deaths attributable to HIV in the five highest-burden countries [3]. After the implementation of the 2016 World Health Organization (WHO) “test and treat” guidelines, which advocate for ART initiation regardless of the CD4 cell count, the CD4 count at HIV diagnosis has increased significantly, and the proportion of clients commencing ART with AHD has also declined [4]. Clients presenting with advanced HIV disease (AHD), defined as those with CD4 measurements < 200 cells/ μL , are at higher risk of death, hospital admission and other unfavourable outcomes [5–7]. Despite widespread access to HIV testing and treatment, 20% of newly enrolled patients with a baseline CD4 test present with AHD, with CD4 cell count measurements below 200 cells/ μL [8, 9].

In the context of near-universal treatment coverage, HIV-associated morbidity and mortality increasingly occur among ART-experienced patients interrupting or failing treatment rather than in the relatively smaller pool of ART naive patients [10]. Hence, identifying clients with AHD at HIV diagnosis and ensuring they are managed appropriately is vital to achieving the UNAIDS 2030 targets of ending AIDS as a public health threat [11, 12]. Understanding factors for delay in health-seeking and presentation with advanced HIV or AIDS-defining illness is essential as HIV clients presenting with AHD are severely immune suppressed with opportunistic infections such as disseminated tuberculosis, cryptococcal meningitis, and cancers [13]. With the implementation of “test and start” guidelines, the de-emphasis of a requirement of baseline CD4 testing for treatment initiation has resulted in lower rates of CD4 test coverage, which may impede the effective identification of clients with AHD for effective management [14].

In 2013, the “Reduction of EARly mortaLITY in HIV-infected Adults and Children Starting Antiretroviral Therapy (REALITY)” study showed that among HIV-infected clients with advanced immunosuppression, enhanced antimicrobial prophylaxis combined with ART resulted in reduced rates of death at both 24 and 48 weeks without compromising viral suppression or increasing toxic effects [15]. To this end, WHO recommended a package for AHD to improve survival and treatment outcomes, including Rapid ART initiation, screening and treatment of opportunistic infections, and treatment support [16]. Within the package, clients with CD4 < 100 cells/ μL should also be screened for serum cryptococcal antigen to

identify those who could benefit from preemptive fluconazole treatment before the onset of cryptococcal meningitis.

The prevalence of AHD at ART enrolment over time in most countries declined with greater ART availability. However, by 2015, when the WHO recommended “test and start” guidelines and strategies to facilitate earlier HIV testing and treatment were published, approximately a third of new ART clients still initiated ART late in African countries, including Mozambique, Namibia, Nigeria, Swaziland, Uganda, and Zimbabwe as well as Vietnam, and Haiti [17]. These strategies contributed to the reduction in HIV incidence. Still, due to late presentation to or disengagement from ART, AHD remains common in SSA. Therefore, there is a need to understand the predictors of AHD and design interventions to address the barriers to early and rapid ART initiation.

Reliable data on the prevalence, predictors, and outcomes of care for PLHIV who present with AHD in SSA is limited. This could be attributed to the different contexts in HIV programming across countries and frequent changes in treatment guidelines to accommodate new treatment algorithms. To address this, we aimed to describe the prevalence, predictors, and treatment outcomes in HIV clients with AHD and to identify opportunities for improving care outcomes for clients with AHD in SSA using a systematic literature review of studies from 2010 to 2022.

2 | Methods

2.1 | Database Search, Search Strategy, and Terms

This review and the original protocol were registered with PROSPERO (Registration Number: PROSPERO 2022 CRD4 2022336487) and are reported based on the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. We searched PUBMED, SCOPUS, Web of Science, JSTOR, and CINAHL with a manual internet search for studies conducted in Africa from 2010 to 2022. We searched for studies that described at least one of the following: the prevalence, predictors, or outcome of care for PLHIV enrolling in treatment. We first searched for keywords and MeSH terms from the title of the review in PUBMED, SCOPUS and Web of Science. Next, we searched the databases for articles using the different keywords and MeSH terms identified in the first step. We conducted database searches from September 7 to September 9, 2022, and search terms used for PUBMED include “(“Prevalence” [MeSH Terms] OR “Prevalence” [Text Word] OR “epidemiolog” * [Text Word]) AND (“Health Belief Model” [MeSH Terms] OR “predict” * [Text Word] OR “factor” * [Text Word]) AND (“Treatment Outcome” [MeSH Terms] OR “Outcomes” [Text Word]) AND (“advanced” [Text Word] OR “late present” * [Text Word]) AND (“HIV Infections” [MeSH Terms] OR “HIV disease*” [Text Word]) AND (2010:2022[mdat]). The search terms for other databases are presented in Supporting Information S1: File 1. Finally, we conducted a manual internet search and references of select articles identified from Step 2 above for additional articles for inclusion.

2.2 | Study Selection

Study selection involved title/abstract screening, and full-text reviews were conducted independently by three different reviewers before final inclusion for data extraction. All extracted articles were initially entered into EndNote (Clarivate Analytics, Philadelphia, USA) for deduplication and afterwards uploaded into Rayyan software (<https://www.rayyan.ai/>) for title abstract screening using prespecified eligibility criteria [19]. Rayyan software enables double-blinded independent review of articles (title/abstract and full text) to limit bias in selected articles. Three reviewers (S.A., V.W., T.M.) independently conducted the title/abstract screening and conflicts were resolved by two other reviewers (S.H., S.O.). The full text of articles from the title/abstract screening considered for full-text review was retrieved, uploaded into Rayyan and matched to their respective titles. Two reviewers conducted the full-text review, and a third (A.M.) resolved conflicts. Articles not meeting the inclusion criteria at both stages and those without the full text were excluded from the review. We could not retrieve the full text for three articles, and the corresponding authors have yet to respond to emails requesting the articles.

2.3 | Eligibility Criteria

Articles included in the review were original studies (case-control, cohort studies, cross-sectional studies, and clinical trials) conducted in SSA (African countries south of the Sahara desert) and published from 2010 to 2022. Additional inclusion criteria were: (a) study participants should be aged ≥ 15 years with a positive HIV status regardless of clinical status, (b) studies should specifically indicate participants were enrolled as they were commencing ART or entering care, and (c) studies should have data on baseline CD4 and/or WHO staging or predictors of AHD. We excluded articles conducted outside Africa, those outside the specified study period, other study designs (case reports, letters to the editor, review papers, and opinion papers), and those including pregnant women and children as study participants. Articles that included population-level analysis, regardless of when the included participants commenced ART or entered, were excluded.

2.4 | Data Extraction

A standardised data extraction form was developed in an Excel spreadsheet (Supporting Information S2: File 2). The reviewers validated this extraction form to address all vital information relevant to the review questions. Two reviewers (V.W., T.M.) independently extracted data from the selected articles. Studies selected for data extraction were assigned similar but different codes before extraction to enable comparison at the end of data extraction, e.g., codes 1A and 1B were assigned to the same article by the two reviewers. At the end of data extraction, the two spreadsheets were reviewed, and conflicts were resolved before merging to form the final spreadsheet for analysis.

2.5 | Quality Assessment of Included Studies

Two reviewers (VW and TM) independently conducted the quality assessment of the studies included in this review using

the Joana Briggs Institute's critical appraisal tool for case series [20] (Supporting Information S1: File 3). We used the tool for case series since, in all our included studies, the participants all had the same clinical condition (HIV cases), and the outcomes considered were those related to HIV [21]. The appraisal tool is a 10-item checklist, and articles were graded as good (score of 8–10), fair (score of 5–7) and poor (score of 1–4). Conflicts in assigned scores were resolved by discussion with a third reviewer (AM).

2.6 | Summary Measures and Statistical Analyses

We used a narrative synthesis approach to describe the methodology and quality of included studies. The study population's three outcomes—the prevalence, predictors, and treatment outcomes—were described separately. As the prevalence summarises the proportion of AHD in the study population, we first summarised the prevalence from the individual study. Then, we conducted a meta-analysis to estimate the pooled prevalence from all the studies using the Stata command *metaprop* and the random-effects model. We also assessed pooled prevalence by the African region (West, East, or Southern African Region) the study was conducted in, the year or timeline the study was published divided into two categories (2010–2016 and 2017–2022) and assessed the effect of female sex and study sample size on AHD prevalence. To assess between-study heterogeneity for the pooled prevalence, we estimated I^2 statistics expressed as a percentage and Cochrane's Q statistic ($p < 0.05$) [22]. We assessed the risk of bias across studies using funnel plots and the Eggers test.

For the studies that described the predictors of AHD, we identified and described the different predictors and also used the forest plot to describe adjusted odd ratios of all the predictors of AHD. The risk ratio reported in one study was recomputed to derive the odds ratio for consistency [23]. Subgroup analysis was conducted to describe the predictors based on the participant's age, sex, marital status, and some clinical parameters.

3 | Results

We extracted 967 articles from the different databases and included 626 articles for the title/abstract screening after excluding duplicates (Figure 1). After title/abstract screening, 151 articles met the inclusion criteria for the full-text review, including 16 additional articles identified through a manual internet search. Following the full-text review, 24 articles [17, 23–45] which met the inclusion criteria were selected for synthesis. One hundred and twenty-seven articles were excluded.

3.1 | Description of Included Studies

Table 1 describes the studies included in this review. They were from 16 African countries, including Botswana, which had four studies; South Africa and Mozambique, which had three studies each; Tanzania, Ethiopia, Senegal, and Rwanda, which had two studies each; and Uganda, Malawi, Cote d' Ivoire, Lesotho,

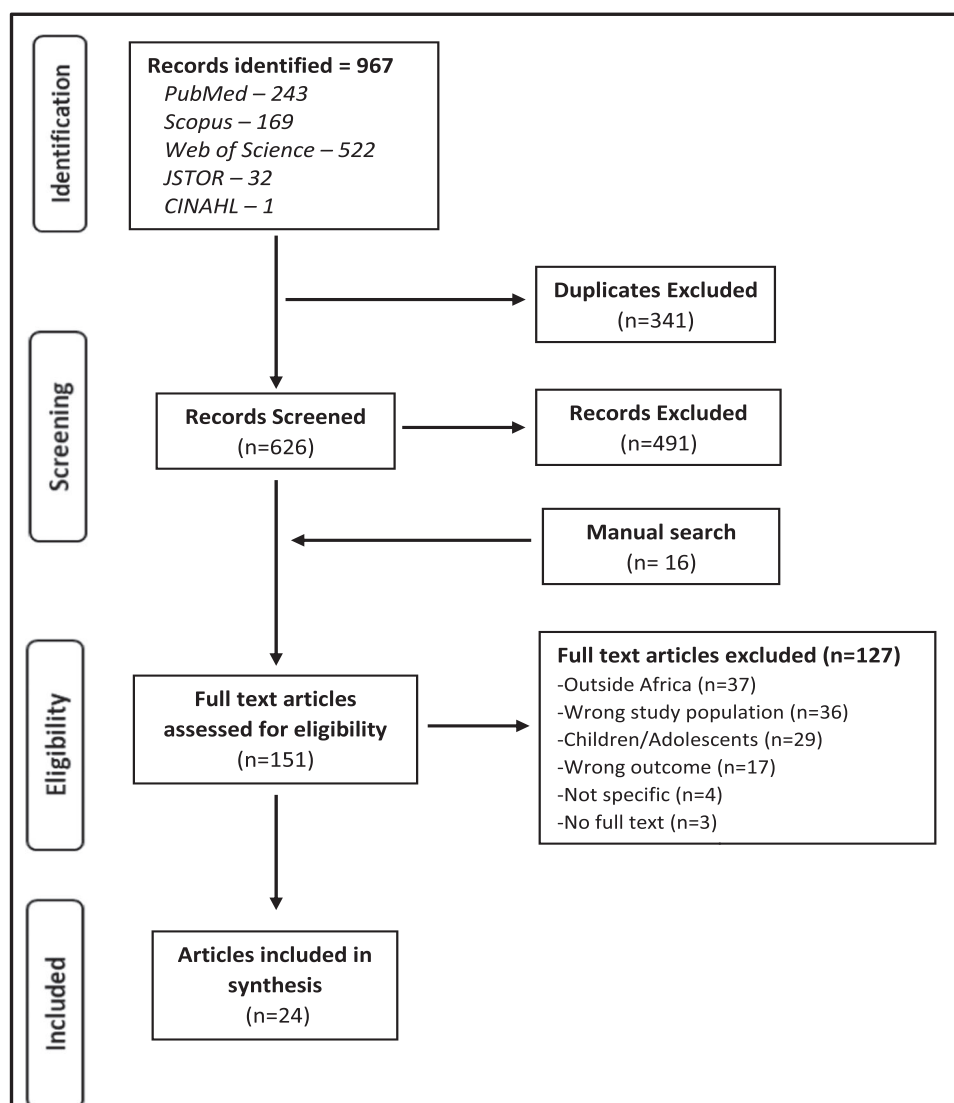


FIGURE 1 | PRISMA flow chart for included studies.

Nigeria, Eswatini, Guinea Bissau, and Cameroon, which each had one study.

The studies aimed at describing characteristics of PLHIV commencing ART, late presentation to care, and treatment outcomes. Two of the studies were multi-country studies conducted in three countries. About half of the included studies used a retrospective cohort design ($N = 11$), with the rest using either a cross-sectional study design ($N = 7$) or a prospective cohort design ($N = 6$). The study population consisted of PLHIV who were newly enrolled on HIV care or were ART naive, mostly aged ≥ 15 years, regardless of sex. One of the studies [27] focused on PLHIV from a rural location. The sample size of included studies ranged from 157 to 90,071 with a combined total sample size of 322,676 PLHIV. Except for one study [39], $\geq 60\%$ of study participants across the different studies were females, and the median age of study participants was 35 years. Most studies included in the review had a satisfactory quality assessment, with 19 studies having a good score across all areas assessed and five studies with a fair score in one or two assessed components. No study had a poor-quality score, and no study was excluded based on the quality assessment. The performance

of each study based on the different assessment parameters is available in Supporting Information S1: File 4.

3.2 | Prevalence of AHD (by Sex, Age)

The prevalence of AHD at baseline in the included studies ranged from 11% to 89.7%. It was primarily determined using the cut-off baseline CD4 count $< 200/\text{mm}^3$ or the presence of WHO stage 3 or 4 diseases at baseline (Table 2). The trend of AHD prevalence declined overall when the studies were ranked by year from 2010 to 2022 (Figure 2). The proportion of participants from the included studies with a baseline CD4 $< 200/\text{mm}^3$ ranged from 17.2% to 88%, while the proportion with WHO Stage 3 or 4 diseases ranged from 11% to 85%; the most common Stage 3 or 4 conditions was tuberculosis.

Presentation with CD4 $< 200/\text{mm}^3$ or WHO Stage 3 or 4 diseases were more common amongst males compared to females [23, 24, 28, 30, 44], and males and other clients with baseline CD4 $< 200/\text{mm}^3$ had higher attrition rates during follow-up [24]. Similarly, clients who presented late with lower baseline

TABLE 1 | Description of studies included in the review.

First Authors Surname, Year, Country	Year patients were seen	Aim of the study	Study design	Study population	Sample size (N)	Female (%)	Age (median/ IQR)
May et al. 2010 [25]; Cote d' Ivoire, South Africa, Malawi	2004–2007	To estimate the probability of death in patients commencing antiretroviral therapy in sub- Saharan Africa.	Cross-sectional	Adults starting ART. ≥ 15 years	11,153	68	34 (29, 41)
Auld et al. 2011 [17]; Mozambique	2004–2007	To investigate mortality rates, attrition (death, loss to follow-up, or treatment cessation), immunologic treatment failure, regimen-switch, and determinants of selected outcomes in patients commencing ART treatment.	Retrospective cohort	Adults initiating ART ≥ 15 years	2596	62	34 (28, 42)
Mills et al. 2011 [26]; Uganda	2004–2010	To determine if men have different treatment outcomes compared to women.	Prospective cohort	Adults initiating ART. ≥ 15 years	22,315	69	
Wandeler et al. 2012 [27]; Zimbabwe, Mozambique, Lesotho	2005–2010	To describe risk factors for no follow-up, LTFU and mortality in patients commencing ART treatment.	Prospective cohort	New patients starting ART. ≥ 15 years. Mainly rural— 90% of farmers	7725	65	38 (32, 46)
Cornell et al. 2012 [28]; South Africa	2002–2009	To examine the magnitude and risk factors for gender differences in mortality for ART clients.	Prospective cohort	ART-naive adults starting ART. ≥ 15 years	46,201	65	35 (30, 42)
Chalamilla et al. 2012 [29]; Tanzania	2004–2008	To describe mortality and immunological outcomes and response to ART treatment, and determine the predictors of mortality in newly enrolled ART clients.	Prospective cohort	New HIV clients starting ART. ≥ 15 years	12,842	66	36 (31–43)
Fatti et al. 2014 [30]; South Africa	2004–2010	To compare baseline features, clinical, virologic and immunologic outcomes of older versus young adults commencing ART.	Retrospective cohort	ART-naive clients starting ART. ≥ 25 years	90,071	66	59 (57, 62) 35 (31, 41)
Aliyu et al. 2014 [31]; Nigeria	2009–2011	To describe the predictors of delayed ART initiation and trends	Retrospective cohort	ART-naive clients starting ART. ≥ 15 years	869	64	34 (28, 40)

(Continues)

TABLE 1 | (Continued)

First Authors Surname, Year, Country	Year patients were seen	Aim of the study	Study design	Study population	Sample size (N)	Female (%)	Age (median/ IQR)
Melaku et al. 2015 [32]; Ethiopia	2006–2011	in mortality and retention in a cohort of patients initiating ART. To describe trends in characteristics and outcomes in adults starting ART treatment and outcomes after enrolment in care and ART initiation.	Retrospective cohort	ART-naive adults starting ART. ≥ 15 years	53,300	59	
Mhozya et al. 2015 [33]; Tanzania	2013	To determine the proportion of HIV patients presenting with WHO clinical stages 3 and 4 diseases and the level of immunity at the time of enrolment.	Cross-sectional	ART-naive adults starting ART. ≥ 15 years	366	64.2	36 (30, 43)
Mutimura et al. 2015 [34]; Rwanda	2003–2012	Describe barriers and enablers to timely ART initiation and compare ART enrolment before and after guideline changes.	Cross-sectional	ART-naive adults starting ART. ≥ 15 years	4486	60	35 (29, 42)
Hønge et al. 2016 [35]; Guinea-Bissau	2004–2014	To describe patients presenting late for ART care and those with AHD, identify risk factors and evaluate patient outcomes at an HIV clinic in Guinea-Bissau.	Retrospective cohort	ART patients newly enrolled into care. ≥ 15 years	3720	67	36 (29, 45)
Naidoo et al. 2017 [36]; South Africa	2004–2013	To describe the users of the current HIV treatment services.	Retrospective cohort	ART-naive adults starting ART. ≥ 15 years	4043	59	32 (28, 36)
Gunda et al. 2017 [37]; Tanzania	2004–2008	To determine the proportion and risk factors of poor immune recovery in adult HIV patients.	Retrospective cohort	ART-naive adults starting ART. ≥ 18 years	734	67	39 (21, 60)
Gessew et al. 2018 [38]; Ethiopia	2003–2015	To determine the prevalence, trends, outcomes, and risk factors for late presentation to HIV care.	Retrospective cohort	HIV-infected adult patients aged ≥ 15 years enrolled in ART care	4900	59.8	30 (15, 81)
Luma et al. 2018 [39]; Cameroon	1996–2014	To describe late presentation for HIV care, associated factors and outcomes of patient follow-up.	Retrospective cohort	Adults newly enrolled in ART care. ≥ 18 years	1886	45	Mean 40 (10)
Benzekri et al [†] ; 2019 [40]; Senegal	2017–2018	To determine the frequency and predictors of traditional healer	Prospective study	Adults living with HIV commencing treatment.	157	70	37 (30, 45)

(Continues)

TABLE 1 | (Continued)

First Authors Surname, Year, Country	Year patients were seen	Aim of the study	Study design	Study population	Sample size (N)	Female (%)	Age (median/ IQR)
Lifson et al. 2019 [23]; Botswana	2015–2017	use, and to determine if traditional healer use is associated with HIV outcomes among people living with HIV. To describe baseline clinical characteristics of adults presenting late to HIV care with advanced HIV disease.	Cross-sectional	Adults newly enrolled in care. ≥ 18 years	1799	59	34
Mupfumi et al. 2019 [41]; Botswana	2011–2015	To determine the incidence of TB in the national database of HIV clients receiving care	Retrospective cohort	Adults newly enrolled in care. ≥ 18 years	45,729	65	37 (31, 45)
Benzekri et al. ² ; 2019 [42]; Senegal	2017–2018	To determine the prevalence and predictors of advanced disease among individuals initiating ART and to evaluate adherence to the WHO guidelines for managing advanced HIV disease.	Cross-sectional	People living with HIV (PLHIV). ≥ 18 years (Included 6 participants < 18)	198	70	35
Lebelonyane et al. 2020 [24]; Botswana	2018	To determine the proportion of HIV-positive individuals presenting for HIV care with AHD, describe factors associated with AHD, and assess clinical outcomes using baseline CD4 count.	Cross-sectional	Clients newly linked to ART 16–64-year-old, new and old HIV+ cases not on ART	2499	62.9	36 (29, 44)
Kerschberger et al. 2020 [43]; Eswatini	2014–2016	To assess different associations with treatment outcomes under Treat-All and the concurrent national standard of care (SOC) at the time and to compare programmatic outcomes between the two interventions.	Prospective cohort	HIV-positive patients initiated on 1st line ART. ≥ 16-year-old	3170	71.3	31 (25, 38)

(Continues)

TABLE 1 | (Continued)

First Authors Surname, Year, Country	Year patients were seen	Aim of the study	Study design	Study population	Sample size (N)	Female (%)	Age (median/IQR)
Magro et al. 2021 [44]; Mozambique	2017	To describe factors associated with early loss to follow-up, retention in care and ART adherence during the first year of follow-up.	Cross-sectional	New ART patients starting treatment. ≥ 14 years	960	73	36 (28, 75)
Musengimana et al. 2022 [45]; Rwanda	2016–2018	To determine the prevalence of AHD in patients presenting for care and compare clinical outcomes between patients.	Retrospective cohort	Patients newly enrolled in care aged ≥ 15 years	957	66	

Abbreviation: ART, antiretroviral therapy.

CD4 $< 200/\text{mm}^3$ had a lower median CD4 at 12 months than those who presented early [39].

3.2.1 | Pooled Prevalence of ADH

The pooled summary of AHD prevalence from the different studies is presented in Figure 3. The prevalence ranged from 10.9% (95% CI: 8.5%, 13.9%) to 89.7% (95% CI: 88.0%, 91.3%), with an overall pooled prevalence of 58.7% (95% CI: 51.3%, 66.0%). The estimated I^2 was 99.95%, $p < 0.01$. A pooled prevalence of studies by major African regions (West, East and Southern Africa) was estimated and is described in Figure 4a. The pooled prevalence was 57.8% (95% CI: 45.4%, 70.2%), 54.4% (95% CI: 44.5%, 64.2%) and 68.2% (95% CI: 46.9%, 89.5%) in the Southern, East and West African region respectively. When assessed by timeline (Figure 4b), for the period 2010–2016, the pooled prevalence was 66.1% (95% CI: 58.8%, 73.4%) and 51.2% (95% CI: 37.7%, 64.6%) from 2017 to 2022. The heterogeneity test for between-study effect showed the different studies were heterogenous (Q statistic = 15.55; $p < 0.01$), while between-group differences indicated the pooled prevalence by region and timeline was homogenous (Q statistic = 1.36; $p = 0.507$ and Q statistic = 3.67; $p = 0.06$, respectively). An assessment of the effect of the female sex on AHD prevalence showed a negative correlation. Still, it was not statistically significant ($p = 0.2850$), while the study sample size had a positive correlation with AHD prevalence, though it was not also statistically significant ($p = 0.287$) (Supporting Information S1: File 5a and 5b). A visual assessment of the funnel plot for small study effects showed well-dispersed estimates without any clear aggregation area around the pooled estimate (Figure 5). An evaluation of the funnel plot with the Eggers test showed no evidence of a small study effect, $p = 0.51$.

3.3 | Predictors of AHD

Of the 24 studies included in this review, eight provided information on the predictors of AHD [23, 24, 34, 35, 38–40, 45] (Table 3). Overall, the male sex compared to females [23, 24, 34, 35]; older age (≥ 35 years) compared to younger age [23, 24, 35, 38, 40]; single, widowed, or divorced compared to living with a partner [24, 35]; unemployment [23]; gap in care of ≥ 12 months before ART initiation [34]; TB co-infection [38]; no history of HIV testing, mobile HIV testing and a new HIV diagnosis [24, 38]; and seeking care from a traditional healer before presenting to HIV care [42] had increased odds for AHD while having a partner and living with a partner [34, 39]; younger adults and being a student [23, 38] and PMTCT/Blood donation [39] had reduced odds for AHD. Seven studies with effect measures (adjusted odd ratio) are summarised in a forest plot (Figure 6). A complete meta-analysis was not feasible as few studies showed a small study effect characterised by an asymmetrical funnel plot and significant Eggers test (Supporting Information S1: File 6).

3.4 | Treatment Outcomes

3.4.1 | Retention in Care and Viral Load Suppression

The presentation of findings on final treatment outcomes for all clients in the different articles varied (Table 4). Nine studies

TABLE 2 | Prevalence of AHD in included studies.

First authors surname, year, country	Number with CD4	Number with CD4 < 200	% CD4 < 200	% WHO Stage 3/4	Stage 3/4 defining disease	Duration of follow-up (months)	AHD Prevalence
May et al. 2010 [25]; Cote d' Ivoire, South Africa, Malawi	11,153	9471	84.9%	85.0%	Severe anaemia 37%	12	85%
Auld et al. 2011 [17]; Mozambique	2596	1500	57.8%	53.0%	TB 11%	Median 1.3 years (0.7, 2.2)	57%
Mills et al. 2011 [26]; Uganda	18,498	9804	53.0%	42.0%	TB 5%	Median months 32 (20, 47)	53%
Wandeler et al. 2012 [27]; Zimbabwe, Mozambique, Lesotho	—	—	—	70.4%	—	36	70.4%
Cornell et al. 2012 [28]; South Africa	39,990	35,191	88.0%	79.0%	—	36	88.0%
Chalamilla et al. 2012 [29]; Tanzania	8655	6855	78.9%	79.2%	TB 13.4%	36	79.2%
Fatti et al. 2014 [30]; South Africa	90,071	63,410	70.0%	47.0%	—	60	70.0%
Aliyu et al. 2014 [31]; Nigeria	790	529	61.0%	67.0%	—	—	67.0%
Melaku et al. 2015 [32]; Ethiopia	44,132	28,686	59.0%	65.0%	—	36	65.0%
Mhozya et al. 2015 [33]; Tanzania	243	153	41.8%	62.6%	—	—	63.0%
Mutimura et al. 2015 [34]; Rwanda	4486	158	21.0%	27.0%	—	—	46.0%
Hønge et al. 2016 [35]; Guinea-Bissau	3720	1810	49.0%	—	—	120	48.0%
Naidoo et al. 2017 [36]; South Africa	4043	2978	74.0%	11.0%	TB 4%	72	74.0%
Gunda et al. 2017 [37]; Tanzania	723	545	75.4%	57.4%	—	48	75.4%
Gesese et al. 2018 [38]; Ethiopia	4900	3607	73.6%	54.3%	TB 28%	49	36.5%
Luma et al. 2018 [39]; Cameroon	1324	1188	63.7%	58.2%	TB 21%	—	89.7%
Benzekri et al.; 2019 [40]; Senegal	128	83	52.8%	65.0%	—	12	65.0%
Lifson et al. 2019 [23]; Botswana	1559	554	39.0%	41.0%	—	—	60.0%
Mupfumi et al. 2019 [41]; Botswana	20,509	7166	35.0%	—	TB 2%	20 (6, 37)	35.0%
Benzekri et al. 2019 [42]; Senegal	144	102	55.0%	53.0%	—	—	71.0%
Lebelonyane et al. 2020 [24]; Botswana	2499	430	17.2%	—	—	12	17.2%

(Continues)

TABLE 2 | (Continued)

First authors surname, year, country	Number with CD4	Number with CD4 < 200	% CD4 < 200	% WHO Stage 3/4	Stage 3/4 defining disease	Duration of follow-up (months)	AHD Prevalence
Kerschberger et al. 2020 [43]; Eswatini	2782	943	29.7%	13.8%	TB 7%	36	33.9%
Magro et al. 2021 [44]; Mozambique	893	416	46.6%	14.8%	—	—	46.6%
Musengimana et al. 2022 [45]; Rwanda	555	61	58.0%	—	—	18	11.0%

provided information on the proportion of clients still in care (retention) at the end of the follow-up period or the termination of the study. Retention in care ranged from 23% for a study conducted in Guinea-Bissau [35] to 97% for a study conducted in Botswana [24]. Besides a South African study with a retention of 92% [36], the reported retention in the other studies ranged between 65%–80% [17, 27, 28, 32, 38]. Six studies had data on viral load suppression, with the highest suppression of 94% each for studies conducted in Botswana and South Africa [36, 41], followed by 87% for another study conducted in Botswana [24]. The other reported viral load suppression rates ranged from 68% to 85% [30, 31, 45]. Three studies reported treatment failure of 2.2%, 18.7%, and 19.7%, respectively [17, 43, 45].

3.4.2 | Loss to Follow-Up, Transfer Out and Death

Twelve studies reported the loss to follow-up (LTFU) rate. The lowest was 6.7% from a Ugandan study [26], while the highest was 58.3% from a study conducted in Guinea-Bissau [35]. Three studies had an LTFU rate of <10% [25, 26, 28] and 10%–20% [30, 36, 45], while five studies had an LTFU rate of 20%–30% [17, 27, 31, 32, 43]. Males, compared to females, weight < 45 kg, WHO stage IV, lower median CD4 count, late ART initiation and lower levels of education increased the likelihood of LTFU while pregnancy and breastfeeding and older adults were less likely to be LTFU [15, 23, 25, 27, 41].

Four studies reported the proportion of clients transferred out to be 3.1%, 4.8%, 5%, and 10.4%, respectively [25, 28, 35, 43]. Sixteen studies reported death outcomes for their clients. The lowest occurrence of death was from a study conducted in Eswatini at 1.8% [43], while the highest was 13.1% from a study conducted in Tanzania [29]. Overall, five studies recorded death rates below 5% [24, 31, 38, 43, 45]; eight studies had death rates of 5%–10% [17, 25–28, 30, 32, 35], while three studies had death rates $\geq 10\%$ [29, 36, 39].

Death as an outcome was associated with the males compared to females, advanced age (≥ 50 years), advanced clinical stages (WHO clinical Stages 3–4), late ART initiation, higher mean log viral load, CD4+ cell count < 50 cells/mm³, and severe anaemia with haemoglobin < 8.5 g/dL [17, 25, 27–29, 36, 45]. During follow-up, two studies reported survival in males was lower than in females [26, 36], and most deaths occurred within the first 3 months of initiating treatment [26, 35, 36].

3.4.3 | Opportunistic Infections (OI) and Who Stages III/IV Conditions

Eleven studies reported the occurrence of opportunistic infections (OIs), and the commonest was tuberculosis (2%–28%), followed by severe anaemia at 37% [17, 25, 26, 29, 36, 38–43]. Opportunistic infections were more likely to occur in males and those with lower CD4 and higher viral loads at baseline than in females and those with a higher CD4 and lower baseline viral load [26, 38, 39, 41]. Other reported OIs include bacterial pneumonia, herpes zoster, skin Kaposi sarcoma, candidiasis,

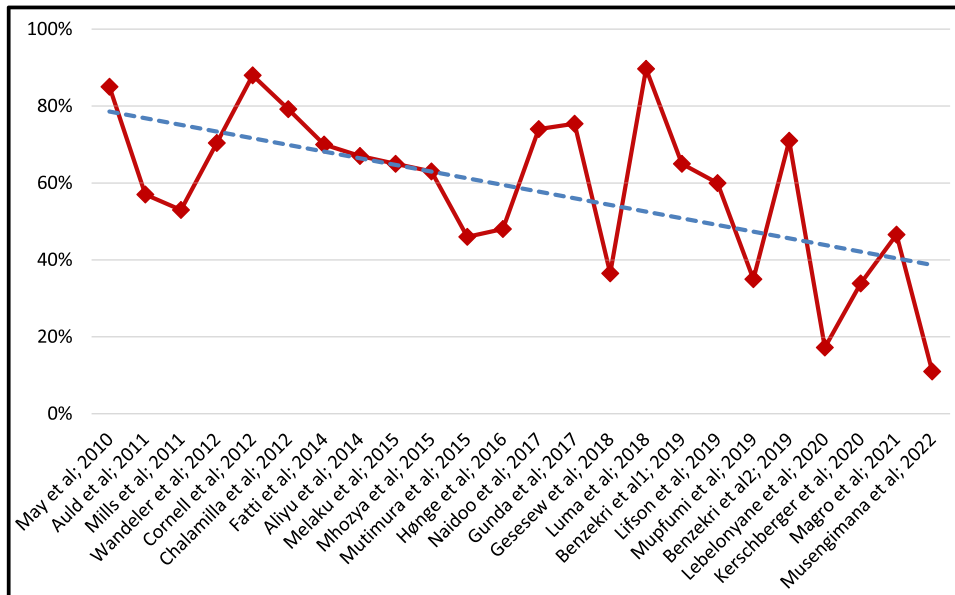


FIGURE 2 | Prevalence of AHD ranked by year of study publication (2010 to 2022).

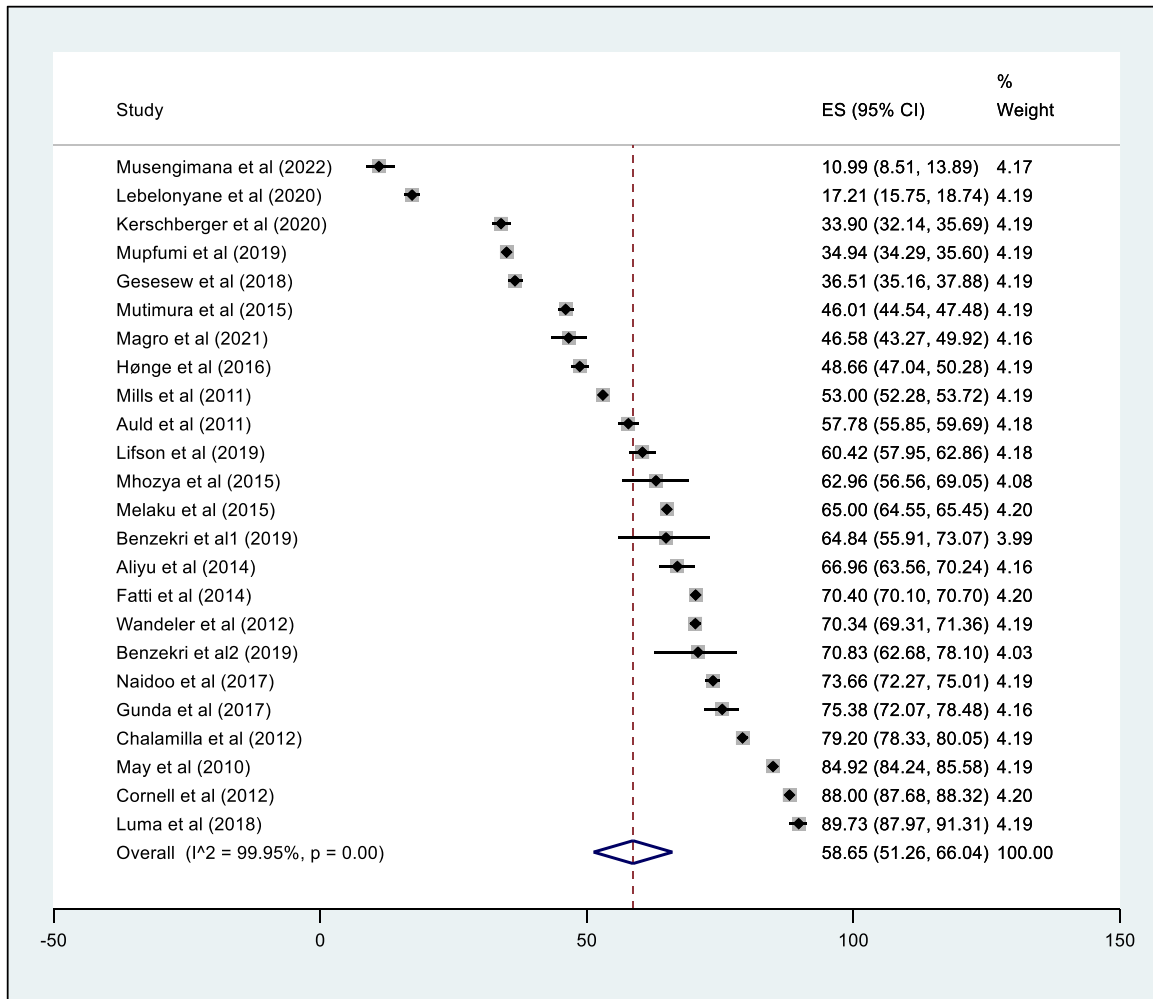


FIGURE 3 | Forest plot showing the pooled summary of AHD Prevalence.

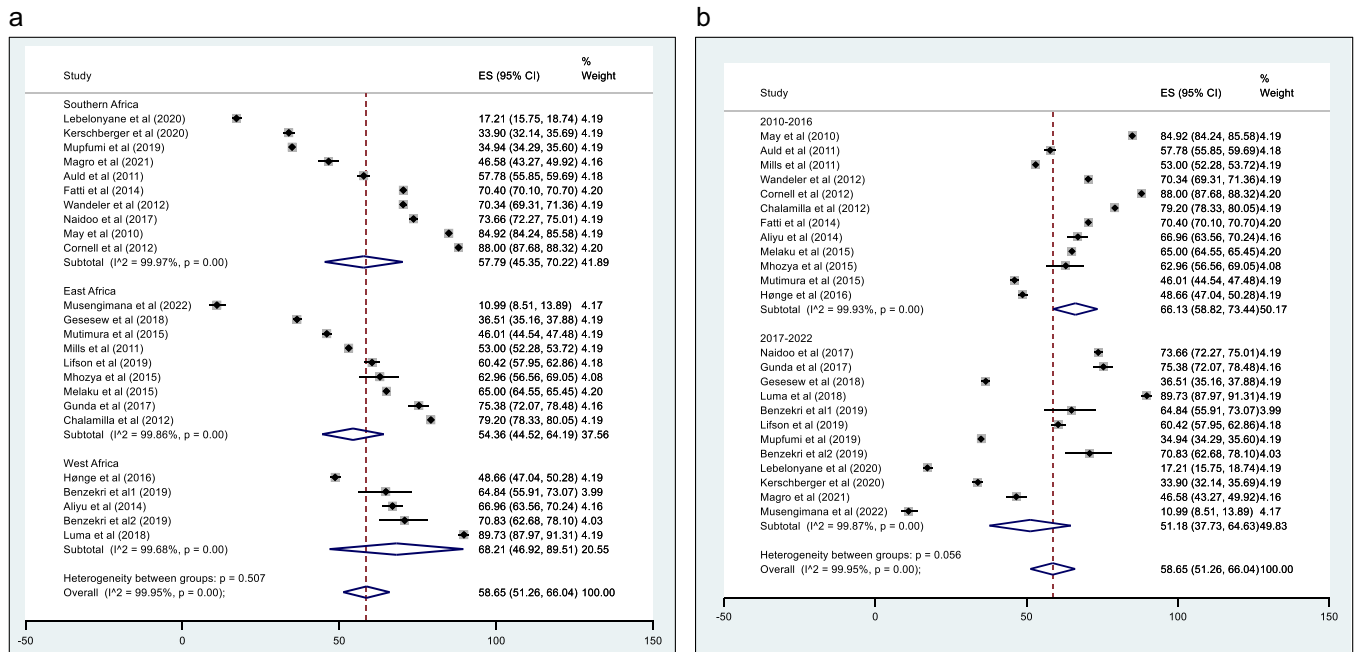


FIGURE 4 | a: Pooled prevalence of AHD by African region (Southern, East and West Africa) b: Pooled prevalence of AHD by Timeline (2010–2016 and 2017–2022).

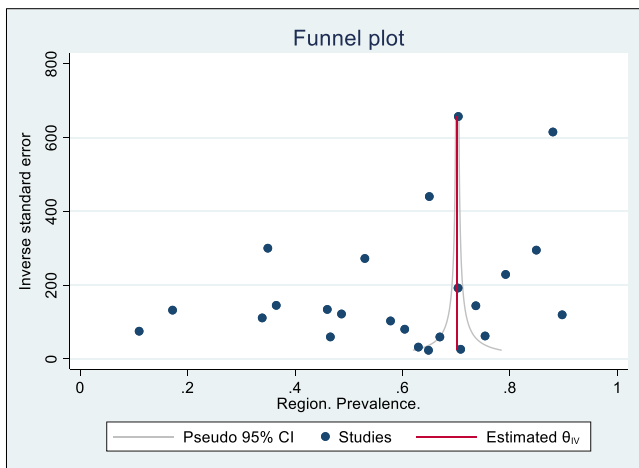


FIGURE 5 | Funnel plot to assess for small study effects (Eggers test: $p = 0.510$).

cryptococcal meningoencephalitis, cerebral toxoplasmosis, tuberculous meningitis, HIV encephalitis, pulmonary aspergillosis, pulmonary Kaposi sarcoma, microsporidia, and cryptosporidiosis. The OIs were more common in clients who presented with $CD4 < 200/mm^3$ than those with $CD4 > 200/mm^3$ at 3, 6, and 12 months. In addition to these OIs, other reported clinical symptoms included weight loss, chronic fatigue, chronic fevers, chronic pain, chronic cough, and chronic diarrhoea. Males were more likely to report these symptoms than females ($p = 0.008$) [23, 40].

4 | Discussion

We aimed to describe the prevalence, predictors, and treatment outcomes in HIV clients with AHD and to identify

opportunities for improving care outcomes for clients with AHD in SSA in the era of accessible case identification services, immediate ART for all, and enhanced guidelines for managing AHD. We included 24 articles from 16 SSA countries in the final review. The prevalence of AHD from the studies ranged from 10.9% (95% CI: 8.5%, 13.9%) to 89.7% (95% CI: 88.0%, 91.3%) and the overall pooled prevalence was 58.7% (95% CI: 51.3%, 66.0%). The pooled prevalence in Southern, East and West African regions was 57.8% (95% CI: 45.4%, 70.2%), 54.4% (95% CI: 44.5%, 64.2%) and 68.2% (95% CI: 46.9%, 89.5%) respectively. Based on the timeline, the pooled prevalence was 66.1% (95% CI: 58.8, 73.4) for the years 2010–2016, decreasing to 51.2% (95% CI: 37.7%, 64.6%) for the years 2017–2022.

The male sex compared to females; older age compared to younger age; single, widowed or divorced; Unemployment; gap in care of ≥ 12 months before ART initiation; TB co-infection; no history of HIV testing; mobile HIV testing; a new HIV diagnosis; and seeking care from a traditional healer before presenting to HIV care were identified as positive predictors of AHD at presentation while having a partner and being a young adult reduced the odds of AHD. The proportion of clients retained in care varied from 23% to 97%, while six studies reported a 68%–94% viral load suppression rate. The LTFU rate ranged from 6.7% to 58.3%, with significant predictive factors being male sex, presenting with WHO stage IV disease and a lower level of education. Death in the study sample population varied from 1.8% to 13.1% and was associated with male sex, advanced age at presentation, WHO stage III-IV, high viral load and severe anaemia. Opportunistic infections were more likely to occur in males with lower baseline CD4 count and high viral load, the most common being tuberculosis.

The pooled prevalence of AHD reported in this review (58.7%) indicates approximately one in two new clients present with

TABLE 3 | Predictors of AHD from the different studies.

First authors surname, year, country	Predictor 1 (OR/RR/HR with 95% CI)	Predictor 2 (OR/RR/HR with 95% CI)	Predictor 3 (OR/RR/HR with 95% CI)
Mutimura et al. 2015 [34]; Rwanda	Male sex (aOR = 1.66, 95% CI: 1.34–2.05). Living with a partner versus married=0.75, 95% CI: 0.58–0.98 Unknown eligibility versus eligible for ART aOR = 0.16, 95% CI: 0.04–0.63.	Older age: (aOR 36–45 vs. < 25 = 1.68, 95% CI: 1.11–2.56, and aOR 46–55 vs. < 25 = 2.26, 95% CI: 1.20–4.30)	Gap in care of 12 or more months before ART initiation (aOR = 5.23, 95% CI: 1.23–21.13).
Hønge et al. 2016 [35]; Guinea-Bissau	Male gender (aOR 1.49), single versus married (aOR 1.30),	age 30–49 years (aOR 1.66), age = 50 years (aOR 1.48),	Fula ethnicity (aOR 1.47) Mandinga ethnicity (aOR 2.04).
Gesese et al. 2018 [38]; Ethiopia	Older adults aged between 25–< 50 years (aOR = 0.4, 95% CI: 0.3–0.6) and 50+ years (aOR = 0.4, 95% CI: 0.2–0.6	Females were 20% high likely (aOR = 1.2, 95% CI: 1.03–1.5) to present late for HIV care than their comparator. TB/HIV co-infection (aOR = 1.6, 95% CI: 1.09–2.1	No previous history of HIV testing (aOR = 1.2, 95% CI: 1.1–1.4) was a risk factor for LP HIV care enrolment period in 2012 and after (aOR = 0.8, 95% CI: 0.7–0.9) was a protective factor for LP
Luma et al. 2018 [39]; Cameroon	PMTCT/blood donation (OR = 0.16, 95% CI 0.10–0.29), Having a positive partner (OR = 0.16, 95% CI = 0.10–0.26), and routine screening (OR = 0.13, 95% CI = 0.10–0.19) reduced the odds of presenting late compared to clinical suspicion.	Students (Unemployed) had lower odds of presenting late compared to people who had employment (OR = 0.50, 95% CI = 0.26–0.98).	Calendar time OR = 1.64, 95% CI = 1.08–2.48 for ≥ 2010 versus < 2005) increased the odds of late presentation.
Lifson et al. 2019 [23]; Botswana	Males were associated with advanced HIV disease (adjusted RR = 1.20, 95% CI, 1.10–1.31, <i>p</i> < 0.001)	Unemployment (adjusted RR = 1.28, 95% CI, 1.15–1.42, <i>p</i> < 0.001)	≤ 25 years of age were less likely to have advanced HIV disease (adjusted RR = 0.83, 95% CI, 0.74–0.94, <i>p</i> = 0.001)
Benzekri et al. ² 2019 [42]; Senegal	Age ≥ 35 (OR 5.80, 95% CI 2.35–14.30)	Having sought care from a traditional healer before presentation at a health facility (OR 3.86, 95% CI 1.17–12.78)	
Lebelonyane et al. 2020 [24]; Botswana	Males [23.7 vs. 13.4%, adjusted odds ratio (aOR) 1.9, 95% CI 1.5–2.3].	Increasing age [9.1% of those < 25 years, 15.0% of those aged 25–34 years, and 20.4% of those > 35 years; aOR relative to the < 25 years category of 1.5 (95% CI 1.0–2.4) and 2.2 (95% CI 1.4–3.2) respectively.	A new (rather than previously known) HIV diagnosis (aOR 1.3, 95% CI 1.0–1.6); HIV testing through mobile rather than home-based contact (aOR 1.3, 95% CI 1.0–1.6); Widowed or divorced (aOR 2.6, 95% CI 1.6–4.3)
Musengimana et al. 2022 [45]; Rwanda	Older age was significantly associated with advanced HIV disease, with 39.0% of advanced HIV patients being ≥ 45 years compared to 19.0% of non-advanced.	Be identified through inpatient settings rather than through voluntary or prenatal testing	Compared to non-AHD patients, AHD patients were more likely to be underweight (BMI < 18.5, 20.9% vs 9.6%) and to be severely underweight (BMI < 16, 8.6% vs. 1.5%).

Abbreviations: HR, hazard ratio; OR, odds ratio; RR, risk ratio.

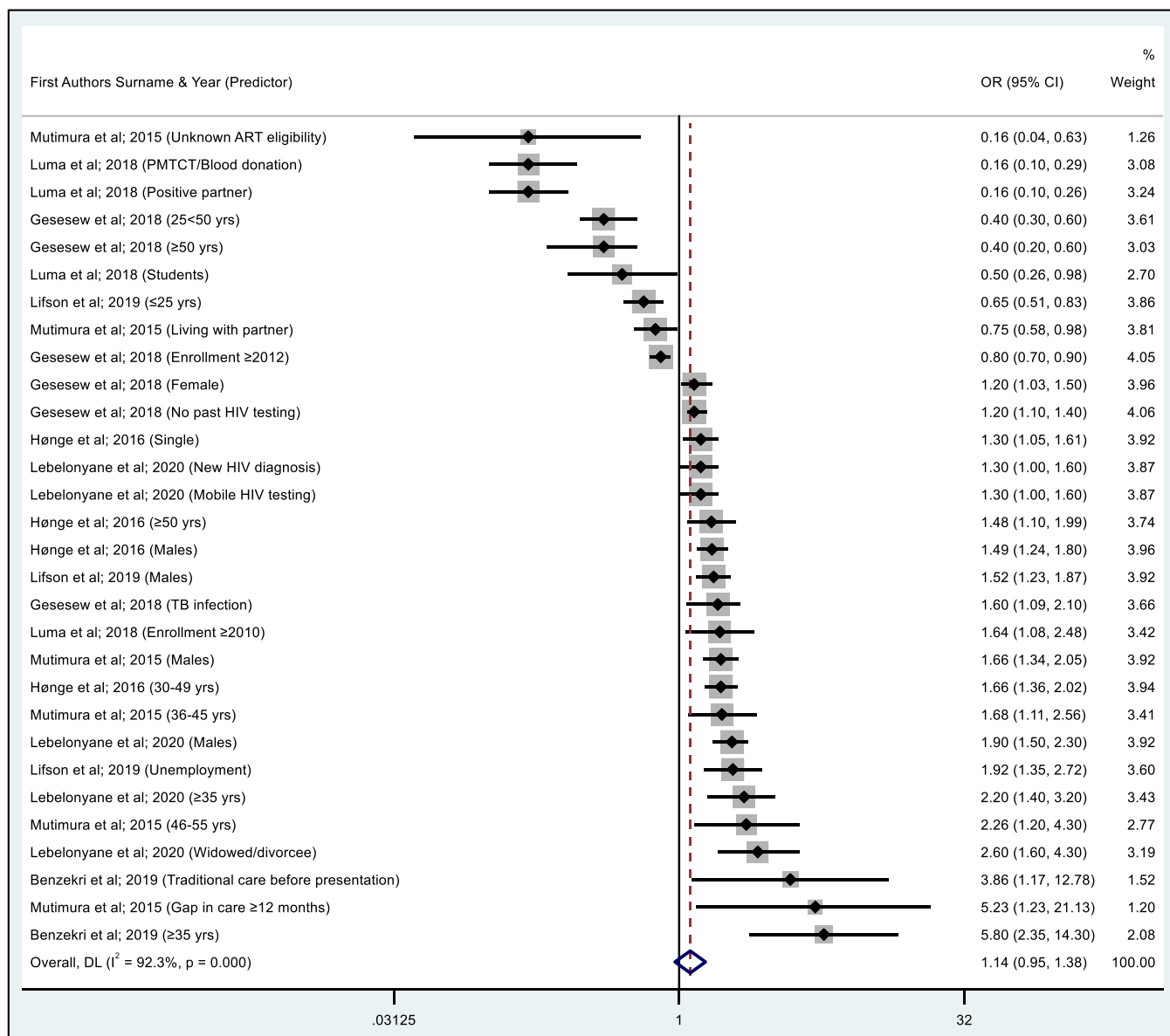


FIGURE 6 | Summary of predictors of AHD from the different studies.

AHD. This prevalence is high, given the increased access to antiretrovirals. It compares with data from a multi-country study on the prevalence of AHD where Mozambique, Namibia, Eswatini and Nigeria had a prevalence of 58%, 58%, 54%, and 60%, respectively in 2010 [17]. A South African study using laboratory data of PLHIV reported a decline in the proportion of clients entering care with AHD from 46.8% in 2004 to 35.6% in 2011, reducing slightly to 32.9% in 2016 [46]. Although we observed a decline in prevalence after commencing “test and treat” compared to the prior period, the observed prevalence is still high. It indicates a need to scale up screening of clients at risk for early diagnosis and treatment to avert possible mortality from Stage 3 and 4 diseases [16, 47]. The pooled prevalence was higher in West Africa than in other regions (East and Southern). This is counter-intuitive as countries in Southern Africa characteristically report the highest prevalence of HIV [48, 49]. The matured HIV programs in Eastern and Southern Africa, which result in increased access to HIV testing and treatment compared to West African countries, may account for these

slight differences. As expected, the prevalence of AHD characterised by different Stage 3 & 4 conditions was highest amongst males, as reported in South Africa, Botswana and Mozambique [23, 24, 28, 30, 44].

The male sex as a predictor of AHD is consistent with previous studies conducted in Guinea-Bissau, Botswana, Rwanda and South Africa [23, 24, 34, 35]. This finding is attributed to gender norms, the limited opportunities men have to visit health facilities compared to most females who, at a certain point, have to attend ante-natal services, and the fact most males are often employed and also have a higher likelihood of being involved in migrant work which limits their access to health services [50–52]. These structural and cultural barriers discourage health-seeking behaviour and contribute to men’s lower participation in HIV testing. Flexibility in operating hours of HIV services, multiple convenient locations, mobile testing and male-dedicated sections at health facilities are cited as facilitating factors enhancing male participation in HIV testing [53].

TABLE 4 | Treatment outcomes by author, year and country study was conducted.

First authors surname, year, country	In-care %	Suppressed VL %	Unsuppressed VL %	Treatment failure	LTFU %	Transferred-Out %	Died %
May et al. 2010 [25]; Cote d' Ivoire, South Africa, Malawi	79.6%	—	—	—	7.4%	5%	8.2%
Auld et al. 2011 [17]; Mozambique	71.5%	—	—	18.7	21.7%	—	6.3%
Mills et al. 2011 [26]; Uganda	—	—	—	—	M-7.5% F- 5.9%	—	8.7%
Wandeler et al. 2012 [27]; Zimbabwe, Mozambique, Lesotho	77.1%	—	—	—	22.9%	—	9.6%
Cornell et al. 2012 [28]; South Africa	64.7%	—	—	—	7.9%	10.4%	8.5%
Chalamilla et al. 2012 [29]; Tanzania	—	—	—	—	—	—	13.1%
Fatti et al. 2014 [30]; South Africa	—	85%	—	—	12.8%	—	5.9%
Aliyu et al. 2014 [31]; Nigeria	—	68%	—	—	29%	—	3%
Melaku et al. 2015 [32]; Ethiopia	70%	—	—	—	23%	—	9%
Hønge et al. 2016 [35]; Guinea-Bissau	23%	—	—	—	58.3%	4.8%	8.7%
Naidoo et al. 2017 [36]; South Africa	92%	94%	—	—	10%	—	10%
Gunda et al. 2017 [37]; Tanzania	—	—	—	—	—	—	—
Gesese et al. 2018 [38]; Ethiopia	72.3%	—	—	—	—	—	3.8%
Luma et al. 2018 [39]; Cameroon	—	—	—	—	—	—	11.6%
Mupfumi et al. 2019 [41]; Botswana	—	94%	6%	—	—	—	—
Lebelonyane et al. 2020 [24]; Botswana	97%	91% (86.6% if CD4 < 200)	9%	—	—	—	2.3% (4.9% if CD4 < 200)
Kerschberger et al. 2020 [43]; Eswatini	—	—	—	2.2%	24%	3.1%	1.8%
Musengimana et al. 2022 [45]; Rwanda	—	77%	23%	19.7%	16.5%	—	2.8%

Abbreviations: LTFU, loss to follow-up; VL, viral load.

Older age (≥ 35 years) as a risk factor for AHD could be attributed to waning immunity, employment, non-adherence to treatment and age-associated comorbidities, which increase susceptibility to complications [54, 55]. A gap in care and accessing alternative care as predictors of AHD indicates limited access and delays to effective treatment, which results in lower immunity and increased viraemia, further predisposing clients to stages 3 and 4 conditions. This necessitates recognising client health education and alternative medicine practitioners as key components of the HIV care cascade [56–60]. The positive impact of having a partner emphasises the importance of partner disclosure, which increases psychosocial support for clients accessing care and limits poor adherence, which may result in treatment failure and AHD [61].

Client retention in care, viral suppression rate, loss to follow-up, transfer out, and death of HIV clients varied by study. These variations depend on several factors, including but not limited to the set-up of the different HIV programs, location, adoption of other international treatment guidelines, various socio-economic and psychosocial factors, and population group. A higher loss to follow-up rate and death in males confirms existing evidence. It could be attributed to increased exposure to risks by males, migratory work, and limited access to health services, resulting in late ART initiation and poor survival compared to females [50–52]. The most common OI remained tuberculosis, although other OIs were reported and more common in males. These OIs usually define the clinical stage of clients, are sometimes difficult to diagnose depending on presentation and may result in increased hospitalisation, morbidity and death with delayed diagnosis and treatment [13, 16, 62]. There are opportunities for using human-centred design (HCD) to improve the implementation of the WHO AHD package. HCD is about understanding human needs and how design can respond to these needs by applying the three core characteristics of HCD: understanding people, stakeholder engagement throughout the HCD process and a systems approach towards the development of new products, services, and strategies. Through HCD, individual settings will engage, segment and respond to predictors of AHD, quality of life among patients with AHD, and care outcomes [63, 64].

This systematic review presents findings on the prevalence, predictors, and treatment outcomes in clients with AHD in SSA. There is no previous review on this topic, and this review fills that gap. Findings can guide country programs as they plan for the ageing population of PLHIV served by their programs. The review was exhaustive, including five major databases and a manual Internet search, thus ensuring that relevant articles were not excluded. Finally, the review adopted a rigorous article screening and selection approach using an article screening software with a double-blinding option to limit bias in article selection, confirmed with a standardised quality assessment for included articles.

This review has some limitations. First, the included studies were from different settings with different approaches to HIV care and treatment and focused on diverse population groups. Second, the included studies are mostly observational studies using programmatic data with limited probability sampling, reducing the quality of the evidence. Third, studies

differed in their approach to recruiting clients for inclusion. For instance, some studies only assessed AHD clients, making it impossible to determine the prevalence of AHD.

In contrast, others included all clients receiving care, making it impossible to determine those with AHD at first presentation. Fourth, we may have missed studies that were not included in any database, but we tried overcoming this by conducting a manual internet search. Finally, our findings may have limited external validity as the studies did not represent all the countries in SSA. To address this, we grouped countries to indicate AHD prevalence by African region. Despite these limitations, our review provides valuable findings to guide country programs in planning care for PLHIV.

With the high AHD prevalence in all the SSA regions and our finding that clients with limited HIV testing had an increased risk of AHD, we recommend increased access to unrestricted HIV testing through any of the available testing modalities and rapid initiation of antiretroviral therapy, which enables screening for different risk factors, OIs and immune responses. To address challenges with males accessing services, country programs should engage with male PLHIV groups and address the structural (such as mobility of men) and cultural (such as gender norms and health-seeking behaviour) factors that contribute to men's lower participation in HIV testing to identify innovative models of service delivery targeting different male sub-population groups. Client information and health education on risks and available services can ensure clients do not drop out of care when encountering treatment-related challenges. Given the critical roles of traditional medicine practitioners and traditional birth attendants within the communities where clients reside, country programs should have fora for frequent engagement and training of these alternative practitioners on where their care intersects with orthodox medical practice, referrals and use of aseptic techniques when attending to clients [65].

5 | Conclusion

Our review indicates the prevalence of AHD in people enrolling on HIV care is still high despite the availability of different modalities of HIV testing and effective ART options. The commonest predictors of AHD were males, older age, and those with limited access to HIV testing. The high mortality in this group indicates an accelerated need for targeted HIV services delivery to increase access to HIV testing and comprehensive care for those in the high-risk group. Further studies to understand regional-level variations and predictors of AHD are required to guide HIV Programs in planning context-specific interventions for clients. Additionally, country HIV programs should ensure the adoption and implementation of the WHO AHD care package with measures for its routine monitoring and evaluation to ensure that provided care is optimal and continuously meets clients' needs.

Author Contributions

S.H., S.A., and S.O. conceptualised the review. S.H., S.A., V.W., T.M., A.M., and S.O. conducted article screening, while V.W., T.M., S.A., and

A.M. extracted data from the selected articles. V.W. and T.M. analysed the data, and S.H., S.A., S.O., and V.W. wrote the first draft of the manuscript. S.H., S.A., and S.O. revised the first draft, and all authors reviewed and approved the final draft.

Acknowledgments

We thank Dr. Sharon Kibwana and Ms. Fezokuhle Khumalo for reviewing the final manuscript for grammatical errors and ensuring consistency. We also thank Ms. Jilly Motsa-Dlamini for refining and formatting the graphical abstract. Finally, we acknowledge Georgetown Global Health Institute for providing a fellowship to one of the authors (S.A.). The authors received no specific funding for this work. However, one of the authors (S.A.) is a beneficiary of the Georgetown Global Health Institute student fellows' program, which provides an opportunity for talented undergraduate and graduate students to work with faculty on research projects, participate in global health-related events, and network with one another and scholars in the global health field. The funding agency had no role in developing the study design, collection, analysis, interpretation of data, writing of the report, and the decision to submit the report for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data for this review is available upon reasonable request to the corresponding author.

Transparency Statement

The lead author Samson Haumba affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.