Journal of Neuroinfectious Diseases
ISSN: 2314-7326

Neuroinfectious Diseases

¬ ¯ ¹ ¯ Á ¯ · • ³ ¡ Â Ã Ã º ½ · ¼ ´ ³ ± Â — · Á
¶ Â Â ¾ ² Æ ² ½ · ½ À µ

Review Article Open Acces

Keywords: HIV; Symptomatic neurocognitive disorders; Mortality; Survival; Systematic review; Meta-analysis

Abbreviations: AIDS: Acquired Immune De ciency Syndrome; ADC: AIDS Dementia Complex; AAN: American Academy of Neurology; ANI: Asymptomatic Neurocognitive Impairment; ART: Antiretroviral erapy; CNS: Central Nervous System; CPE: CNS Penetration E ectiveness; CSF: Cerebrospinal Fluid; COWAT: controlled oral word association test; CD4: Cluster of Di erentiation; CI: Condence Interval; ddi: Didanosine; ddC: Zalcitabine; d4T: Stavudine; FEM: Fixed E ect Model; HAART: Highly active Antiretroviral erapy; HCV: Hepatitis C virus; HIV: Human Immunode ciency Virus; HIV+-HIV Seropositive; HAND: HIV-associated Neurocognitive Disorders; HAD: HIV-associated Dementia; HIVD: HIV Dementia; HIVE: HIV Encephalopathy; HR: Hazard Ratio; NCI: Neurocognitive Impairment; MeSH: Medical Sub-heading; MND: Mild Neurocognitive Disorder; MCMD: Minor Cognitive Motor disorder; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; REM: Random E ects Model; RR: Relative Risk; SSA: Sub: Saharan Africa; SNCD: Symptomatic Neurocognitive Disorders; SE: Standard Error; 3TC: Lamivudine; WAIS: Weischler Adult Intelligence SCALE; WMS: Weischler Memory Scale; ZDV: Zidovudine

Introduction

Neurocognitive alterations in HIV-1 infection have been recognized since the beginning of HIV epidemic. Several terminologies were initially used to describe it: ADC, HIVE, subacute encephalitis, AIDS-related dementia, HAND and HIVD. ese conditions were clinically de ned and represent the same disease with di erent severity. e AAN 1991 criteria was developed to provide a consensus nomenclature for both clinical and epidemiological purposes [1]. Subsequently it was reviewed in 2007 incorporating severity, functional impairment and effect of confounders to develop an algorithm for identifying HAND [2]. Most notable change was recognition of ANI.

*Corresponding author: Yakasai AM, Public Health and Diagnostic Institute, College of Medical Sciences, Northwest University, Kano, Nigeria, Tel: +234 806 541 9097; E-mail: mailto:ahmadmaifada@gmail.com

Received October 20, 2014; Accepted December 18, 2014; Published December 20, 2014

Citation: December

importance of SNCD in relation to mortality [6]. In that classi cation ADC was found to have a moderate impact on mortality among HIV+ subjects. Despite e orts to grade HIV-associated neurocognitive syndromes and explore their impact on mortality, the magnitude and risk of mortality remains unclear due to variability in reported gures. In pre-HART era the RR of mortality from SNCD ranged from 1.47 to 6.40 while in post-HAART era the HR of mortality associated with SNCD ranged from 1.0 to 6.1 [3,5,7,10]. We conducted this meta-analysis to derive pooled estimates of the risk of mortality as a result of SNCD.

Methodology

Relevant English language publications on HIV- related SNCD and risk of mortality were searched for electronically in data bases. ese included MEDLINE, Google scholar, the Cochrane data base, PsycINFO and EMBASE. Manual search of the references of relevant articles identi ed, systematic reviews and dissertations was also done. MeSH terms used in electronic search included 'HIV', 'Neurocognitive disorders', 'HIV-associated Neurocognitive disorders', 'HIV-associated Dementia', 'Mild Neurocognitive Disorder, 'Minor Cognitive Motor Disorder, 'HIV Dementia', 'AIDS dementia complex', 'HIV-encephalopathy', 'Subacute encephalitis', 'Neurocognitive impairment', 'Dementia', 'Neurocognitive dysfunction', 'Neuropsychological impairment', 'Acquired Immune De ciency Syndrome', 'mortality', 'death' and 'survival'. ese MeSH terms were applied in di erent combinations to search for relevant publications up to April 2014. is meta-analysis adhered to the guidelines of PRISMA statements [11].

Inclusion and Exclusion Criteria

All the studies identi ed for possible inclusion in the meta-analysis were reviewed independently by two assessors. Whenever disagreement was encountered a third reviewer was consulted for clari cation. Studies were included if they satis ed the following criteria.

1) HIV- related SNCD was reported.

2) E ect measure of mortality risk was reported or could be calculated from available data. For studies that provided risk of death for each neurocognitive domain without overall risk, data for psychomotor speed was extracted [5]. is is because psychomotor speed is commonly and consistently altered in HIV+ patients early in the disease and has been shown to predict development of dementia, AIDS and death [10]. Studies were excluded if they involved adolescents, had no required data or not meeting any of the inclusion criteria.

Extraction of Data

Information from relevant studies was collected on a Microso excel spread sheet. Subsequently relevant data was extracted for the meta-analysis.

Data Analysis

Hazard Ratios (HR) or Relative Risk (RR) of mortality among HIV+ subjects with SNCD were obtained from included studies. Log HR, log RR, SE of log HR and SE of log RR were computed for all the included studies. One study provided adjusted RR without con dence intervals hence unadjusted RR with 95% CI was calculated from the raw data available [10]. For studies that provided adjusted and unadjusted HR or RR, the adjusted e ect measure is selected. Two parallel meta-analyses [12] were done to derive pooled estimates of HR and RR of mortality among patients with HIV-related SNCD. e probability of subjects with SNCD dying rst as compared to those without SNCD was derived from the estimated HR using appropriate formula [13]. Effect measures derived from subgroup analyses were compared for statistical signi cance using test of interaction [11]. We assessed clinical and methodological heterogeneity via subgroup analyses while statistical heterogeneity was explored using Cochran's Q test and I-squared (I^2) statistic. Between-study heterogeneity was considered substantial when I^2 is greater than 50%. Begg's and Egger's tests were employed to assess small study e ect and publication bias [14,15]. Funnel plot derived from these tests and Galbraith plot were also used to visually assess publication bias. When heterogeneity is signi cant a REM is used to derive pooled estimates otherwise a FEM is used. e relationship between study-level covariates (CD4 count, age, proportion of female subjects, follow-up duration, sample size and proportion of subjects with AIDS and risk of death was analyzed using univariable weighted random e ects meta-regression. Quality of included studies was also assessed. Statistical analysis was done with Stata version 10.0 (Stata Corp., College Station, TX, USA).

Characteristics of Included Studies

As shown in Figure 1, thirteen studies (including 2 sub-studies) met the inclusion criteria and their sociodemographic, clinical and neuropsychological characteristics are given in Tables 1 and 2 [3-10,13,14,16-20]. ey all had satisfactory quality as indicated in Table 3. One study provided data for subjects with and without virological failure [11] and another study provided data for pre- HAART and post- HAART era [19]. All the studies were conducted in Europe and America. ree

Figure 1: Flow diagram for selecting studies for systematic review and meta-analysis.

HIVE or ADC) the REM pooled estimate of HR (95% CI) of mortality among HIV+ subjects was 2.50 (2.07-3.03) [3,6,17,19,20]. e FEM estimate of HR (95% CI) of mortality pooled from 2 studies that assessed both mild and severe forms of SNCD (MCMD and HAD) was 2.83 (1.81-4.42) [7,8].

Studies that used age-, sex- and education-adjusted normative data to rate and classify neuropsychological test scores yielded mortality HR (95% CI) of 3.16 (2.09-4.78) [3,4,7,8]. ose studies that did not use demographically adjusted normative scores for establishing the diagnosis of SNCD yielded HR (95%) of mortality of 2.44 (2.02-2.94) [5,6,10,17,20]. Comparison of these estimates via test of interaction yielded ratio of HR=1.3, 95% CI=0.675-1.670, p=0.887.

Meta-regression

Figure 4 shows the signi cant relationship between risk of death and declining CD4 count. Other study-level parameters including proportion of female subjects, age, sample size and duration of follow-up were not associated with risk of mortality (respective p-values were 0.273, 0.445, 0.724 and 0.266).

Discussion

ese meta-analyses involved 84 421 HIV+ individuals across 21 countries from Europe and America. In the absence of publication bias we found both HR and RR of mortality among HIV+ subjects with SNCD to be more than twice that of neurocognitively unimpaired HIV+ subjects. ese two e ect measures should be interpreted with caution as di erences exist between them. A HR of 2.1 means that at any point in time HIV+ subjects with SNCD have more than twice chance of dying as compared to unimpaired HIV+ subjects. On the other hand RR of 2.46 indicates that among HIV+ subjects the risk of mortality among those with SNCD is more than twice that of subjects without SNCD. Nonetheless, a relationship does exist between HR and RR. e similarity or di erences between these two e ect measures is determined by a combination of 3 factors; duration of follow-up, risk of exposed group relative to unexposed group and rate of occurrence of desired event/outcome. When the follow-up duration is short and rate at which events occur is small, these two e ect measures tend to approximate each other and their convergence increases with reducing product of the 3 determining factors [21].

e course of HIV- related neurocognitive disorders has been modi ed by HAART. Following the introduction of HAART in 1996 the incidence of ADC has reduced while its prevalence has increased due to prolonged survival a er diagnosis. At CD4 count <100 cells/ml in pre-HAART era subjects with ADC had 5 months median survival duration. However, at the same CD4 count in post- HAART era the median survival duration was 38 months [22]. In Australia 4 fold survival bene t was reported for ADC as against 2 fold for other NeuroAIDS diseases [23]. Despite the documented bene ts of HAART in management of NeuroAIDS, patients with SNCD still had higher risk

Author/ publication year	Neurocognitive syndrome assessed	Criteria	Neurocognitive domains assessed							
			SIP	Motor	Attention/ WM	Memory	9 H U E Ð OE Ècy	Executive function	Learning	Visuospatial construction
Vivithanaporn 2010 [20]	MCMD/ HAD	AAN 1991	NA	NA	NA	NA	NA	NA	NA	-
Sevigny 2007 [5]	HIV-D	AAN 2007	+	+	-	+	+	-	-	-
Tozzi 2005 [19]a	MCMD/ HIV-D	AAN 1991	+	-	+	-	+	+	-	-
Tozzi 2005 [19]b	MCMD/ HIV-D	AAN 1991	+	-	+	-	+	+	-	-
Chaisson 1998 [14]	ADC	NA	NA	NA	NA	NA	NA	NA	NA	-
Conti 2000 [15]a	HIVE	NA	NA	NA	NA	NA	NA	NA	NA	-
Conti 2000 [15]b	HIVE	NA	NA	NA	NA	NA	NA	NA	NA	-
Mocroft 1997 [17]	ADC	NA	NA	NA	NA	NA	NA	NA	NA	NA
ART-CC 2009 [4]	ADC	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ellis et al. 1997 [16]	MCMD	AAN 1991	-	+	+	+	+	+	+	-
Mayeux 1993 [6]	MCMD	AAN 1991	+	+	+	+	+	+	+	+
Sacktor 1996 [9]	NCI*	AAN 1991	+	+	+	+	+	+	+	+
Wilkie 1998 [7]	NCI*	NA	+	-	-	+	+	-	+	+
Hutchinson 1997 [21]	ADC	NA	+	-	-	+	-	-	+	-
Petruckevitch 1998 [18]	ADC	NA	NAA	NA	NA	NA	NA	NA	NA	NA

ART-CC- Antiretroviral therapy Cohort Collaboration, SIP- Speed of information processing, ADC- AIDS dementia complex, HIVE- HIV encephalopathy, MCMD- Minor cognitive motor disorder, HIV-D- HIV dementia, HAD- HIV-associated dementia, NA- not available, HR- Hazard Ratio, RR- Relative Risk, AAN- American Academy of 1HXURORJ\ FULWHULD :0 :RUNLQJ PHPRU\ 1&, 1HXURFRJQLWLYH LPSDLUPHQW 1&, GH¿QHG DV VXVW

Table 2: Neuropsychological characteristics of included studies.

Citation: Yakasai AM, Muhammad H, Ibrahim A, Owolabi LF, Dalhat MM (2014) Impact of Symptomatic HIV- Related Neurocognitive Disorders in Survival of HIV- Infected Individuals: A Systematic Review and Meta-Analyses. J Neuroinfect Dis 5: 166. doi:10.4172/2314-7326.1000166

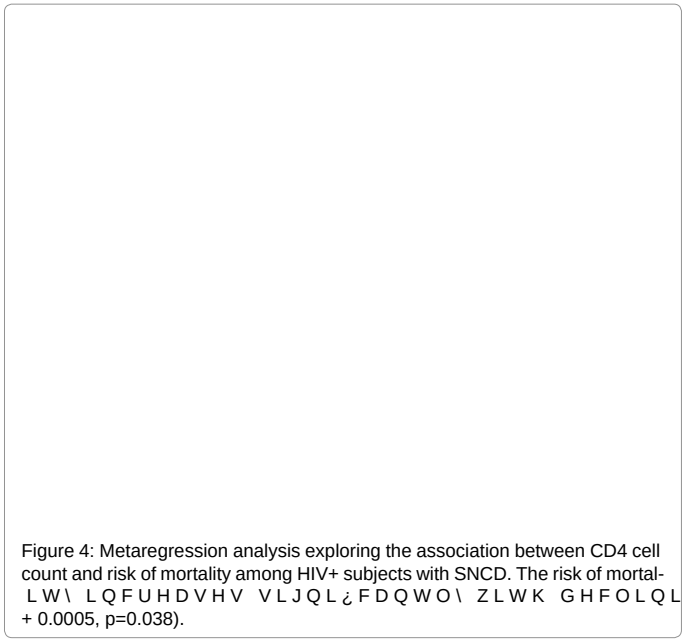

Figure 4: Metaregression analysis exploring the association between CD4 cell count and risk of mortality among HIV+ subjects with SNCD. The risk of mortality increases significantly with decreasing CD4 cell count (coefficient = + 0.0005, p=0.038).

acterize the pattern and magnitude of neurocognitive de cits in HIV+ patients with increased risk of mortality.

Our ndings should be interpreted within the limits of the meta-analyses. e e ect of clade diversity has been mentioned above.

17. Mocroft AJ, Lundgren JD, Monforte AD, Ledergerber B, Barton SE, et al. (1997) For the AIDS in Europe study group. Survival of AIDS patients according to W\SH RI $,'6 GH¿QLQJ HYHQW ,QWHUQDWLRQDO -RXUQDO RI 6RFLDO 0HGLFLQH

18. Petruckevitch A, Del Amo J, Phillips AN, Johnson AM, Stephenson J, et al. 'LVHDVH SURJUHVVLRQ DQG VXUYLYDO IROORZLQJ KLY VHURFRQYHUVLRQ HYLGHQFH IURP D FRKRUW VWXG\ RI +,9 VXEMHFWV LQ /RQGRQ $,'6 12: 1007-1013.

19. Conti S, Masocco M, Pezzoti P, Toccaceli V, Vichi M, et al. (2000) Differential impact of combined antiretroviral therapy on the survival of Italian patients with VSHFL¿F $,'6 GH¿QLQJ LOOQHVVHV -RXUQDO RI $FTXLUHG ,PPXQH 'H¿FLHQF\ 6\QGURPHV

20. Chaisson RE, Gallant JE, Keruly JC, Moore RD (1998) Impact of opportunistic disease on survival in patients with HIV infection. AIDS 12: 29-33.

21. Symons MJ, Moore DT (2002) Hazard rate ratio and prospective epidemiological studies. J Clin Epidemiol 55: 893-899.

22. Dore GJ, McDonald A, Li Y, Kaldor JM, Brew BJ, for the national HIV surveillance committee. (2003) Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS 17:1539 -1545.

23. Dore GJ, Li Y, McDonald A, Ree H, Kaldo JM, for the national HIV surveillance committee. (2002) Impact of highly active antiretroviral therapy on individual $,'6 GH¿QLQJ LOOQHVVHV LQFLGHQFH DQG VXUYLYDO LQ $XVWUDOLD 'H¿FLHQF\ 6\QGURPHV

24. &KULVWR 33 *UHFR '% $OHL[R $: /LYUDPHQWR -$)DFWRUV LQIXHQFLQJ FHUHEURVSLQDO ÀXLG DQG SODVPD +,9 51$ GHWHFWLRQ UDWH LQ SDWLHQWV ZLWK DQG without opportunistic neurological disease during the HAART era. BMC Infectious Diseases 7:147.

25. Baeten JM, Chohan B, Lavreys L, Chohan V, McClelland RS, et al. (2007) HIV-1 subtype D infection is associated with faster disease progression than subtype A in spite of similar plasma HIV-1 loads. J Infect Dis 195: 1177-1180.

26. Kiwanuka N, Laeyendecker O, Robb M, Kigozi G, Arroyo M, et al. (2008) Effect of human immunodeficiency virus type 1 subtype on disease progression in persons from Rakai, Uganda, with incident HIV-1 infection. J Infect Dis 197: 707-713.

27. Sacktor N, Nakasujja N, Skolasky RL, Rezapour M, Robertson K, et al. (2009) HIV subtype D is associated with dementia, compared with subtype A, in immunosuppressed individuals at risk for cognitive impairment in Kampala, Uganda. Clin Infect Dis 49: 780-786.

28. Price RW, Yiannoutsos CT, Clifford DB, Zaborski L, Tselis A, et al. (1999) Neurological outcomes in late HIV infection: adverse impact of neurological impairment on survival and protective effect of antiviral therapy. AIDS Clinical Trial Group and Neurological AIDS Research Consortium study team. AIDS 13: 1677-1685.

29. Altman DG, Bland JM (2003) Interaction revisited: the difference between two estimates. BMJ 326: 219.

30. Staehelin C, Rickenbach M, Low N, Egger M, Ledergerber B, et al. (2003) Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: access to antiretroviral therapy, disease progression and survival. AIDS 17: 2237-2244.

31. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, et al. (2002) HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? AIDS 16: 597-603.

Citation: Yakasai AM, Muhammad H, Ibrahim A, Owolabi LF, Dalhat MM (2014) Impact of Symptomatic HIV- Related Neurocognitive Disorders in Survival of HIV- Infected Individuals: A Systematic Review and Meta-Analyses.