Worldwide Prevalence of HIV Associated Neurocognitive Disorders (HAND) and its associated factors: A systematic review and meta-analysis

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Abstract

**Background:** HIV associated neurocognitive disorders are common in people living with HIV/AIDS and affects adherence of patients to prescription, activities of daily living and quality of life of patients. However, there is a lack of summative evidence in the area. The present meta-analysis was therefore employed to address this gap.

**Methods:** we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines during our electronic search in Psych-Info, EMBASE, Scopus and PubMed. The retrieved articles were stored with endnote reference manager and data was extracted using Meta-XL version 5.3. The quality of studies were evaluated with modified Newcastle–Ottawa Scale (NOS). A random-effect model and STATA-16 were used to compute the average estimate of HAND. Heterogeneity was weighed with $I^2$ statistics. A sensitivity analysis and subgroup analysis were employed. The existence /nonexistence of a publication bias were checked with the eye ball test and eggers test of publication bias.

**Results:** The average prevalence of HAND was 50.41% (95% CI: 45.56, 55.26). The average estimate of HAND in Europe was found to be 50.015% whereas in Africa, Asia and United States of America (USA) it was 49.566%, 52.032 %, 50.407% respectively. The prevalence of HAND in studies which used HIV Dementia Scale (IHDS) was 36.883% & 59.956% at a cutoff points of IHDS< 9.5 & IHDS <10 respectively. In addition the estimated average of HAND with the global dementia scale (GDS) was 40.766%. The prevalence of HAND in cross-sectional, cohort and case control studies was 49.52%, 54.087% and 44.45% in that order. Sociodemographic variables such as low level of education and older age, clinical and HIV related variables such as advanced stage of the illness and CD4 count of 500 cells/dl or less and psychological variables such as comorbidity of depression increases the risk of HAND.

**Conclusion:** The average prevalence of HAND was high (more than half of participants) and factors such as low level of education, older age, advanced stage of the illness and comorbidity of depression increases the risk of HAND. Public health interventions to HIV patients should target these essential problems.

1. **Introduction**

HIV/AIDS is a global public health issue with more than 34 million individuals living with the virus currently (1). Mental, neurological and substance (MNS) related disorders are very common in individuals living with HIV/AIDS (2). Latest systematic review and Meta-analysis studies by Necho et al 2020 (3) revealed that 35.8% of HIV/AIDS patients had depressive symptoms (3). Another systematic review and meta-analysis studies reported that the prevalence of post-traumatic stress disorder (PTSD), alcohol use disorder (AUD), suicidal ideation in individuals living with HIV/AIDS were 32.67%(4), 22.02% (5) and 21.7%(6) respectively.

Since HIV is a neurotropic virus, it affects the cortical and sub-cortical parts of the brain resulting in cognitive impairment (7). This impact of HIV on cognitive domain of patients is known as HIV-associated neurocognitive disorder (HAND)(8, 9). The level of HAND arrays from asymptomatic impairment to minor neurocognitive disorder and full blown dementia (10-13). HIV-associated neurocognitive disorder affects memory, attention, problem solving ability, language, higher executive functioning and independent activities of daily living (14).

HIV associated neurocognitive disorders are very common in HIV/AIDS patients. A study by Abdulrazaq G. Habib et al 2013(15) reported that the burden of neurocognitive impairment (NCI) among ART attendants was 30.39%. Based on the report of multiple earlier studies the world wide burden of HIV associated neurocognitive disorders(HAND) varies from a minimum of 7.3% to a maximum of 85% (8, 10, 12-14, 16-49). In addition, the frequency of HIV
associated neurocognitive disorder (HAND) in developed and developing countries varies between 19% to 52% (30, 50), and 14% to 64% (12, 13) respectively.

Different studies reported varieties of sociodemographic and clinical factors associated with HIV associated neurocognitive disorders in individuals living with HIV/AIDs. For example studies from, Cameroon, Nigeria, Botswana, Singapore, Malawi and Dessie Ethiopia reported that sociodemographic variables such as older age, female sex, and lower educational level were a risk factors for HIV associated neurocognitive disorder(13, 14, 45, 49, 51, 52). In addition, from Clinical variables CD4 count of < 500 cells/mm3 was related to HIV-associated neurocognitive disorder based on reports of studies from Brazil, Singapore and Northern Nigeria (14, 49, 53). Moreover, advanced stage of AIDS and not being on highly active anti-retroviral treatment (HAART) were associated with HIV-associated neurocognitive disorder in South Africa (50-52). In Uganda behavioral and psychological variables such as depression, Body mass index and alcohol abuse were associated with HIV-associated neurocognitive disorder (10). Moreover, medication non-adherence and opportunistic infections were associated with HIV-associated neurocognitive disorder (45, 54).

Presence of HIV-associated neurocognitive disorder predisposes HIV infected patients substance abuse, poor medication adherence, and unsafe sex so that poor quality of life and lost to follow up from treatment are final outcomes. These conditions speed up the progression of the virus to its advanced stages and development of severe opportunistic infections and death (11, 12).

Despite the fact that high proportion of the world population has been living with HIV/AIDS and high prevalence of mental, neurological and substance use disorders in this population, these problems especially neurocognitive disorder are not investigated well. Despite the presence of some studies in the area, they are of mostly confined to a small population and to a narrow geographical area (8, 10, 12-14, 16-49). Consequently, there arises a need to have aggregate data regarding HIV-associated neurocognitive disorder and its associated factors.

Therefore, this systematic review and meta-analysis study was designed to have summative empirical data on (1): The commonness of HIV-associated neurocognitive disorder on people living with HIV AIDS (2): The associated factors for HIV-associated neurocognitive disorder in people with HIV AIDS and in conclusion to clear a reference point for officials, future scientists and clinicians.

2. Methods

2.1: Search strategy

This systematic review and meta-analysis study was done using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as a framework (55). We have performed our search strategy for this review in different ways. Initially we did an electronic exploration for eligible articles regarding HIV-associated neurocognitive disorder on people living with HIV AIDS in the databases of Psych-Info, EMBASE, Scopus and PubMed. As a sample of our search strategy with PubMed database, we have used the following key terms: (Prevalence OR screening OR burden AND “neurocognitive disorder” OR “neurocognitive deficit” OR “neurocognitive impairment” OR “HIV-associated neurocognitive disorder” OR “Intellectual impairment” OR “HAND” AND “PLWHA” OR “HIV/AIDS” OR HIV OR AIDS OR ART AND “associated factor” OR determinant OR “risk factor”). Moreover, Psych-Info, EMBASE and SCOPUs databases were investigated in line with the searching guidelines of each database. In addition, the reference lists of included studies were searched manually for additional eligible articles. There was no time restriction to the publication year of the articles during the searching process.
2.2: Eligibility criteria's

During our study of a systematic review and meta-analysis on HIV-associated neurocognitive disorder in people living with HIV AIDS, we have set the following inclusion and exclusion criteria's based on the PICO criteria: (1) the primary inclusion criteria was the design of the study. In this context all observational studies (case control, cross-sectional ad cohort) were eligible for analysis. (2) The next criteria for inclusion to analysis were the study should assessed prevalence OR associated factors of HIV-associated neurocognitive disorder in people living with HIV AIDS. (3) The HIV-associated neurocognitive disorder had also to be investigated using International HIV Dementia Scale (IHDS), Frascati criteria, Mini-mental state exam(MMSE), global dementia scale(GDS), Brief Neurocognitive Screen, Neuropsychological battery, Montreal Cognitive Assessment (MoCA), In-depth neuropsychological assessment, Wechsler Adult Intelligence Scale and ADC.

We excluded studies 1) that assessed neurocognitive disorder in samples other than people living with HIV/AIDS. 2) That assessed neurocognitive disorder in individuals that had a history of depression or other forms of mental illness or those taking a psychotropic medication. 3) Studies which are letters to the editor with non-original data content, earlier reviews, case studies, studies involving non-human subjects, articles published in a language other than English language were also excluded from the analysis. After all relevant articles were searched in the mentioned data bases; they were stored in an endnote reference manager. Two of the authors (MN and YZ) individually screened the titles and abstracts of articles stored in an endnote reference manager using the eligibility criteria's. Next to that, the above two authors carefully read the full length of articles which passed the initial screening and decided independently articles suitable for inclusion in the final meta-analysis. Any disagreement in between them regarding eligibility criteria was resolved by agreement and with a third reviewer (WY).

2.3: Data extraction and quality assessment techniques

Once the articles for inclusion to the final analysis were settled, the previously mentioned two authors (MN and YZ) extracted all the necessary data individualistically using an identical data extraction form. The forty final incorporated studies were extracted using the data extraction template as suggested by PRISMA guidelines (55), using Meta-XL version 5.3 (56) and the result was summarized in a table presentation. The contents of the data extraction template were author name, year of publication, country where the study was done, study design, studied sample population, assessment tool for HIV associated neurocognitive disorders, number of cases with HIV associated neurocognitive disorders, prevalence of HIV associated neurocognitive disorders, sampling technique employed to recruit participants, and response rate of the study.

The quality of forty included studies (8, 10, 12-14, 16-49) had been evaluated using modified Newcastle–Ottawa Scale (NOS) (57) as gold standard. Representativeness of sample and sample size, statistical quality, comparability among participants and ascertainment of cases were the components of this quality assessment scale. Based on this scale studies with a quality score of 7 to 10 were categorized as very good/good, score of 5 to 6 were categorized as having satisfactory quality, and a score less than 5 was take as unsatisfactory quality.

2.4: Data analysis and synthesis

The random-effect model was used to compute the average estimate of HIV associated neurocognitive disorders and its associated factors with 95% CIs (58). The STATA-16 Meta-prop package (59) was employed to find the
average estimate of HIV associated neurocognitive disorders. Heterogeneity among the forty involved studies \((8, 10, 12-14, 16-49)\) was weighed with \(Q\) and \(I^2\) statistics \((60)\). An \(I^2\) numerical value of more than 50% imply a significant degree of heterogeneity among forty studies \((60)\). As there existed a potential heterogeneity during analysis, we further conducted a sensitivity analysis to identify an influential study outweighing the study finding. Additionally, we did a subgroup analysis regarding the country of the study, study design and the assessment tools used to screen HIV associated neurocognitive disorders. The presence /absence of a publication bias was done visually with the eye ball test \((61)\) and eggers test of publication bias.

### 2.5: Review registration

This systematic review and meta-analysis has been registered in PROSPERO with a registration number of __________________

### 3. Results

#### 3.1: Identification of studies

Our electronic search in Psych-Info, EMBASE, Scopus and PubMed gave to a total of 10231 articles. Additionally 12 articles were retrieved by looking for reference list of earlier articles. Thus, a total of 10243 articles were retrieved during the overall searching process, of which 39 were removed as they were duplicates. During the initial stage of screening, most of the articles \((10118)\) were excluded merely by looking at their title or abstract. The lasting 86 articles were completely inspected for suitability of inclusion to the study but only 40 articles were suited for final meta-analysis as the 46 studies were excluded with limitations in methodology (Figure 1).

#### 3.2: Characteristics of included studies

A total of forty studies \((8, 10, 12-14, 16-49)\) that surveyed HIV associated neurocognitive disorders in 14107 HIV/AIDS patients were integrated in the current systematic review and meta-analysis study. Of the forty included studies; eleven were from Europe \((8, 14, 20, 22, 23, 26, 27, 39, 40, 43)\), twenty one were from Africa \((10, 13, 17, 19, 24, 29, 30, 34, 36-38, 44-49)\), and six were from Asia \((16, 25, 33, 35, 42)\) and two from United States of America (USA) \((28, 40)\). Most of the included studies \((28)\) \((8, 10, 12-14, 16-19, 22, 24, 25, 27, 29, 30, 33-39, 44-49)\) were cross-sectional in design whereas the remaining ten and two were cohort \((8, 20, 22, 23, 26, 28, 40, 42, 43)\) and case control \((29, 62)\) respectively. Regarding tools used for the assessment of HIV associated neurocognitive disorders, half of the included studies (twenty) used International HIV Dementia Scale (IHDS) \((8, 10, 12-14, 16, 19, 24, 34-36, 38, 42, 43, 45, 47-49, 62)\). Frascati criteria, global dementia scale (GDS) and Montreal Cognitive Assessment (MoCA) were also used to assess HIV associated neurocognitive disorders in three \((25, 30, 46)\), three \((29, 37)\) (Yechoor et al.2016) and three \((18, 22)\) (Chan et al.2016) studies respectively. HIV associated neurocognitive disorders were assessed on a total of 14107 HIV/AIDS patients (Table 1).

#### 3.3: Quality of Included Studies

Using the modified version of Newcastle Ottawa quality assessment scale, we assessed the quality of forty studies \((8, 10, 12-14, 16-49)\). This scale divides the quality score of 40 studies in to three; 7 to 10 categorized as very good/good, 5 to 6 categorized as having satisfactory quality and a score less than 5 as unsatisfactory quality.
Among the forty included studies; the majority (twenty nine) had scored from 7 to 10 so that good quality scores on the scale. Of the remaining eleven studies, seven had a satisfactory quality and remaining four of the studies had unsatisfactory quality.

3.4: The prevalence of HIV associated neurocognitive disorders among HIV/AIDS patients

Forty studies that evaluated HIV associated neurocognitive disorders in HIV/AIDS had been included to determine the average prevalence of HIV associated neurocognitive disorders. The reported prevalence of HIV associated neurocognitive disorders included in the meta-analysis differs from 7.3% in United Kingdom(27) to 88% in Kenya(34). The average prevalence of HIV associated neurocognitive disorders using the random effect model was 50.41% (95% CI: 45.56, 55.26). This average prevalence of HIV associated neurocognitive disorders has been affected by substantial heterogeneity ($I^2=100\%$, p-value $\leq 0.001$) from the difference among forty included studies (Figure 2).

3.4: Subgroup analysis of the prevalence of HIV associated neurocognitive disorders among HIV/AIDS patients

Since the average estimate of HIV associated neurocognitive disorders was predisposed to a considerable heterogeneity, we employed a subgroup analysis based on country where the study was done, the assessment tool used to screen HIV associated neurocognitive disorders and study design. The average prevalence of HIV associated neurocognitive disorders in Europe (8, 14, 20, 22, 23, 26, 27, 39, 40, 43) was found to be 50.015% (95% CI: 43.339, 56.691) whereas in Africa (10, 13, 17, 19, 24, 29, 30, 34, 36-38, 44-49), Asia (16, 25, 33, 35, 42) (fazel) and United States of America (USA) (28, 40) the average prevalence of HAND were 49.566% (95% CI: 41.342, 57.791) with ($I^2=96.6\%$, p-value <0.001), 52.032 % (95% CI: 34.46, 69.604) with ($I^2=98\%$, p-value<0.001) and 50.407% (95%CI: 45.555, 55.258) ($I^2=100\%$, P<0.001) respectively (Table 2).

3.5: Sensitivity analysis

In addition to a subgroup analysis, we did a sensitivity analysis to know whether one or more of the individual studies outweighed the overall estimate of HIV associated neurocognitive disorders. The result however reported that the average estimate of HIV associated neurocognitive disorders ranges from 46.92638% (95% CI: 46.889656, 46.963104) to 50.478935% (95% CI: 50.439026, 50.518841) when each studies were omitted from the analysis (Table 3). This implies that there was no single influential study outweighing the average estimate.
3.6: Publication bias

The Eggers test of publication bias had been runned and its p-value is not significant; (P-value=0.55) suggesting that there was no publication bias for the prevalence HIV associated neurocognitive disorders. Additionally, a graphical inspection from a funnel plot for a Logit event rate of occurrence of HIV associated neurocognitive disorders in HIV AIDS patients alongside its standard error suggests an accommodating evidence for the nonexistence of a publication bias (Figure 3).

3.7: Associated factors of HIV associated neurocognitive disorders among HIV/AIDS patients

Among the forty studies, only fifteen studies described the factors related with HIV associated neurocognitive disorders (8, 10, 12, 14, 17, 19, 20, 24, 25, 33, 34, 45-48). The most frequently reported sociodemographic variable as associated factor of HIV associated neurocognitive disorders were low level of education(12, 14, 17, 20, 29, 45, 46) and older age (8, 14, 19, 45, 48) Among clinical and HIV related variables late clinical stage of the illness (19, 20, 24, 48) and CD4 count of 500 cells/dl or less (8, 17, 45) were the most commonly described factor for HIV associated neurocognitive disorders. In addition, from psychological variables comorbidity of depression increases the risk of HIV associated neurocognitive disorders (14, 20, 34). Moreover, clinical and HIV related variables such as impairment in the activity of daily living(19), duration of HIV infection > 5 years (25), poor medication adherence (45), co-morbid medical illness, highest prior VL >100,000 copies/ml (8), history of neurological disease(20), use of benzodiazepines(33), body mass index< 16 kg/m² (24), plasma HIV-1 RNA load between 1.7log10 and 3log10 copies/ml (48), having co-morbid opportunistic infection(19) and psychological variables like negative life events, high stress score index (score>10) (10), generalized anxiety symptoms (20), and substance use (19, 48) were related to HIV associated neurocognitive disorders (Table 4).

3.7.1 Association between old age and HIV associated neurocognitive disorders among HIV/AIDS patients

Older age was reported as the risk factor for HIV associated neurocognitive disorders by five studies (8, 14, 19, 45, 48).

3.7.2 Association between depression and HIV associated neurocognitive disorders among HIV/AIDS patients

As reported with three studies (14, 20, 34) that assessed HIV associated neurocognitive disorders, depression increases the risk of HIV associated neurocognitive disorders.

3.7.3 Association between advanced stages of AIDS and HIV associated neurocognitive disorders among HIV/AIDS patients

Advanced clinical stages of the illness (stage III and stage IV AIDS) (19, 20, 24, 48) were also associated factor for HIV associated neurocognitive disorders.
4. Discussion

To our knowledge, this is the first systematic review and meta-analysis that assessed the global burden of HIV associated neurocognitive disorders in HIV/AIDS patients. So, the data synthesized will be important suggestion to varied stakeholders. Overall, forty studies (8, 10, 12-14, 16-49) that measured the prevalence of HIV associated neurocognitive disorders in 14107 participants and fifteen studies that described the factors related with HIV associated neurocognitive disorders (8, 10, 12, 14, 17, 19, 20, 24, 25, 33, 34, 45-48) were included.

The average worldwide prevalence of HIV associated neurocognitive disorders in this study was 50.41% (95% CI: 45.56, 55.26). This was higher than the result of a meta-analysis that assessed 16 studies in sub-Sahara Africa where the prevalence of HAND was 30.39% (Neurocognitive impairment in HIV-1-infected adults in Sub-Saharan Africa: a systematic review and meta-analysis).

This review and meta-analysis has its own strengths and limitations. Its strength begins with the use of a prespecified search strategy that minimizes reviewer’s bias. The second strength was that the data extraction and quality assessment of the study was done by independent reviewers that also further minimize reviewer’s bias. The implementation of subgroup analysis and sensitivity analysis to detect the source of heterogeneity was strength. On the contrary, the limitations of the present study rise from the existence of heterogeneity that might affect the conclusion of the study findings. Another limitation is that inclusion of few numbers of studies in the subgroup analysis might minimize validity of estimate.

Conclusion And Recommendation

This systematic review and meta-analysis study reported a high prevalence of HIV associated neurocognitive disorders (more than half of the participants), Sociodemographic variables such as low level of education and older age, clinical and HIV related variables such as advanced stage of the illness and CD4 count of 500 cells/dl or less and psychological variables such as comorbidity of depression increases the risk of HAND. Therefore, to increase independent functioning and improve the quality of life of individuals living with HIV/AIDS, much attention has to be given to lessen these neurocognitive disorders and adjust the allied factors essentially through routine screening and timely intervention of HAND. Moreover, policies and procedures that integrate routine screening and timely intervention of HAND to the routine anti-retroviral therapy should be designed and implemented. Further experimental and follow up studies with greater samples population in the area should be done.

Abbreviations

AIDS: Acquired Immune-Deficiency Syndrome, ANI: Asymptomatic neurocognitive impairment, CC: case control, CD: Cognitive decline, CS: cross-sectional, F: female, GDS: global dementia scale, HAD: HIV associated dementia, HAND: HIV associated neurocognitive disorders, IHDS: International HIV Dementia Scale, II: Intellectual impairment, M: male, MMSE: Mini-mental state exam, MND: Mild neurocognitive disorders, MoCA: Montreal Cognitive Assessment, NA: Not available, NCI: Neurocognitive impairment, SNI: Symptomatic neurocognitive impairment, UK: United kingdom, USA: united states of America.

Declarations

Data availability
All relevant data regarding this research work is included in the manuscript.

**Ethical approval**

N/A

**Conflict of interest**

No potential conflict of interest for this study.

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**Authors contribution**

YZ imagined the idea for the study. YZ & MN established the search approach, extract the relevant data, accomplished the analysis, and inscribed the manuscript. MN, YZ, BA & WY did the quality assessment studies. All authors confirmed the last draft of the manuscript.

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Tables

Table 1:
| ear | Country       | Study design | Sample size | Tools with cut off points       | Sampling Technique              | Response Rate | Age of respondents | Prevalence of outcome Cases with the outcome |
|-----|---------------|--------------|-------------|---------------------------------|---------------------------------|---------------|-------------------|---------------------------------------------|
| t   | Botswana      | CS           | 120         | IHDS \( \leq 9.5 \)            | Randomly selected               | 100%          | M & F 21-50 years | 47                                          |
| et  | Brazil        | CS           | 434         | IHDS \( \leq 10 \)             | NA                              | 90.3%         | M & F \( \geq 18 \) years | 235                                         |
| et  | Iran          | CS           | 93          | Frascati neuropsychological criteria | NA                            | 100%          | M & F 18-60 years | 47                                          |
| et  | UK            | CS           | 150         | ADC                             | Randomly selected               | M & F Median age = 43 years | HAND = 7.3% | 11                                          |
| et  | Malawi        | CS           | 106         | Frascati criteria               | Consecutively                   | 93.8%         | M & F \( > 18 \) years | HAND = 70% | 74                                          |
| et  | Nigeria       | CS           | 80          | Frascati criteria               | NA                              | 100%          | \( \geq 18 \) years | HAND = 40% | 32                                          |
| et  | Ethiopia      | CS           | 254         | International HIV Dementia Scale (IHDS) \( \leq 9.5 \) | Systematic random sampling technique | 92.1%         | M & F 18-64 years | HAND = 33.3% | 85                                          |
| t   | Ethiopia      | CS           | 584         | Mini-mental state exam          | Systematic random sampling      | 99.49%        | \( \geq 18 \) years | HAND = 35.6% | 208                                         |
| t   | Ethiopia      | CS           | 328         | International HIV Dementia Scale (IHDS) | Systematic random sampling      | 97.04%        | \( \geq 18 \) years | HAND = 37.7% | 124                                         |
| t   | Ethiopia      | CS           | 423         | International HIV Dementia Scale (IHDS) | Systematic random sampling      | 100%          | \( \geq 18 \) years | HAND = 24.8% | 105                                         |
| t   | Zimbabwe      | CSC          | 155         | GDS \( \geq 0.5 \)              | 100%                           | M & F \( 18 \) years or older | HAND = 49.7% | 77                                          |
| t   | Ethiopia      | CS           | 595         | International HIV Dementia Scale (IHDS) \( \leq 9.5 \) | Systematic random sampling technique | 99%           | M & F 18 and 65 years | HAND = 36.4% | 217                                         |
|     | Italy         | cohort       | 206         | MMSE                            | 100%                           | \( > 18 \) years | HAND = 47.1% | 97                                          |
|     | Central African Republic | CS            | 244         | International HIV Dementia Scale (IHDS) \( \leq 8.36 \) | 100%                           | M & F \( > 18 \) Years | HAND = 25% | 61                                          |
|     | Kenya         | CS           | 218         | MoCA < 26.                     | Consecutively sampled          | 98.6%         | 18 – 65 years | HAND = 69% | 150                                         |
| et  | India         | CS           | 307         | International HIV Dementia Scale (IHDS) \( \leq 10 \) | Convenient sampling            | 100%          | M & F 18-60 years | HAND =90.1% | 91                                          |
| et  | Nigeria       | Prospective  | 58          | WAIS                            | 100%                           | M & F \( > 16 \) years | HAND =63.8% | 37                                          |
| et  | Europe and Canada | CS            | 2884        | Brief Neurocognitive Screen     |                                 | 99.3%         | M & F \( > 18 \) years | HAND =41.5% | 1197                                        |
|     | Singapore     | CS           | 132         | MoCA                            | 100%                           | M & F 21 to 80 years | HAND =22.7% | 30                                          |
|     | China     | Cohort | 192 | Neuropsychological battery | 94.6% | Mean (SD) = 40.2 (6.3) | HAND = 27% |
|-----|-----------|--------|-----|------------------------------|-------|-------------------------|-----------|
|     | USA       | cohort | 268 | ADC stage ≥ 1               | 89.6% | Median=47.0 (43.0–57.0) | HAND = 48% 129 |
| a et| Uganda    | CS     | 156 | IHDS                         | 100%  | M & F                   | HAND =64.7% 101 |
| n et| USA       | cohort | 1160| Brief Neuro-Cognitive Screen | Randomized Trials | M & F 34-55 years | HAND=65% 754 |
|     | Singapore | Cohort | 53 | Montreal Cognitive Assessment (MoCA)= ≥ 26 MMSE IHDS≤10 | 100%  | Males >21 years | HAND=52.8% 28 |
| t   | Zambia    | C-C    | 266 | GDS ≥ 0.5                    | 100%  | M & F 18 to 65 years | HAND=34.6 % 93 |
|     | Uganda    | CS     | 181 | GDS≥ 0.5                     | 100%  | M & F 18-50 years | HAND=38% 69 |
| :  | Uganda    | CS     | 680 | International HIV Dementia Scale (IHDS)≤10 | 90.9% | M & F ≥18 years | HAND=64.4% 438 |
| :  | Brazil    | CS     | 114 | International HIV Dementia Scale (IHDS)≤10 | 97.4% | M & F ≥18 years | HAND =53.2% 61 |
|     | Switzerland | Cohort | 30 | In-depth neuropsychological assessment | 100%  | M & F ≥18 years | HAND =83% 25 |
| e et| Nigeria   | CC     | 208 | IHDS≤10 MMSE=26              | Consecutively 100% | M & F 18-60 years | HAND=54.3% 113 |
| :  | Cameroon  | CS     | 400 | International HIV Dementia Scale (IHDS)≤10 | Consecutively 100% | M & F 18 to 55 years | HAND=85% 340 |
| t   | France    | Cohort | 400 | Neurocognitive tests         | Consecutively 100% | M & F ≥18 years | HAND =58.5% 234 |
| st  | Belgium   | Cohort | 200 | International HIV Dementia Scale (IHDS)≤10 |                     | M & F Median age of 46 (range 30.3-69.6) years. | HAND= 84% 168 |
|     | India     | cohort | 80  | International HIV Dementia Scale (IHDS)≤10 | Randomly selected 100% | 21 to 50 years | HAND=32.50% 29 |
|     | Germany   | Cohort | 480 | International HIV Dementia Scale (IHDS)≤10 |                     | M & F 19 to 80 years | HAND=43% 207 |
|     | Nigeria   | CS     | 418 | International HIV Dementia Scale (IHDS) ≤ 9.5 | 100%  | M & F ≥18 years | HAND =21.5% 90 |
| ra et| Ireland   | CS     | 604 | Weschler Adult Intelligence Scale | 100%  | M & F >18 years | HAND =51.5% 311 |
| t   | Ethiopia  | CS     | 684 | International HIV Systematic | 98%    | M & F | HAND =67.1% 459 |
Dementia Scale (IHDS) < 9.5
random sampling method
18 to 64 years

| Country     | Number of studies | Estimates Prevalence | 95% CI          | Heterogeneity | I² | P-value |
|-------------|-------------------|----------------------|-----------------|---------------|----|---------|
| Africa      | 21                | 49.566               | 41.342, 57.791  | 96.6%         | P<0.001 |        |
| Europe      | 11                | 50.015               | 43.339, 56.691  | 46.6%         | P=1.00  |        |
| Asia        | 6                 | 52.032               | 34.46, 69.604   | 98%           | P<0.001 |        |
| USA         | 2                 | 50.407               | 45.555, 55.258  | 100%          | P<0.001 |        |
| Assessment tools used |      |                     |                 |               |     |         |
| IHDS< 9.5   | 6                 | 36.883               | 21.196, 52.571  | 99.4%         | P<0.001 |        |
| IHDS< 10    | 14                | 59.956               | 49.985, 69.928  | 56.6%         | P<0.05  |        |
| Frascati criteria | 3          | 53.5                 | 36.457, 70.543  | 90.6%         | P<0.001 |        |
| ADC         | 2                 | 27.65                | -12.234, 67.536 | 99%           | P<0.001 |        |
| MMSE        | 2                 | 41.349               | 30.080, 52.619  | 100%          | P<0.001 |        |
| GDS         | 3                 | 40.766               | 31.995, 49.537  | 99.8%         | P<0.001 |        |
| MoCA        | 3                 | 48.17                | 18.482, 77.852  | 0%            | P=1.00  |        |
| Others      | 7                 | 55.75                | 45.851, 65.653  | 68%           | P<0.05  |        |
| Study design |                   |                      |                 |               |     |         |
| Cross-sectional | 28              | 49.52                | 43.490, 55.545  | 48.6%         | P=1.00  |        |
| Cohort      | 10                | 54.087               | 45.087, 63.087  | 96%           | P<0.001 |        |
| Case control | 2                 | 44.45                | 25.144, 63.756  | 94.8%         | P<0.001 |        |

Keys: ANI: Asymptomatic neurocognitive impairment, CC: case control, CD: Cognitive decline, CS: cross-sectional, F: female, GDS: global dementia scale, HAD: HIV associated dementia, HAND: HIV associated neurocognitive disorders, IHDS: International HIV Dementia Scale, II: Intellectual impairment, M: male, MMSE: Mini-mental state exam, MND: Mild neurocognitive disorders, MoCA: Montreal Cognitive Assessment, NA: Not available, NCI: Neurocognitive impairment, SNI: Symptomatic neurocognitive impairment, UK: United kingdom, USA: united states of America.

Table 2: A subgroup analysis of the prevalence of HIV associated neurocognitive disorders in HIV/AIDS patients based on random effect analysis

Table 3: a sensitivity analysis of the prevalence of HIV associated neurocognitive disorders in HIV/AIDS patients when each indicated studies are omitted at a time with its 95% confidence interval.
| No | Study omitted               | Estimated prevalence of HAND [95% Conf. Interval] |
|----|-----------------------------|--------------------------------------------------|
| 1  | Lawler et al. 2010          | 48.55587, 48.520576-48.591164                    |
| 2  | Pinheiro et al.2016         | 48.256584, 48.220829-48.292343                    |
| 3  | Elham et al.2020           | 48.443535, 48.408272-48.478798                    |
| 4  | Haddow et al.2012          | 48.594143, 48.558952-48.629333                    |
| 5  | Kelly et al.2014           | 48.303158, 48.267899-48.338417                    |
| 6  | Yakasai et al.2015         | 48.511402, 48.476162-48.546646                    |
| 7  | Belete et al.2017          | 48.739456, 48.703999-48.77491                      |
| 8  | Araya et al.2020           | 49.037079, 49.001163-49.07299                       |
| 9  | Yitbarek et al.2019        | 48.732273, 48.696697-48.767849                     |
| 10 | Belete et al.2014          | 49.074566, 49.038979-49.110153                     |
| 11 | DeBalkie et al.2019        | 47.50845, 47.472431-47.544464                     |
| 12 | Tsgeaw et al.2017          | 49.017803, 48.981865-49.053738                     |
| 13 | Nyamayaro et al.2020       | 48.478603, 48.407894-48.443249                     |
| 14 | Focà et al.2016            | 48.41682, 48.446255-48.517109                      |
| 15 | Pascal et al.2016          | 48.808884, 48.773487-48.844276                     |
| 16 | Awori et al.2018           | 48.145374, 48.109974-48.180775                     |
| 17 | Achappa et al.2014         | 48.337997, 48.302814-48.37318                      |
| 18 | Summonu et al.2015         | 48.392574, 48.357368-48.427784                     |
| 19 | Robertson et al.2014       | 50.478935, 50.439026-50.518841                     |
| 20 | Chan et al.2016            | 48.652199, 48.616936-48.687466                     |
| 21 | Cysique et al.2010         | 48.723553, 48.688022-48.7589                         |
| 22 | Harezlaket et al.2011      | 48.468979, 48.43346-48.504494                        |
| 23 | Nakasuja et al.2012        | 48.270924, 48.235588-48.306259                       |
| 24 | Robertson et al.2007       | 46.92638, 46.889656-46.963104                       |
| 25 | Chan et al.2019            | 48.440395, 48.40519-48.475601                        |
| 26 | Kabuba et al.2016          | 48.73357, 48.698093-48.769051                       |
| 27 | Yechoor et al.2016         | 48.604374, 48.568996-48.639748                       |
| 28 | Nakku et al.2013           | 47.618401, 47.582355-47.654449                      |
| 29 | Troncoso et al.2015        | 48.415298, 48.380005-48.450592                      |
| 30 | Fasel et al.2014           | 48.41259, 48.377434-48.447746                       |
| 31 | Oshinaike et al.2012       | 48.360401, 48.324974-48.395828                      |
| 32 | Atashili et al.2013        | 47.850132, 47.814709-47.885555                      |
| 33 | Bonnet et al.2013          | 48.135502, 48.099808-48.171196                      |
| 34 | Simioni et al.2010         | 48.149261, 48.113976-48.184547                      |
| 35 | Saini et al.2014           | 48.55426, 48.519024-48.589497                       |
| 36 | Webb et al.2016            | 48.673512, 48.637695-48.709328                      |
| 37 | Yusuf et al.2017           | 49.084835, 49.049297-49.120373                      |
| 38 | McNamara et al.2016        | 48.30397, 48.267956-48.339989                       |
| 39 | Muniyandi et al.2012       | 48.421654, 48.386478-48.456829                      |
| 40 | Mugendi et al.2019         | 47.994511, 47.959171-48.02985                       |

**Key:** HAND: HIV associated neurocognitive disorders

**Table 4:** Characteristics of associated factors for HIV associated neurocognitive disorders in HIV/AIDS patients by their Odds ratio, Confidence interval, association strength, author and year of publication.
| Associated factors | Odds ratio (AOR) | 95% CI       | Strength of association | Author, year of publication |
|--------------------|-----------------|--------------|-------------------------|----------------------------|
| Age of 50 years and older | 4.85            | 2.34, 10.03  | Strong and positive     | Pinheiro et al. 2016       |
| Less than eight years of education | 6.72            | 3.98, 11.32  | Strong and positive     | Pinheiro et al. 2016       |
| Non-white skin color | 1.71            | 1.04, 2.83   | Moderate and positive   | Pinheiro et al. 2016       |
| Depression          | 1.96            | 1.12, 3.42   | Moderate and positive   | Pinheiro et al. 2016       |
| Duration of HIV infection > 5 years | 3.1             | 1.70, 7.40   | Strong and positive     | Elham et al. 2020          |
| Low level of education | 1.2             | 1.04, 1.44   | Weak and positive       | Ahmad M. Yakasai et al. 2015 |
| Late clinical stage of the illness | 4.2             | 1.19, 14.44  | Strong and positive     | Tilahun B et al. 2017      |
| Impairment in the activity of daily living | 7.19            | 1.73, 21.83  | Strong and positive     | Tilahun B et al. 2017      |
| CD4 count of 500 cells/dl or less | 2.368           | 1.524, 3.680 | Moderate and positive   | Tsegaw et al. 2017         |
| No formal education | 4.287           | 2.619, 7.016 | Strong and positive     | Tsegaw et al. 2017         |
| Poor medication adherence | 1.487           | 1.010, 2.180 | Weak and positive       | Tsegaw et al. 2017         |
| Older age           | 3.309           | 1.259, 8.701 | Strong and positive     | Tsegaw et al. 2017         |
| 6 to 10 Negative life events | 2.14            | 1.45, 3.15   | Moderate and positive   | Nakku et al. 2013          |
| 11 ad more Negative life events | 2.35            | 1.33, 4.13   | Moderate and positive   | Nakku et al. 2013          |
| Medium Stress Score index (score 1-10) | 2.55            | 1.73, 3.77   | Moderate and positive   | Nakku et al. 2013          |
| High Stress Score index (score >10) | 3.29            | 1.99, 5.45   | Strong and positive     | Nakku et al. 2013          |
| Female gender       | 2.66            | 1.22, 5.82   | Moderate and positive   | Troncoso & Conterno 2015   |
| Older age           | 2.87            | 1.24, 6.64   | Moderate and positive   | Troncoso & Conterno 2015   |
| Co-morbid medical illness | 2.56            | 1.17, 5.55   | Moderate and positive   | Troncoso & Conterno 2015   |
| CD4 count <200 cell/mm3 | 2.71            | 1.25, 5.86   | Moderate and positive   | Troncoso & Conterno 2015   |
| Highest prior VL >100,000 copies/ml | 2.62            | 1.12, 6.16   | Moderate and positive   | Troncoso & Conterno 2015   |
| Low level of education | 8.33            | 3.85, 16.67  | Strong and positive     | Atashili et al. 2013       |
| Having HIV symptoms | 12.16           | 3.08, 48.05  | Strong and positive     | Atashili et al. 2013       |
| Advanced AIDS stage | 4.87            | 1.59, 14.90  | Strong and positive     | Bonnet et al. 2013          |
| Technical school level of education | 2.16            | 1.31, 3.55   | Moderate and positive   | Bonnet et al. 2013          |
| Lower than diploma level of education | 3.39            | 1.48, 7.80   | Strong and positive     | Bonnet et al. 2013          |
| Generalized anxiety symptoms | 2.99            | 1.67, 5.14   | Strong and positive     | Bonnet et al. 2013          |
| Depression symptoms | 2.11            | 1.23, 3.63   | Moderate and positive   | Bonnet et al. 2013          |
| History of neurological disease | 2.05            | 1.18, 3.58   | Moderate and positive   | Bonnet et al. 2013          |
| African country of birth | 11.075          | 4.94, 24.84  | Strong and positive     | McNamara et al. 2016       |
| Use of benzodiazepines | 6.746           | 2.37, 19.18  | Strong and positive     | McNamara et al. 2016       |
| Unemployed | 2.16           | 1.2, 3.84    | Moderate and positive   | McNamara et al. 2016       |
| Body mass index< 16 kg/m² | 4.39            | 1.60, 12.02  | Strong and positive     | Debalkie Animut M et al. 2019 |
| Unemployed status of occupation | 3.18            | 1.752, 5.777 | Strong and positive     | Debalkie Animut M et al. 2019 |
| Advanced stage of AIDS | 3.56            | 1.406-9.006  | Strong and positive     | Debalkie Animut M et al. 2019 |

**Table:** Characteristics of associated factors for HIV associated neurocognitive disorders in HIV/AIDS patients by their Odds ratio, Confidence interval, association strength, author and year of publication (continued).
| Associated factors                                                                 | Odds ratio(AOR) | 95% CI       | Strength of association | Author, year of publication |
|-----------------------------------------------------------------------------------|-----------------|--------------|-------------------------|----------------------------|
| Depression                                                                        | 7.47            | 1.69, 43.53  | Strong and positive     | A. G. Mugendi et al.2019    |
| Female gender                                                                     | 2.17            | 1.02, 4.71   | Moderate and positive   | A. G. Mugendi et al.2019    |
| Older age                                                                         | 3.1             | 1.3, 7.4     | Strong and positive     | Yitbarek et al.2019         |
| Plasma HIV-1 RNA load between 1.7log10 and 3log10 copies/ml                       | 2.2             | 1.1, 4.3     | Moderate and positive   | Yitbarek et al.2019         |
| Plasma HIV-1 RNA load ≥ 3log10 copies/ml                                           | 7.5             | 2.6, 21.5    | Strong and positive     | Yitbarek et al.2019         |
| Khat chewing                                                                      | 4.4             | 2.3, 8.3     | Strong and positive     | Yitbarek et al.2019         |
| Advanced stage of AIDS                                                            | 5.6             | 1.7, 19.2    | Strong and positive     | Yitbarek et al.2019         |
| Having no education                                                               | 3.11            | 1.37, 7.04   | Strong and positive     | T B Mossie et al 2014       |
| Older age                                                                         | 4.25            | 1.05, 17.18  | Strong and positive     | T B Mossie et al 2014       |
| Having co morbid opportunistic infection                                          | 7.48            | 4.1, 13.64   | Strong and positive     | T B Mossie et al 2014       |
| Substance use                                                                     | 4.64            | 2.3, 9.36    | Strong and positive     | T B Mossie et al 2014       |
| Having no education                                                               | 5.16            | 2.20, 12.07  | Strong and positive     | Araya et al.2020            |
| Primary education                                                                 | 3.29            | 1.46, 7.29   | Strong and positive     | Araya et al.2020            |
| Having a CD4 count (cells/μl) ≤ 500                                               | 1.61            | 1.11, 2.39   | Moderate and positive   | Araya et al.2020            |
| Lifetime use of tobacco                                                           | 2.4             | 1.44, 4.01   | Moderate and positive   | Araya et al.2020            |

Key: AIDS: Acquired Immune deficiency Syndrome