



Meta-analysis of factors affecting prevalence estimates of HIV-associated neurocognitive disorder in sub-Saharan Africa

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Successful treatment of HIV with anti-retroviral therapy (ART) is resulting in more people living with HIV-associated neurocognitive disorder (HAND). In sub-Saharan Africa, this calls for strategic planning and judicious allocation of scarce resources, which requires an accurate estimate of the prevalence of HAND. Estimates of the prevalence of HAND in sub-Saharan Africa vary greatly, between 18.8% and 88.3%. This variability may be explained by factors such as different diagnostic approach, neuromedical examination, ART status, sampling method, substance abuse, assessors' qualification, depression and outcome measure. Different methods of diagnosing HAND, different outcome measures and non-random sampling techniques make it almost impossible to accurately estimate the prevalence of HAND in sub-Saharan Africa, often resulting in overestimation of the burden of disease. Consumers of health research should consider certain study characteristics and exercise appropriate caution when interpreting burden of disease in sub-Saharan Africa, especially when pursuing policy shift. Underestimating the prevalence of HAND will certainly affect the capacity and speed of containment, while overestimating will draw unnecessary attention and result in the misallocation of scarce resources.

Significance:

- The high prevalence of HAND in sub-Saharan Africa as estimated in this review calls for further research on the impact of HAND on activities of daily living and putative therapeutic modalities.
- We highlight which study characteristics should be critically checked when using prevalence estimates for the purpose of health policy and distribution of scarce resources in sub-Saharan Africa.
- By favouring certain factors, this review will guide HIV health researchers in which techniques should be used to estimate the burden of HAND. These factors may also apply to estimating the burden of other diseases in sub-Saharan Africa.

Introduction

Human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) is one of the most common neurological complications of HIV in the antiretroviral therapy (ART) era.¹ The growing burden of HAND justifies a quintessential global response to address this important mental health challenge among people living with HIV (PLWHIV).² Before ART was introduced in 1996, 20–30% of people with advanced HIV infection displayed symptoms of severe HAND^{3,4}, with death occurring within 6 months⁵. In the ART era, the prevalence of HAND varies between 19% and 64%, averaging globally at about 50%.^{6–10} Without a doubt, widespread ART and early intensification with ART are associated with a remarkable drop in HIV-associated dementia.¹¹ The prevalence of less severe but limiting forms of HAND has continued to increase.^{8,12} The rising prevalence of HAND is chiefly associated with HIV becoming a chronic disease because more people are surviving HIV with the use of ART¹³, often surviving into their late fifties^{14,15}. The chronic nature of HIV has created new challenges for health policymakers and legislators.¹⁶ The neuropsychological complications associated with HIV need to be treated to secure a better well-being and adequate reintegration of PLWHIV into society. The symptoms of HAND include behavioural and cognitive difficulties such as memory loss, poor attention and concentration span, acalculia, poor information processing and inadequate multitasking resulting in poor executive function.¹⁷ Most PLWHIV contract the virus early in life, usually in their late thirties.¹⁸ Long-term treatment and inability to work may have severe economic consequences for many families. Impaired neurocognitive function further predisposes PLWHIV to low productivity, job losses, restricted social participation and poverty.¹⁹

The recent up-scaling of ART for PLWHIV in sub-Saharan Africa has been appreciable.²⁰ Consequently, sub-Saharan African healthcare systems need to prepare for and address the surge of chronic complications of HIV such as HAND and accelerated ageing.²⁰ This will provide a safe trajectory into older adulthood for PLWHIV – a privilege enjoyed by their HIV-seronegative counterparts. More than 50% of the global population of PLWHIV currently resides in sub-Saharan Africa despite comprising less than 10% of the world's population.²¹ To ensure a fair quality of life for PLWHIV in sub-Saharan Africa, insight and scholarship are needed for optimal allocation of limited resources. To achieve scholarship in strategic planning for PLWHIV, we need accurate and precise estimates of the prevalence of HAND in sub-Saharan Africa.²² Underestimating the prevalence of HAND may result in under-budgeting, whereas overestimating may impair the feasibility of such projects by deterring funding agencies. The prevalence of HAND in sub-Saharan Africa has been estimated in several studies^{11,23,24}; however, conflicting findings may distort strategic planning.

Hence, there is need for a meta-analysis of the prevalence estimates of HAND in sub-Saharan Africa. Aside from our meta-analysis of HAND prevalence estimates, we explored the effect of different study characteristics such as diagnostic criteria, outcome measures, ART status and duration, assessors' qualifications, assessment

of neuropsychological confounds and other factors on prevalence estimates. Researchers should be able to evaluate the quality of a study based on outcome measure used, the assessor's qualification, sampling technique and other study characteristics.²² The assessment of outcomes constitutes an important domain in clinical practice, and influences the success of strategic plans and treatment.²⁵ We reviewed all published estimates of HAND in sub-Saharan Africa.

Materials and methods

Design

This is a systematic review of observation studies including retrospective surveys, cross-sectional studies and cohort studies, focussing on the effects of different outcome measures and assessors on prevalence estimates in sub-Saharan Africa. The protocol was structured using a hybrid of the preferred reporting items for systematic review and meta-analysis (PRISMA) checklist and the *Meta-analysis of Observational Studies in Epidemiology* (MOOSE) guideline.^{26,27} The protocol was registered with Open Science Framework: <https://osf.io/vb52y>.²⁸

Eligibility criteria

Study characteristics

This review included observational studies of epidemiological design written in English, irrespective of sample size and test statistics. Studies had to have been conducted in sub-Saharan Africa.

Participants: This review only included studies in which participants were diagnosed with HAND by a physician or trained person using instruments such as the international HIV dementia scale (IHDS), HIV dementia scale (HDS), Montreal Cognitive Assessment Scale, or neuropsychological battery tests. We included studies irrespective of whether neuropsychological confounds were assessed or whether activities of daily living were evaluated.

Intervention: Not applicable. This is a systematic review of epidemiological studies reporting prevalence of HAND in the sub-Saharan African region.

Control: We included studies irrespective of whether the study had a control group.

Outcomes: For each study, we assessed the estimated prevalence of HAND, sampling method, sub-Saharan African region, measuring instrument and assessors' qualification, neuromedical exam, depression screening, alcohol dependence and substance abuse.

Inclusion criteria

1. Studies conducted among PLWHIV in sub-Saharan Africa reporting prevalence of HAND
2. Studies conducted in which assessment tool and/or assessor's qualification was stated
3. Studies conducted between 2009 and 2019

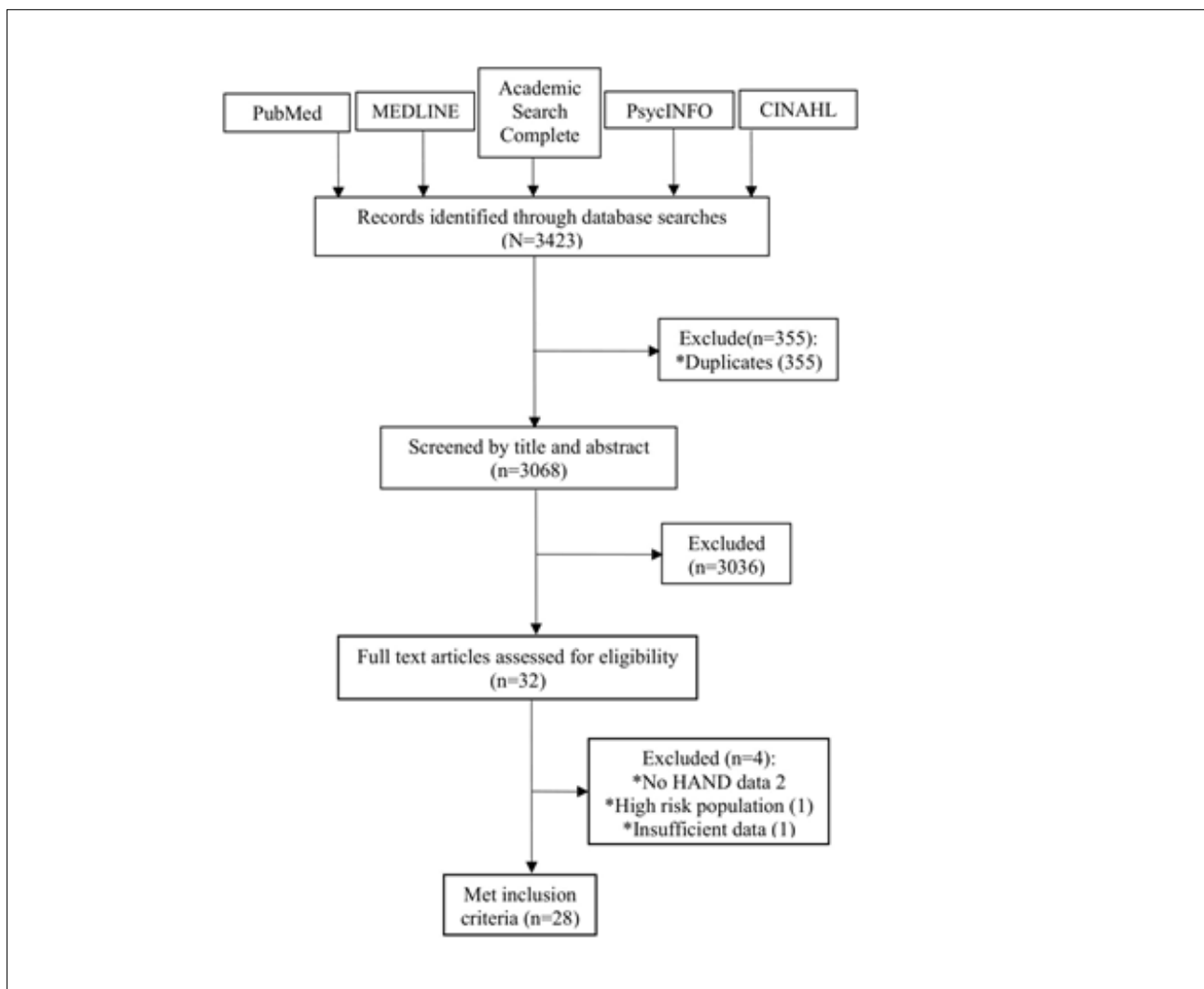


Figure 1: PRISMA flow diagram of the systematic review of articles estimating the prevalence of HIV-associated neurological disorder (HAND) among people living with HIV in sub-Saharan Africa (2009–2019).

Table 1: Studies included in a meta-analysis of the prevalence estimates of HIV-associated neurological disorder among people living with HIV in sub-Saharan Africa (2009–2019). Socio-demographic characteristics of the participants in the studies and study quality.

Study	Sample size	Age (years) Mean±s.d.	Sex (% male)	Education (years)	Study quality
Akolo et al. ⁵⁵	133	31.5±7	40.5	13.36 ± 2.40years	Low risk
Anderson et al. ⁶¹	80	35±0.00	20	12±2.00	Low risk
Asiedu et al. ⁶²	104	37.15±10.06	21.2	11.55±1.55 years	Low risk
Atashili et al. ⁷	400	41.0±6	25.8	69% ≤ 6years 39% > 6years	Low risk
Belete et al. ⁵⁹	234	18-64	35.5	73.1% ≤ 6years 12.8% > 6years 14.1% > 12years	Low risk
Debalkie et al. ⁴⁴	684	38.8±8.8	44.0	80.7% ≤ 6years 19.3% > 6years	Low risk
Hestad et al. ⁶³	275	38.0±8.1	34	9.45±2.3	Low risk
Joska et al. ⁶⁴	170	29.5±3.7	25.9	10.06 ± 1.85years	Low risk
Joska et al. ⁶⁵	536	34.0±7.9	26.7	45.1% < 9years 54.9% ≥ 10years	Low risk
Joska et al. ³⁶	55	68.53±4.1	29.7	70% ≤ 6years 30% > 6years	Low risk
Kelly et al. ⁹	106	39.0±2.0	27.0	70% ≤ 7years 30% > 7years	Low risk
Lawler et al. ⁶	120	37.5±6.5	50.0	37% ≤ 7years 48% 8-12years 15% > 12years	Low risk
Milanini et al. ³⁷	2472	40±11	41	60% ≤ 6years 40% > 6years	
Mogambery et al. ³⁸	146	35.0±3.3	45.9	NR	Low risk
Mohamed et al. ⁶⁶	360	40.2±11.5	35	9.9±3.1	Low risk
Mugendi et al. ⁴⁵	345	42.0±9.5	58.6	24.06% ≤ 6 years 47.83% ≤ 12 years 28.11% > 12 years	Low risk
Nakasujja et al. ⁶⁷	127	32.2±5.11	33.8	9.7±4,25	Low risk
Nakku et al. ⁶⁸	618	NR	27.3	57.3% ≤ 6 years 42.7% > 12 years	Low risk
Namagga et al. ²³	393	37.9±8.7	27	43% < 6years 57% > 6years	Low risk
Njamnshi et al. ⁶⁹	185	37.6±8.8	33	37% ≤ 6years 63% > 6years	Low risk
Nweke et al. ⁷⁰	120	NR	24.2	21.67% ≤ 6years 25% ≤ 12years 53.33% > 12years	Low risk
Nyamayaro et al. ⁷¹	231	37.8±11.2	33.5	19.4% < 7years 80.6% > 7years	Low risk
Patel et al. ⁴⁰	179	36.7	35.2	34.6 < 7years 65.4 > 7years	Low risk
Sacktor et al. ³⁹	77	37.0±3.4	38.0	Average of 8 years	Low risk
Tomita et al. ⁷²	200	34.5±2.3	19.5	10.88±1.29	Low risk
Tsegaw et al. ⁷³	593	38.6±10.6	47.9	50.4% < 6years 49.6% > 6years	Low risk
Yakasai et al. ¹¹	80	36.8±9.0	55.0	Average of 12years	Low risk
Yusuf et al. ⁷⁴	418	37.2±9.3	22.2	7.9±6.2years	Low risk

Exclusion criteria

1. Studies conducted among PLWHIV in sub-Saharan Africa but not reporting on prevalence of HAND
2. Studies conducted in which assessment tool and/or assessor's qualification was not stated
3. Studies conducted before 2009

Information sources and search strategy

We searched the literature using several combinations of search terms from medical subject headings (MeSH), and keywords in the title, abstract and/or text of the articles. First, we did a pilot search in PubMed to establish the face sensitivity of the search strategy. The PubMed pilot search included various MeSH terms and keywords/free text terms generated from articles that were key to the research question. We conducted the pilot search using several combinations of the search terms. The most sensitive and specific terms were chosen and reported. The terms were adapted to the syntax and subject headings of the remaining databases. Finally, we searched the following databases: PubMed, MEDLINE, Academic Search Complete, CINAHL and PsycINFO. We also searched the reference lists of identified observational and review articles for relevant studies.

Study records and data management

We exported all literature search results into EndNote 8 and removed all duplicate articles. We screened all bibliographic records in EndNote 8 and then selected articles that met the inclusion criteria. We developed, piloted and refined screening forms that included eligibility questions to aid in the screening process.

Selection process

Initially, one author screened all the articles to identify those that met the inclusion criteria. The rest of the authors then applied the exclusion criteria simultaneously to the database. Any conflicts were then resolved until all authors agreed on the articles to be included. The primary author (MCN) critically cross-checked the initial screening results and read through the full texts of the selected studies for further screening to ensure that the eligibility criteria were met. We emailed the authors of selected studies to clarify issues that impacted on the selection of an article. Details of the flow of studies throughout the selection process, along with the reasons for exclusion, are presented using a PRISMA diagram (Figure 1).

Data collection process

Quality appraisal and risk of bias assessment

We assessed the quality and risk of bias of each article using the quality assessment checklist for prevalence studies adapted from Hoy et al.²⁹ The checklist examines the appropriateness and adequacy of methodology, study design, participant recruitment, data collection, data analysis and presentation of findings. It is suitable for appraising most studies reporting prevalence. The tool contains 10 items/questions with the 10th item being the summary score. Studies were classified as unclear when there was not enough information to evaluate the risk of bias. All the authors independently assessed the risk of bias, and the primary author (MCN) collated the results.

Data items

Data collected from each article were: authors' affiliations, participants' characteristics, inclusion criteria, exclusion criteria, study sample size, sampling methods, diagnostic criteria/method of assessment, ART status, duration on ART, country, region, instrument used, the assessors' qualification/experience, neuropsychological confounds and results/conclusions.

Data synthesis and assessment of heterogeneity

We used a random-effect model of meta-analysis to estimate the pooled prevalence estimates of HAND, as well as estimates for different

measuring instruments and categories of assessors.^{30,31} Measures of heterogeneity, i.e. study characteristics, were sorted by year of publication and are presented in an evidence table (Table 1). Measure of heterogeneity, the Cochrane's Q statistics, and I^2 were computed in line with Higgins and Thompson³². The I^2 -value was interpreted in line with the Cochrane Handbook for Systematic Reviews of Intervention as follows: 0–40% might indicate low heterogeneity, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity, and 75–100% may indicate considerable heterogeneity.³³

Ethical consideration

This review is related to a clinical trial approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (ethics reference number: 152/2020), which complies with the ICH-GCP guidelines and the US Federal wide Assurance.

Data analysis

The pooled prevalence of HAND was estimated using MedCalc. The effects of study characteristics on prevalence estimates of HAND were explored using SPSS version 2, with α set at 0.05. First, we tested the effect of each study characteristic on prevalence using an independent test or ANOVA, and then repeated the test while adjusting for all significant covariates using univariate analysis. To differentiate statistical significance from epidemiological significance, an increase or decrease in prevalence by $\geq 7\%$ was termed epidemiologically significant. A covariate was deemed significant if it accounted for a variation in prevalence of $\geq 7\%$. We calculated the burden of HAND by multiplying the number of PLWHIV in sub-Saharan Africa by the estimated prevalence of HAND (with 95% confidence intervals [CIs]).³⁴ We obtained the number of adults with HIV in sub-Saharan Africa (25.6 million) from the 2018 UNAIDS report.³⁵

Results

Review profile

We identified 3423 records. After removing duplicates, 3068 records remained. After screening all the titles and abstracts, we excluded 3036 irrelevant records, leaving 32 records for full-text review. Of the 32 full texts, 4 publications were excluded. Ultimately, our review included 28 articles involving 9315 participants from 12 countries (Figure 1). Of these 28 articles, 24 were found in PubMed, 2 in Academic Search Complete, and 1 each from MEDLINE and PsycINFO. The sample sizes in each study varied from 55³⁶ to 2471³⁷. More than half (61%) of the sample population were from East Africa; 39% of the studies were conducted in East Africa, 10 (35.7%) in Southern Africa and 7 (25%) in West Africa. Seventeen studies (71%) used non-probability sampling methods. All studies included adult participants, with a mean age of approximately 38 ± 7 years. The ratio of women to men was approximately 2:1. Most of the participants had formal education (≥ 7 years of formal education).

Neuro-psychiatric disorder was assessed and excluded in 19 (68%) studies. Comprehensive neuropsychological assessment was carried out in 10 (35.7%) studies, 14 (53.6%) studies used IHDS, 2 (7.1%) employed HDS, and 1 each employed a combination of IHDS and Montreal Cognitive Assessment Scale and a community screening interview for dementia. We noted that different studies used different definitions and criteria to diagnose HAND. Six studies used the 2007 Frascati criteria, with three of them being East African studies. Sixteen (57%) studies diagnosed HAND if participants had ≤ 10 on IHDS/HDS, with most being East African studies. Four (14.3%) studies used the Global Deficit Score. One study from Kenya used an aggregate score derived from the Montreal Cognitive Assessment Scale and IHDS. In terms of methodological quality, risk of bias assessment revealed that all studies had a low risk of bias (Table 1). Of the 28 studies included in this review, 6 reported prevalence of depression, with the prevalence of depression being significantly higher (35.6%) in studies in which depression was associated with HAND than those in which the prevalence of depression (14.3%) was not associated with HAND. In 13 (46.4%) studies, depression was excluded or the rate was not associated with HAND, as opposed to 11 studies in which depression

was included or rate was not associated with HAND. Four studies reported level of alcohol use. Mogambery et al.³⁸ reported that higher alcohol use (42.5%) was protective of HAND as opposed to studies that reported low levels of alcohol use (13.5%) which found no association between prevalence of HAND and alcohol use. Of the studies that did not outrightly exclude participants with substance abuse, only three reported rate of substance abuse, which was not associated with HAND (Table 1).

Prevalence and burden of HAND in sub-Saharan Africa

The prevalence of HAND in sub-Saharan Africa varies greatly between 14% (9.2 to 19.9%)³⁹ and 88% (79.0 to 94.5%)⁴⁰. With a considerable degree of heterogeneity, the pooled prevalence was pegged at 53% (CI=44.3 to 61.5%; $I^2=98.5$). Thirteen (46%) of the studies reported prevalence rates higher than the summary prevalence (Figure 2). The estimated burden of HAND in sub-Saharan Africa was 1356.8 million (m) (CI: 1134.08–1574.4 m). The prevalence of HAND in East Africa, West Africa and Southern Africa was 66.7 m (CI: 35.0–98.4 m), 49.6 m (CI: 23.6–75.6 m) and 48.4 m (CI: 22.5–74.4 m), respectively.

Effects of study characteristics on prevalence of HAND in sub-Saharan Africa

Our data were normally distributed (Shapiro–Wilk statistic=0.940; $p=0.111$), hence we used parametric statistics. Table 2 shows the effects of study characteristics on the prevalence estimates of HAND in sub-Saharan Africa.

Epidemiologically, studies from East Africa reported significantly higher prevalence estimates of HAND ((66.7 (CI: 35.0–98.4)) compared to studies from Southern Africa and West Africa. Studies that utilised random sampling recorded an epidemiologically significantly lower rate ((46.5% (CI: 26.1–66.9)) compared with studies that used consecutive sampling ((68.4 (CI: 44.8–92.0)). Epidemiologically, similar prevalence estimates of HAND were obtained using comprehensive neuropsychological tests and validated composite measures. Nineteen (68%) studies diagnosed HAND using a neuromedical exam. Prevalence estimates of HAND were significantly lower (44.7% (CI: 32.2–57.3)) in studies with neuromedical exam compared to studies without neuromedical exam (71.3% (CI: 48.0–94.5)). Epidemiologically higher prevalence estimates of HAND were reported in studies in which physicians/PhD holders were the outcome assessors (58.8%) than those studies with paramedics (49.6%). A large proportion of studies did not exclude neuropsychological confounds such as depression (79%), alcohol use (57%) and substance abuse (61%). We classified studies into two categories: (1) studies in which neuropsychological confound(s) were excluded or potential confounds were not associated with HAND prevalence estimates and (2) studies that included neuropsychological confound(s) which were associated with HAND prevalence estimate. Studies that excluded depression and substance abuse reported epidemiologically lower prevalence estimates of HAND (51.9% and 45.7%, respectively) than studies that included depression and substance abuse ($p < 0.05$) (Table 2).

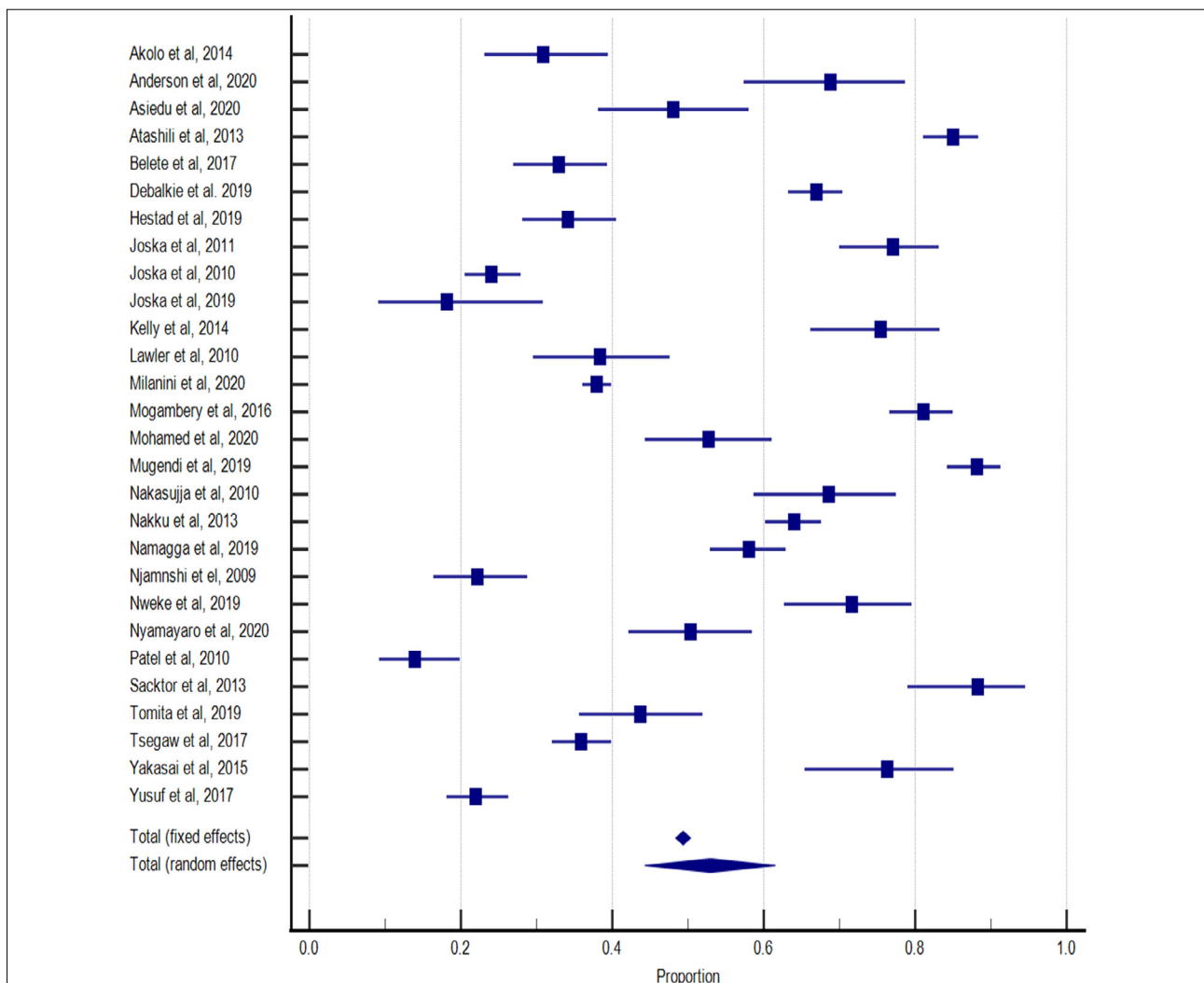


Figure 2: Forest plot displaying pooled prevalence of HIV-associated neurological disorder in sub-Saharan Africa. Estimates are generated from studies published between 2009 and 2019.

Table 2: Effects of study characteristics on prevalence of HIV-associated neurological disorder among people living with HIV in sub-Saharan Africa

Study characteristics	Publications <i>n</i> (%)	Prevalence % (95% CI)	t/F-value	P	Adjusted prevalence α % (95% CI)	F-value	<i>p</i> -value
ART status							
Experienced	14 (50)	55.7(42.8–68.7) ^a	1.720	0.200†	64.7 (45.8–83.6) ^a	2.721*†	0.125
Naïve	5 (17.9)	63.5 (35.7–91.7) ^b			41.9 (-0.5–84.3) ^b		
Mixed	9 (32.1)	41.8 (23.9–59.8) ^c			29.4 (0.4–58.3) ^c		
Outcome measure							
Comprehensive NP	10 (35.7)	55.9 (38.9–72.9)	0.307	0.588	58.2 (32.7–83.7)	0.127	0.732
Validated but non-NP	18 (64.3)	50.8 (39.1–62.5)			51.7 (28.0–75.4)		
Diagnostic criteria							
Frascati	6 (21.4)	62.6 (34.9–90.3) ^a	0.751	0.482†	45.4 (12.0–78.8) ^a	4.547*†	0.048
Global deficit score	4 (14.3)	50.8 (39.1–62.5) ^b			69.7 (44.7–94.8) ^b		
IHDS/HDS (≤ 10)	18 (64.3)	46.0 (18.1–73.8) ^{bc}			4.6 (-35.8–44.7) ^c		
Sampling technique							
Random	8 (28.6.0)	46.5 (26.1–66.9) ^a	1.254	0.303†	46.5 (19.1–73.9) ^a	2.014†	0.196
Consecutive sampling	7 (25.0)	64.3 (43.4–85.2) ^b			68.4 (44.8–92.0) ^b		
Convenience	10 (46.4)	50.1 (36.6–63.2) ^{ac}			43.7 (26.6–60.8) ^a		
Neuromedical exam?							
Yes	19 (67.9)	49.6 (38.3–60.9) ^a	1.004	0.326†	44.7 (32.2–57.3) ^a	3.843†	0.074
No	9 (32.1)	59.0 (41.6–76.5) ^b			71.3 (48.0–94.5) ^b		
Outcome assessor							
Paramedics	7 (25.0)	49.9 (35.5–64.4) ^a	0.087	0.917†	39.7 (13.6–65.9) ^a	0.793†	0.477
Physicians/PhD	20 (71.4)	58.8 (41.5–66.1) ^b			56.5 (44.4–68.6) ^b		
Exclusion of neuropsychological confounds							
Depression							
Yes	13 (46.4)	48.1 (38.2–57.9) ^a	2.340	0.117†	51.9 (32.8–71.0) ^a	0.955†	0.415
No	11 (39.3)	63.2 (46.1–80.3) ^b			59.3 (36.2–82.3) ^b		
Missing data	4 (14.3)	38.4 (-9.2–86.0) ^c			37.07 (9.5–64.7) ^c		
Alcoholism							
Yes	17 (60.7)	51.0 (37.7–64.4) ^a	0.897	0.558†	53.0 (38.7–67.2) ^a	0.015	0.985
No	4 (14.3)	64.5 (51.4–77.7) ^b			49.9 (-0.6–100.3) ^a		
Missing data	7 (25.0)	49.8 (29.1–70.4) ^{ac}			51.0 (30.8–71.2) ^a		
Substance Abuse							
Yes	15 (53.6)	52.3 (39.5–65.0) ^a	0.639	0.536†	45.7 (39.9–143.9) ^a	0.904†	0.434
No	2 (7.1)	70.3 (53.2–87.5) ^b			80.9 (17.8–76.9) ^b		
Missing data	11 (39.3)	49.9 (32.8–67.0) ^{ac}			58.4 (39.4–76.9) ^c		
Region							
West Africa	7 (25)	50.7 (25.9–76.9) ^a	2.498	0.103†	49.6 (23.6–75.6) ^a	0.525†	0.616
East Africa	11 (39.3)	63.5 (50.0–76.9) ^b			66.7 (35.0–98.4) ^b		
Southern Africa	10 (35.7)	42.0 (27.2–56.9) ^c			48.4 (22.5–74.4) ^a		

*Significant at $\alpha=0.05$; †: epidemiologically significant at difference of $\geq 7\%$.

Note: Pairs with the same superscripts are not statistically or epidemiologically significantly different, while pairs with different superscripts are statistically or epidemiologically significantly different.

Discussion

The estimated prevalence of HAND in sub-Saharan Africa in this review was approximately 53% (CI: 44.3–61.5%). Unfortunately, none of the reviewed studies assessed for self-report of difficulty in cognitive ability as part of the criteria for diagnosing HAND. It is likely that use of diagnostic criteria void of a patient's perspective of the symptom may have resulted in exaggerated prevalence estimates.^{34,41} Given that the false positive rate can exceed 20%.^{41,42} We estimate the prevalence of HAND to be pegged at 33%. Our prevalence estimates are 10% higher than estimates obtained in a similar study conducted 7 years ago.⁴³ This increase reflects the widespread use of ART in sub-Saharan Africa and indicates that asymptomatic and mild cognitive impairment are common amongst PLWHIV.

The prevalence of HAND seems to be higher among ART experienced PLWHIV compared to ART naïve individuals.^{14,15} ART naïve PLWHIV showed a higher prevalence of HAND compared to PLWHIV in a mixed ART group, suggesting that duration of use of ART is an important factor influencing the prevalence of HAND and the severity of symptoms. This is consistent with the findings of Habib et al.⁴³ in which individuals on ART for ≥ 6 months achieved a lower prevalence of dementia. We included studies from 2009 to 2019 only, and no cases of acute HAND were diagnosed in any of these studies, suggesting that ART has been successful in combating severe forms of neurocognitive impairment among PLWHIV in sub-Saharan Africa. In other words, non-use of ART among ART-naïve PLWHIV is a risk for HAND, while longer duration of ART is a risk for mild forms of HAND among ART-experienced PLWHIV.^{14,15} Interestingly, we found an inverse relationship between the prevalence of HAND and the prevalence of HIV. In sub-Saharan Africa, Southern Africa has the highest prevalence of HIV, followed by Eastern Africa and then West Africa. Our review suggests that East Africa had the largest burden of HAND, followed by West Africa and then Southern Africa. This may be due to the South African HIV care system being more effective than those of East and West Africa^{44,45} or due to a larger proportion of PLWHIV in South Africa being on ART⁴⁶.

Our findings also suggest that the prevalence estimates of HAND were associated with sampling technique. Studies that used consecutive sampling generated significantly higher prevalence estimates compared to studies that employed random sampling. Estimating prevalence using non-probability sampling may be prone to a type-1 error due to selection bias⁴⁷, and may have contributed to the wide prevalence gap across studies. We suggest that policymakers cautiously interpret studies that employ non-probability sampling, especially when using such evidence for strategic planning. Random sampling is the gold standard procedure for selecting participants for medical research.⁴⁸

Several measures, ranging from generic to disease-specific measures, are used to assess neurocognitive disorder among PLWHIV. These include the popular mini-mental state exam⁴⁸, the HDS⁴⁹, community screening interview for dementia⁵⁰, IHDS²⁹, and several combinations of neuropsychological tests such as Hopkins verbal learning test revised, Wechsler adult intelligence scale III symbol search, grooved pegboard, colour trails 2, Wechsler memory scale III spatial span and controlled oral word association test¹¹. In this review, cognitive measures included IHDS, HDS, community screening interview for dementia, Montreal Cognitive Assessment Scale and multidomain neuropsychological tests. Consistent with the literature^{9,51}, we found that studies using comprehensive multidomain neuropsychological battery tests delivered higher prevalence estimates of HAND. Neuropsychological tests are generally more sensitive than composite measures such as IHDS and HDS.^{51,52} Generally, HAND is diagnosed with a IHDS/HDS score less than 10. We found that prevalence estimates of HAND were statistically and epidemiologically lower in studies that used the Frascati criteria and Global Deficit Score compared to studies that relied on IHDS/HDS score alone. This suggests that the Frascati criteria are stricter and more specific than the IHDS/HDS score.^{39,53} Neuropsychological tests are the gold standard for assessing HAND, especially when the Frascati criteria are fulfilled.⁵⁴ The Frascati criteria seems to be gaining wide utility in clinical research across sub-Saharan Africa^{40,55}; however, use of composite measures remains the norm amongst clinical researchers in

the region⁵⁶. This may be due to battery tests being expensive and health professionals not being skilled in administering these tests to diagnose HAND.^{57,58} Our findings suggest that the Frascati criteria may be more sensitive, generating higher prevalence estimates than the Global Deficit Score. Based on this review, we recommend comprehensive neuropsychological screening and application of the Frascati criteria to diagnose HAND for improved sensitivity as well as reduced false positive rate, especially when planning treatment.

We found that studies that conducted neuromedical exams and screened for depression generated significantly lower prevalence estimates. This is consistent with the findings of Belete et al.⁵⁹ and Lawler et al.⁶ who maintain that neurological and neuropsychiatric confounds, such as depression and a positive history of psychiatric disorder, constitute major bias and often result in exaggerated prevalence estimates. Non-exclusion of neuropsychological confounds such as depression, substance abuse or lack of neurological and/or medical examination may also result in false positive diagnoses. We recommend compulsory neuromedical examination as well as screening for exclusion of putative neuropsychological confounds such as depression, alcoholism and substance abuse. Employing the Frascati criteria may also help to eliminate confounding variables.⁴ The Frascati criteria were developed in 2007 to allow for uniformity in the diagnosis of HAND. These criteria involve neuropsychological testing across various cognitive domains. Activities of daily living and ruling out other potential factors/causes for cognitive decline are also part of the diagnostic criteria.¹⁶ Our review reveals a grey area of controversy: whether alcohol use is protective of, or a risk for HAND. Studies by Debalkie Animut et al.⁴⁴ and Patel et al.⁴⁰ concluded that alcohol use is a significant predictor of HAND prevalence in a population. Interestingly, an important study³⁸ that found a high rate of alcohol use achieved a reciprocal association between alcohol use and the prevalence of HAND. It is possible that alcohol use in this population negatively influenced ART use (adherence), which might protect against mild forms of HAND.⁶⁰ We found that studies with more highly qualified and experienced assessors resulted in higher prevalence estimates of HAND, possibly due to physicians or assessors with a PhD being less likely to miss a diagnosis. This shows that the qualification or experience of outcome assessors is an important consideration when screening for HAND in clinical research across sub-Saharan Africa.

Conclusions

Prevalence of HAND in sub-Saharan Africa is high and widespread, with HAND being most prevalent in East Africa. In sub-Saharan Africa, HAND is estimated under circumstances that differ: using different diagnostic approaches, different degrees of neuromedical examination, across people with different ART status, different sampling methods, assessment of substance abuse, assessors' qualification, depression and different outcome measures. These variables, in this order, account for different prevalence estimates of HAND reported in different studies. We recommend that estimating the prevalence of HAND should be standardised, favouring the use of Frascati criteria and multidomain comprehensive neuropsychological screening, neuromedical examination, factoring in of ART status and duration, random sampling technique, assessing and excluding current history of substance abuse and depression, and inter-professional collaboration with at least one of the assessors being a physician or PhD graduate. Importantly, policymakers should consider study characteristics when interpreting prevalence estimates for strategic planning and policymaking.

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Competing interests

We have no competing interests to declare.



Authors' contributions

M.C.N. who is a funded PhD student under the supervision of N.M. conceived the idea and wrote the study protocol. Independent screening was undertaken by A.J.O., E.M.U., and C.N. Differences were resolved in consultation with M.C.N. Data extraction was independently carried out by A.J.O., E.M.U., C.N. and P.I.U., while M.C.N. serves as the data curator. M.C.N. together with A.J.O., C.N., and P.I.U. wrote the initial draft of the manuscript. All the authors revised the initial draft of the manuscript and approved the final draft.

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