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Profile of Neurocognitive Impairment in Individuals Coinfected with Human Immunodeficiency Virus and Hepatitis C Virus: Meta-analysis and Meta-regression

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Authors' contributions

This work was carried out in collaboration between all authors. Author AMY designed the study, performed the statistical analyses, wrote the protocol and wrote the first draft of the manuscript. Authors HM, IMY, HS, AMN, MN, AA, JAY and NI managed the literature searches. Authors AI and MIG managed the data extraction. Authors ZGH, AS, BGI, AMS and UT managed the analyses of the study. Author AGH cross checked the statistical analyses and interpreted the data. All authors read and approved the final manuscript.

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ABSTRACT

HIV and HCV are neurotrophic viruses with great potential to cause neurocognitive impairments (NCI). Yet, results of neuro studies among Coinfected individuals are still inconclusive. This study pooled estimates to define the neurocognitive profile and neuroepidemiology of Coinfection in relation to monoinfection. Data from the qualified studies was grouped in to seven neurologic domains to yield weighted average effect sizes (WAES) which were pooled together in meta-analyses. Further assessments were meta-regression analysis, sensitivity analysis and computation of heterogeneity diagnostic indices. From eleven studies the pooled estimates showed that only the Coinfected group had a medium effect size (ES) in speed of information processing (SIP). Other neurologic domains exhibiting a medium ES across all the study groups were executive function (EF) and attention/working memory. These neurocognitive deficits epidemiologically translates in to NCI prevalence of 47% among Coinfected group who were also twice more likely to be neurocognitively impaired compared to HIV monoinfection group. Despite substantial heterogeneity, Kernel density plot of WAES approximates to normal distribution making publication bias unlikely. Coinfection is associated with deficit in SIP, EF and attention/working memory with substantial risk of global NCI underscoring the need for medical and psychosocial interventions to improve the lives of affected individuals.

Keywords: Neurocognitive impairment; HIV; HCV; coinfection; meta-analysis; meta-regression; systematic review.

1. INTRODUCTION

Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV) shared several neurological characteristics such as cerebral metabolic derangements [1], invasion of brain parenchyma [2], high levels of neurotoxic proteins [3] and frontostriatal pattern of cognitive dysfunction [4,5]. Coinfection with these two viruses is seen in about 16 to 40% of HIV infected individuals [6]. This group of patients dually infected with these two viruses experience neuropsychological disturbances as a result of neuronal injury and neuronal network disruption from the neurotrophic viruses [6].

HIV-associated neurocognitive diseases have been extensively studied [7,8] and the American Academy of Neurology in 2007 proposed definitions to uniform future researches [9]. While this algorithm has led to the establishment of a large pool of studies in HIV neuroscience [7], HCV and HIV/HCV Coinfection neuro studies are still few. To speed up understanding of HCV neurology, HIV neuropsychological researches have been proposed to serve as role model for HCV neuropsychological research [10]. In the interim period before arrival of more studies on HIV/HCV coinfection neuropsychology, there is need to synthesize information from available studies to see whether the aforementioned clinical and neuropathological characteristics shared by the two neurotrophic viruses translates in to similar or differing neurocognitive profile and degree of neurocognitive deficits as well as functional impairments in Coinfected patients.

Three review studies have addressed the epidemiological aspect and the neuropsychological profile of neurocognitive impairment (NCI) mainly among HIV monoinfected individuals (HIVm) [7,8,11]. A study in 2005 reviewed the neuropsychology of Coinfection and could not conclude due to the heterogeneity of the few data analyzed [12]. Now more than a decade after, a recent review of cognitive function in Coinfected patients had estimated the severity of neurocognitive deficits by pooling estimates from four studies [13]. Although, the global deficit score utilized in that study is a good indicator of overall cognitive functioning, it is not very sensitive to milder degrees of NCI and may not identify impairments directly arising from HIV disease when there is heterogeneity [14]. Thus, to address these gaps in the neuropsychology and neuroepidemiology of Coinfection, we intend to utilize a holistic approach to systematically pool estimates while simultaneously pre-specifying and exploring sources of heterogeneity and confounders in a statistical manner. Emphasis will be made in quantifying the risk of NCI and defining the profile of the neurocognitive deficits to guide the medical and psychosocial management of Coinfected patients.

2. METHODS

2.1 Literature Search

Literature search was conducted up to 30th August 2015. Medical sub-heading (MeSH) terminologies for the study search were “HIV”, “HCV”, “Coinfection”, “Multiple infection”, “Dual infection”, “Monoinfection”, “Neurotrophic”, “Neuroinfection”, “Cognitive”, “Neurocognitive’, “Neuropsychological”, “Neuropathological”, ‘Impairment”, “Dysfunction” and “Domain”. These MeSH terminologies were combined in multiple formats for the study search in MEDLINE, Google scholar, PSYCHinfo, relevant journal websites (Infectious diseases, Neurology, Psychiatry, Psychology and Gastroenterology), relevant book chapters and other data bases. References of identified articles and dissertations were also manually searched.

2.2 Criteria for Study Selection

The following criteria were used to select studies for inclusion in the systematic review and meta-analyses;

1. Involved one or all of the following three study groups: HIV/HCV Coinfected; HIV monoinfected (HIVm); HCV monoinfected (HCVm);
2. NCI has been assessed and domains/tests reported.
3. Had provided sufficient data to extract effect size (ES), odds ratio (OR) or prevalence of NCI.
4. Involved adults (≥18 years old).

We excluded dissertations, reviews and other studies not meeting any of these criteria.

2.3 Determination of the Quality of Selected Studies and Strength of Conclusions/ Recommendations

The GRADE system was used to assess the quality of studies included in the meta-analysis. Here quality or strength of conclusions and recommendations could either be upgraded or downgraded accordingly. Reasons for upgrading include large effect size (ES) and absence of plausible confounding while down grading may result from inconsistency, lack of response gradient and plausible confounding among others. Given the expected large heterogeneity from the available studies and the multiple sources of confounding likely to be encountered, this system seems most appropriate for this meta-analysis [15,16].

2.4 Data Analysis

Before analyzing the data, two reviewers independently extracted all relevant information from the studies included in the meta-analyses. Final data for analysis was cross checked and standardized by a third reviewer.

2.4.1 Neuropsychological profile

The basic unit of statistical analysis was the Cohen’s *d* ES [17] computed for all the studies according to the neurocognitive domains tested. The ES provides an opportunity for having a uniform measure of performance of subjects (data harmonization) relative to controls that is comparable across studies. It generates an absolute value irrespective of the unit of measurement, type of tool used or definitional criteria applied. All ESs were coded in such a way that all positive values indicates better scores by the HIV and HCV negative comparator arm compared to the Coinfected, HIVm or HCVm groups. Depending on the number of tests administered in each neurocognitive domain in a study, weighted average effect size (WAES) is

computed for that domain using the formula outlined below [7,17-19]. Taking this domain weighted average ensures that the magnitude of the contribution of each study to the final estimate is determined by its degree of precision [20]. Subsequently similar analyses were done for all the included studies according to the neurocognitive domains tested. For the computed WAES, standard error (SE) and log of the WAES were generated for further analysis using the DerSimonian and Liard meta-analysis principles [21].

$$ES = (X1 - X2) / SP \quad (1)$$

$$SP = \sqrt{[(n1 - 1)s1^2 + (n2-1)s2^2] / (n1+n2-2)} \quad (2)$$

$$\text{Average weighted } ES = \sum (wiESi) / \sum wi \quad (3)$$

$$SE_{ES} = \sqrt{1 / \sum wi} \quad (4)$$

X1 and *X2* referred to the mean of the infection and comparator groups respectively, *n1* and *n2* referred to the respective sample size, *s1* and *s2* are the respective variance and SP indicates the square root pooled variance. *SE* is the standard error of the *ES*, wi indicates the inverse weight of the *ES* while i refers to the number of *ES*. The magnitude of an *ES* was defined according to the Cohen's guidelines (small = .20 – .40, medium = > .40 – .80 and large > .80) [17].

2.4.2 Meta-regression and subgroup analyses to explore sources of heterogeneity

The frame work of these analyses is provided by the study-level and participant-level characteristics known to affect neurocognitive function and they will be investigated as potential sources of significant heterogeneity. These include number of tests administered in each domain, NCI, proportion of female subjects, proportion of patients with Acquired immune deficiency syndrome (AIDS), antiretroviral therapy (ART) utilization, current CD4 count, nadir CD4 count, age, education, and viral load. This analysis employed random-effects meta-regression to provide residual maximum likelihood (REML) estimates. Other procedures to assess heterogeneity were sensitivity analysis, subgroup analysis and I^2-statistics. Higgins guidelines were used to classify the degree of statistical heterogeneity quantified by the I^2-statistics: small degree of heterogeneity when I^2 = 25%; moderate degree of heterogeneity when I^2 = 50%; large degree of heterogeneity when $I^2 \geq$ 75% [21]. For I^2 > 50% we used random effects model (REM) to pool estimates whereas for I^2 < 50% we used fixed effect model (FEM) to pool estimates. Publication bias was examined using Begg's and Egger's tests and only considered present when *P*- values in all the tests were ≤ .05 [22,23]. To further augment this assessment, exploratory data analysis was performed by plotting Kernel density estimates of WAES on background normal distribution curve for comparison to determine the extent of deviation from normality which could suggest the possibility of publication bias [24].

2.4.3 Estimation of OR and prevalence of NCI among the coinfected group

For all the studies with the relevant data or figures for extraction of desired data, we recorded the odds ratio (OR) of NCI using the numerator and denominator, log of the OR, SE of the Log OR and the 95% confidence interval (CI). The prevalence of NCI among Coinfected, HIVm and HCVm groups was determined by recording the numerator and denominator together with the log of the prevalence, SE of the prevalence and the respective 95% CI.

2.4.4 Grading strength of evidence (SOE)

SOE was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Here evidence is downgraded to one or two levels if there is publication bias, imprecision (random error), inconsistency (unexplained significant heterogeneity), indirectness (measuring intermediate or surrogate markers instead of patient-related direct outcomes) and study limitations (including sparse data defined as < 200 subjects analysed in a study) [15,16,25]. Quality of evidence is however upgraded to one or two levels when there is large ES and dose-response gradient. Plausible confounding could upgrade or downgrade quality of evidence depending on the direction of effect [15,16]. Because observational studies are generally considered to be of low quality, downgraded evidence becomes very low quality evidence and if upgraded it becomes moderate or high quality evidence. However, where evidence is neither downgraded nor upgraded, it remains a low quality evidence [15,16].

3. RESULTS AND DISCUSSION

3.1 Description of Included Studies

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) [26] flow chart for studies selection is shown in Fig. 1. Out of the 55 studies that were fully evaluated, 12 of them [27-38] satisfied the inclusion criteria and their characteristics are shown in Table 1. Three of the studies [29,34,35] were included in the meta-analyses to derive ES, OR and prevalence of NCI while 6 studies [27,30-33,36] had data for OR and NCI prevalence meta-analyses. Two studies [28,37] had data only for ES estimation and one study [38] had data only for NCI prevalence estimation. One study [28] had data for 4 sub-studies (2 each for Coinfection and HIVm groups depending on AIDS status). Overall, a total of 14 studies (and sub-studies) were included in the meta-analyses.

3.2 Characteristics of Subjects in the Included Studies

The range of the mean/median of the characteristics of the study subjects were: sample size (15 to 480); age (33.8 to 54.5 years); education (5.4 to 13.9 years); current CD4 count (164.7 to 530 cells/ml) and nadir CD4 count (181 to 301 cells/ml). Neuroimaging and cerebrospinal fluid (CSF) analysis were performed in some of the studies to exclude neuro-AIDS and other Central nervous system (CNS) opportunistic infections. Other exclusion criteria applied in the studies were neuropsychiatric diseases, depression, substance use, intravenous drug use (IVDU), epilepsy, head injury with loss of consciousness, pregnancy and liver diseases. Assessment of the severity of liver disease in the studies mainly employed the use of both invasive and noninvasive methods. Two of the included studies involved participants without liver disease [30,34] while in ten studies liver disease was either reported to be present or not assessed [27-29,31-33,35-38]. Adjustment for liver disease and other confounders of neuropsychological performance in multivariate analysis was done in some of the studies [27,28,33,38]. Across all the included studies computation of neuropsychological test scores was done by comparing scores of the study groups with that of controls or demographically adjusted published normative data. Other characteristics of the study subjects are provided in Table 2.

3.3 Meta-analyses

3.3.1 Neuropsychological profile of NCI

Table 3 contains the summary of WAES according to the neurocognitive domains. For the Coinfection group, medium ES was obtained in SIP, EF and attention/working memory domains whereas small ES was obtained in motor and verbal fluency/learning domains. Although large ES was found in motor and learning ability domains, the overlapping confidence limits reduce the reliability of these estimates. HIVm group had medium ES in attention/working memory domains and small ES in all the other domains. Similarly, HCVm group also had medium ES in attention/working memory but with additional medium ES in EF and memory domains. All other domains in HCVm group had small ES. There was no publication bias in these analyses as detected by Egger's and Begg's tests and further confirmed by Kernel density estimates plot which approximates to normal distribution (see Fig. 2). The SOE was moderate for SIP and EF in the Coinfection and HIVm groups. Other domains with moderate SOE in the HIVm group were memory, learning and verbal fluency domains. For the HCVm group moderate SOE was only found in the memory domain. As shown in Table 3, sparse data is the commonest reason for downgrading the SOE across all the study groups. However, among the Coinfection and HIVm groups SOE was further downgraded due to imprecision.

3.3.2 OR and prevalence of NCI among the coinfected group

The REM derived OR (95% CI) of NCI among the coinfected group was 1.88 (1.11 – 3.18) with significant heterogeneity (1^2 = 76.5%, P < .0001) but no publication bias (Begg's P = .18 and Egger's P = .001). In sensitivity analysis none of the study estimate unduly weighed on the derived OR of NCI.

From ten studies [27,29,30-36,38] the REM derived prevalence (95% CI) of NCI among the Coinfected subjects was 47.3% (32% – 63%) with significant heterogeneity (1^2 = 98%, P < .0001) but no publications bias (Begg's P = .42 and Egger's P = .49). In subgroup analysis, NCI prevalence estimates based on presence [26,27,32,34,36,37] or absence of liver disease [30,34] were 44.4% and 58.8% respectively (P = .03). There was significant heterogeneity but no publication bias detected.

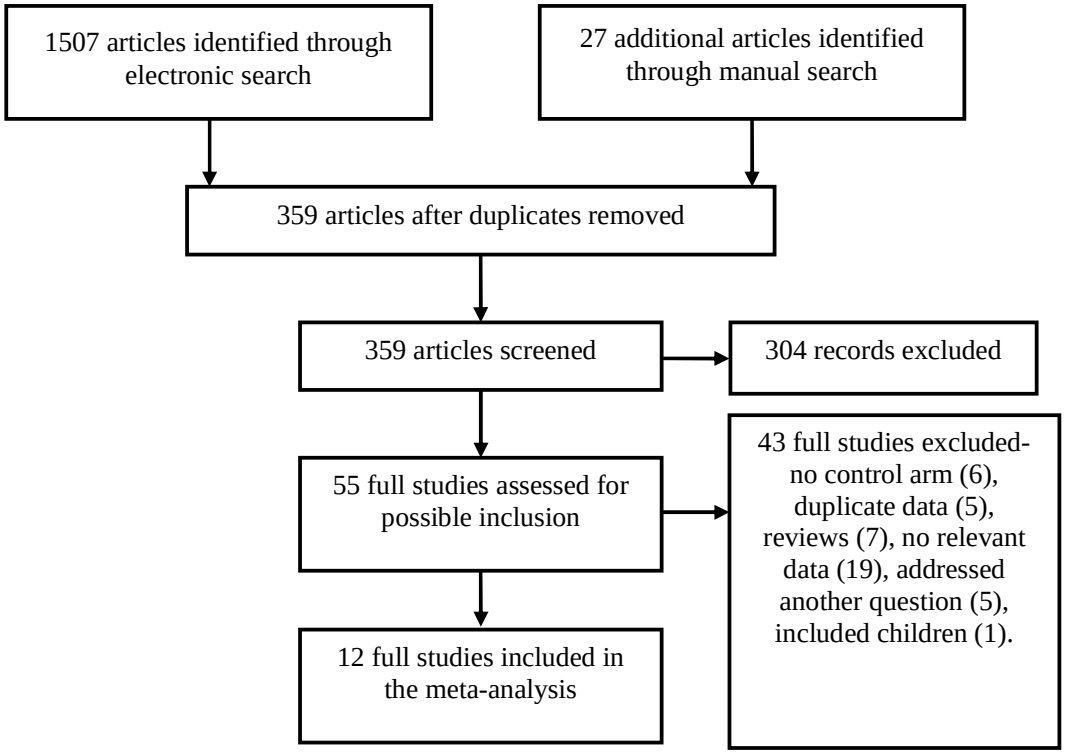

Fig. 1. Flow chart indicating how studies were identified, screened and selected for the systematic review and meta-analysis

3.4 Meta-regression

Among the Coinfected group WAES significantly increases with increasing age (*P* = .02, slope coefficient = .015 to .06). There was a non-significant association between WAES and years of education, sample size, proportion of female subjects, nadir CD4 count and proportion of subjects with AIDS. Among the HIVm group, WAES significantly increases with increasing sample size (*P* = .03, slope coefficient = .0005 to .0002) while non-significant associations were seen with the other pre-specified covariates.

3.4.1 Meta-analysis paradox

In the Coinfected group WAES increases with increasing ART utilization (*P* = .03, slope coefficient = .003 to .001) and current CD4 count (*P* = .04, slope coefficient = .001 to .0006). For the HIVm group, WAES decreases with increasing proportion of subjects with AIDS (*P* = .03, slope coefficient = -.002 to .001) and increases with increasing nadir CD4 count (*P* = .01, slope coefficient = .002 to .001). In the HCVm group, WAES significantly increases with increasing current CD4 count (*P* = .01, slope coefficient = .0005 to .0001).

4. DISCUSSION

This study defines the neurocognitive profile and neuroepidemiology of HIV/HCV Coinfected and monoinfected individuals using meta-analytic and meta-regression principles. The pooled estimates showed that only the Coinfected group had a medium ES in SIP domain. Across all the study groups medium ES was found in EF and attention/working memory domains while small ES was found in motor and verbal fluency/learning domains. SOE for the derived ES estimates among the Coinfected group ranged from very low in attention, memory and learning domains to moderate in SIP and EF domains. The estimated neurocognitive deficits epidemiologically translates in to NCI prevalence of 47% among the Coinfected group who were also twice more likely to be neurocognitively impaired compared to the HIVm group.

Table 1. Baseline characteristics of included studies

Author	Study design	Groups (*n*)	Comments/ sources of bias
Clifford et al. 2005 [27]	Cross-sectional	Coinfection-30, HIVm-234	HIVm group significantly more educated than the coinfection group. Coinfected subjects had significantly higher liver enzymes elevation and rate of depression compared to HIVm.
Crystal et al. 2012 [28]	Cross-sectional	Coinfection (88 AIDS, 96 non-AIDS), HIVm (480 AIDS, 241 non-AIDS), HCVm (42), control (392)	In comparison with the control group, all the other groups had significant CSU and/or IVDU.
Heaton et al. 2008 [29]	Cross-sectional	Coinfection (93), HIVm (108), HCVm (51), control (141)	Significantly more AIDS cases, ART use and DVL in HIVm compared to coinfection group.
Hinkin et al. 2008 [30]	Cross-sectional	Coinfection (35), HIVm (83)	Subjects had no cirrhosis but had advanced HIV disease. Groups had similar sociodemographic characteristics.
Parsons et al. 2006 [31]	Prospective	Coinfection (20), HIVm (45)	All groups had HIV DVL and significantly differed in ethnicity, education, heroin use and cocaine use.
Richardson et al. 2005 [32]	Cross-sectional	Coinfection (70), HIVm (75), HCVm (27), control (48)	Provided only OR and prevalence of NCI without raw cognitive scores. Groups were not well matched for age and education.
Ryan et al. 2004 [33]	Cross-sectional	Coinfection (67), HIVm (49)	Subjects had advanced AIDS with DVL. Liver severity indices do not influence scores. Coinfected were significantly older than HIVm group.
Sun et al. 2013 [34]	Cross-sectional	Coinfection (17), HIVm (14), HCVm (19), control (28)	Subjects had no cirrhosis and the control group were significantly more educated. All HIV infected subjects had UVL while all HCV infected had DVL.
Vivithanaporn et al. 2012 [36]	Prospective	Coinfection (91), HIVm (356)	Among subjects screened for NCI coinfected were significantly older than HIVm. All groups had HIV DVL and similar liver function.
Thein et al. 2007 [35]	Prospective	Coinfection (15), HIVm (30), HCVm (19), control (30)	Included subjects with chronic HCV infection. Excluded decompensated cirrhosis, PLCC and non-HCV liver disease. Coinfection and HCVm groups had high IQ hence could not detect NCI. Also they had HCV DVL.
Devlin et al. 2012 [37]	Cross-sectional	Coinfection (42), HIVm (73), HCVm (9), control (63)	Included subjects with active HCV infection. HCVm and the control groups were significantly more educated than the coinfection and HIVm groups. All subjects had significant rate of life time substance use.
Cherner et al. 2005 [38]	Cross-sectional	Coinfection (48), HIVm (174), HCVm(35), control (90)	Coinfected were significantly older and less educated with higher liver function derangement compared with HIVm group.

AIDS = Acquired immune deficiency syndrome; ART = Antiretroviral therapy; CSU = Current substance use; DVL = Detectable viral load; HCVm = Hepatitis C virus monoinfected; HIVm = Human immunodeficiency virus monoinfected; IQ = Intelligence quotient; IVDU = Intravenous drug use; n = number of subjects tested; NCI = Neurocognitive impairment; OR = Odds ratio; PLCC = Primary liver cell carcinoma; UVL = Undetectable viral load

Our finding of deficit in SIP among the Coinfected group relative to the monoinfection groups is similar to previous reports [13] and reaffirms that this domain function is commonly and consistently impaired not only in HIVm subjects but also HIV/HCV Coinfected subjects. Slowed performance in this domain practically implies delayed execution and completion of activities of daily living [39] with associated poor quality of life (QOL) [40]. Further, SIP impairment negatively affect performance of IADL whereas impairment in the domains of fine motor activity negatively influence the capacity to perform physical ADL [39]. Subjects with NCI may experience frustration and low self esteem at home or work place due to reduced capacity to

Table 2. Sociodemographic, clinical and laboratory characteristics of study groups

Variables	Clifford et al. 2005 [27]	Crystal et al. 2012 [28][a]	Heaton et al. 2008 [29]	Hinkin et al. 2008 [30]	Parson et al. 2006 [31][b]	Richardson et al. 2005 [32]	Ryan et al. 2004 [33]	Sun et al. 2013 [34]	Vivithanaporn et al. 2012 [36]	Thein et al. 2007 [35]	Devlin et al. 2012 [37]
HIV/HCV coinfected group											
	40.3	48.3; 47.8	39.5	45	42.8	39.6	45.1	54.5	41.4[c]	35.5	NC
Female (%)	23	100; 100	46.3	11.4	40	100	26.9	0	28.6	0	NC
Education	11.7	NC	5.4	13.2	11.5	10.7	12.3	13.4	NA	NA	NC
AIDS (%)	100	0/100	39	100	66.7	NA	100	0	100	0	NC
ART (%)	0	100; 100	48	NA	0	NC[d]	NC[d]	100	100	40	NC*
CD4 count	299	425; 454	350	190	218	437	165	501	410	368	NC
HIV VL[f]	0.67	2.4; 2.0	3.9	NA	4.3	NA	3.7	UVL	4.4	NA	UVL[e]
HCV VL[f]	NA	1.9; 1.6	NA	NA	NA	NA	NA	6.2	NA	DVL	DVL
HIV monoinfected group											
Age	38	38.3; 43.2	40.8	42	40	33.8	41.9	51.6	41.6[c]	34.7	NC
Female (%)	20	100; 100	33.3	20.5	32	100	22	0	16.8	0	NC
Education	13.9	NC	5.5	13.5	13.1	12.3	11.8	13.6	NA	NA	NC
AIDS (%)	100	0;100	31	100	61.7	NA	100	0	100	0	NC
ART (%)	0	100;100	64	NA	0	NC[d]	NC[d]	NC	100	0	NC
CD4 count	201	531; 423	321	226	267.9	376	141.8	516	299	530	NC
HIV VL[f]	0.73	1.9; 2.0	4.2	NA	4.2	NA	4.1	UVL	4.4	NA	UVL[e]
HCV monoinfected group											
Age	NR	45.9	40	NR	NR	37.3	NR	56.6	NR	42.6	NC
Female (%)	NR	100	51	NR	NR	100	NR	0	NR	36.8	NC
Education	NR	NC	5.6	NR	NR	11.3	NR	13.1	NR	NA	NC
INFα (%)	NR	0	0	NR	NR	0	NR	0	NR	O	NC
CD4 count	NR	1204	NA	NR	NR	1006	NR	NR	NR	NA	NC
HCV VL[f]	NR	0.67	NA	NR	NR	NA	NR	5.9	NA	DVL	NC
HIV negative HCV negative control group											
Age	NR	36.1	40.5	NR	NR	33	NR	53.2	NR	34.8	NC
Female (%)	NR	100	36.2	NR	NR	100	NR	0	NR	0	NC
Education	NR	NC	5.8	NR	NR	12.3	NR	15.4	NR	NA	NC
CD4 count	NR	1061	NA	NR	NR	1260	NR	NA	NR	NA	NA

[a]Provided data for 2 subgroups (AIDS; non-AIDS). [b]Only pre-ART data was utilized since post-ART data has no required information. [c]Median age at first neuroAIDS diagnosis and/or seizure disorder. [d]Subjects were on ART but relevant percentages not provided. [e]Majority had UVL but percentages not provided. [f]Expressed as Log_{10}. AIDS = Acquired immune deficiency syndrome; DVL = Detectable viral load; INFα = Interferon α; NA = Not available; NC = Not clear; NR = Not relevant; UVL = Undetectable viral load

accurately and efficiently perform many activities either singly or simultaneously. Reduced attention and working memory could negatively affect how they plan, coordinate and execute

important daily tasks. Moreover, slowed SIP could potentially limit their ability to process and learn new information and inconsequence may lead to time wasting in undertaking even minor tasks. Other domains impairments like attention and working memory functions common in HCVm [41] and in early stage of HIVm [42] and fine motor function also adversely affects how subjects perform routine physical activities like driving [43]. Impaired EF has been reported in chronic Coinfection, HIVm and even acute phase of HCV infection among Coinfected subjects [44, 45]. Impairment in this domain is associated with reduced QOL [40] and poor management of finances and medications [46].

Neuro-chemical studies have found that high levels of neurotoxic proteins are commonly seen in HIVm and HCVm [47] and both viruses independently leads to impaired glutamate clearance in astrocytes by inhibiting the glutamate transporter [48,49]. Despite these neuro-pathological similarities, the cascades of immunological events following HIVm and HCVm differ and as a result HIV/HCV Coinfection is associated with monocyte activation which significantly correlates with neurocognitive dysfunction even in individuals with undetectable HIV VL [50]. Further, several studies have established that Coinfected patients have significantly elevated likelihood of neurocognitive dysfunction when compared to monoinfection with either virus [30,36,50,51]. A recent meta-analysis found HIVm individuals to be more than six times at risk of developing NCI compared to HIV negative control individuals [11]. Here in this study we found Coinfected subjects to be twice more likely to experience NCI compared to HIVm subjects. Given this predisposition, it is likely that the neurocognitive interaction between HIV and HCV infections is additive among subjects Coinfected with both viruses and needs confirmation in future studies [52].

Meta-regression analysis in this study found multiple sources of heterogeneity two of which were in agreement with the literature. These include age of study participants and study sample size. WAES estimates significantly increases with increasing age of study participants and study sample size. Other significant covariates showed unexpected association with WAES. Normally WAES should decrease with increasing current CD4 count and ART utilization whereas increasing WAES should be seen with increasing proportion of subjects with AIDS. However, the reverse is the case as shown in Fig. 2. This phenomenon where there is reversal of the direction of an effect is called Simpson's paradox [53]. Sources of confounding in this meta-analysis ranged from participant-level to study/investigator-level characteristics. Simpson's paradox possibly resulted from these multiple confounders and has the potential to eliminate an association or changes its direction of effect as seen in this meta-analysis. Few instances of Simpson's paradox have been reported in epidemiology and the findings encountered in this meta-analysis have contributed to the available literature on this important topic [54]. It is worthy to note that all the variables in this meta-analysis that assumed Simpson's paradox were all patient-level characteristics (current CD4 count, nadir CD4 count, ART utilization and AIDS status). It has been observed that some disease biomarkers like current CD4 count and viral load may not always correlate with neurocognitive function [55, 56]. With respect to this meta-analysis, Simpson's paradox should therefore be interpreted with caution since Current CD4 count may be modified by ART, but the previous CD4 nadir cannot be modified by ART. To explain further, WAES may not decrease with increasing current CD4 count because current CD4 count may not reflect previous CD4 nadir, not necessarily being a Simpson's paradox.

In addition to the afore mentioned traditional confounders of neurocognitive performance of HIVm individuals, this study was challenged by liver disease which is a major confounder and modifier of neurocognitive performance with great potential to cause NCI [57,58]. HIV facilitates development and rapid progression of hepatic fibrosis in Coinfected patients [59] and the stage of hepatic fibrosis has been shown to be associated with neurocognitive tests score [60-62]. Sensitivity analysis in this meta-analysis revealed that omitting studies in which liver fibrosis was excluded did not alter the derived estimates, thus liver disease may not have exaggerated the neurocognitive deficits attributed to HIV/HCV Coinfection. However, this finding should be interpreted with caution since neuropsychological and neurophysiological cognitive dysfunction among HCVm subjects without cirrhosis has been established [60,63]. These impairments could be asymptomatic but detectable by neurophysiological tests which were not done in all the included studies [63].

Among the recently published studies [64-66] that did not the meet criteria for inclusion in this meta-analysis is a high profile study by Clifford et al. where they found no evidence of NCI from

HCV infection among Coinfected individuals [67]. Although this study has a lot of good methodological qualities with high statistical power, strength of conclusions might have been better if functional assessment of everyday activities was properly captured.

The statistical framework employed in previous meta-analyses [12,13] of Coinfection did not fully incorporate extensive meta-analytical principles and techniques of examining and controlling heterogeneity and multiple confounding. In this meta-analysis we used meta-regression analysis, stratified analysis, sensitivity analysis and heterogeneity assessment to explore modifiers of the size of effect derived across multiple comparable study groups. This is quite relevant since much has been said about the heterogeneity of Coinfected data but no study had properly explored possible reasons for such heterogeneity and Coinfected patients continue to experience deleterious impact of NCI on their lives. Information derived from this meta-analysis could thus guide the planning and conduct of larger studies taking in to consideration the identified sources of confounding to yield reliable and conclusive evidence on the nature of NCI in Coinfected subjects.

Several ways in which this meta-analysis differs from the recently published meta-analysis [13] is that we have provided epidemiologic figures to help understand the burden of Coinfection to aid strategic planning and decision making. Secondly we pooled a large number of ESs and quantified the degree of NCI and also identified specific cognitive domains impairment with extrapolation to everyday functional decline to boost quality of psychosocial and medical measures to be implemented. Other strength of this meta-analysis is the utilization of heterogeneity diagnostic principles such as meta-regression analysis, stratified analysis and sensitivity analysis. Meta-regression analysis has the advantage of comparing study-level and participant-level characteristics with the size of an effect measure. To improve the reliability and strength of results of meta-regression analysis in this study, relevant covariates were initially identified and targeted for exploration as potential sources of heterogeneity and confounding thereby avoiding data dredging [68]. Further, weighted REM meta-regression analysis was used in order to reduce the inconsistency and uncertainty that could arise from FEM meta-regression analysis [68]. Despite all these efforts made to ensure reliable meta-regression analysis, findings should be interpreted with caution since absence of significant covariate effect does not rule out the possibility of an association in practice [64]. Other limitations of meta-regression analysis include false positive results from data dredging, imprecision, measurement error, confounding and aggregation bias. Thus strong conclusion may be difficult when analyzed studies were few [68].

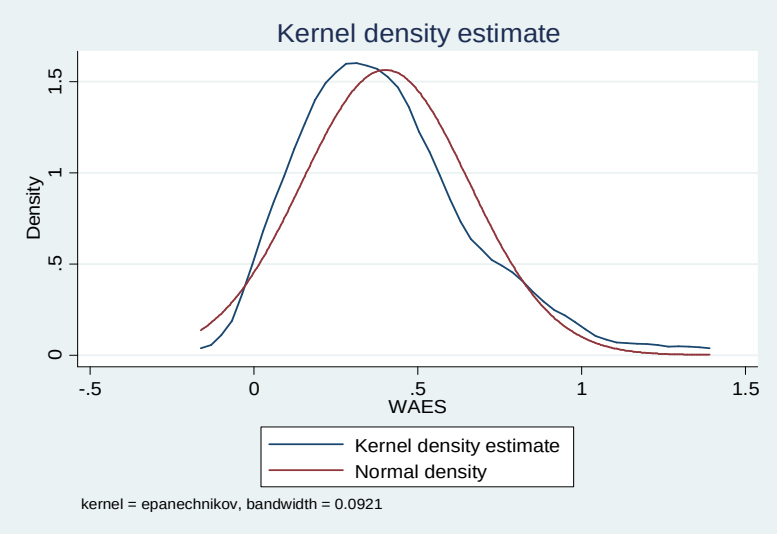

Fig. 2. Kernel density estimates plot compared to normal density plot of WAES

Table 3. Strength of evidence (SOE) using the grading of recommendations assessment, development and evaluation (GRADE) system*

Domain	Risk of bias	Precision	Consistency	Directness	Plausible confounding	Sparse data	Pooled ES	Domain SOE
HIV/HCV coinfected *vs* control								
SIP	Low	Precise	Consistent	Direct	Present	No	Medium	Moderate
EF	Low	Precise	Consistent	Direct	Present	No	Medium	Moderate
Attention	Low	Imprecise	Consistent	Direct	Present	Yes	Medium	Very low
Memory	Low	Imprecise	Inconsistent	Direct	Present	Yes	Medium	Very low
Learning	Low	Imprecise	Inconsistent	Direct	Present	Yes	Large	Very low
Motor	Low	Precise	Consistent	Direct	Present	Yes	Small	Low
Verbal	Low	Precise	Consistent	Direct	Present	Yes	Small	Low
HIV monoinfected *vs* control								
SIP	Low	Precise	Consistent	Direct	Present	No	Small	Moderate
EF	Low	Precise	Consistent	Direct	Present	No	Small	Moderate
Attention	Low	Imprecise	Inconsistent	Direct	Present	Yes	Medium	Very low
Memory	Low	Precise	Consistent	Direct	Present	No	Small	Moderate
Learning	Low	Precise	Consistent	Direct	Present	No	Small	Moderate
Motor	Low	Imprecise	Consistent	Direct	Present	No	Small	Low
Verbal	Low	Precise	Consistent	Direct	Present	No	Small	Moderate
HCV monoinfected *vs* control								
SIP	Low	Precise	Consistent	Direct	Present	Yes	Small	Low
EF	Low	Precise	Consistent	Direct	Present	Yes	Medium	Low
Attention	Low	Precise	Inconsistent	Direct	Present	Yes	Medium	Very low
Memory	Low	Precise	Consistent	Direct	Present	Yes	Medium	Moderate
Learning	Low	Precise	Consistent	Direct	Present	Yes	Small	Very low
Motor	Low	Precise	Inconsistent	Direct	Present	Yes	Small	Very low
Verbal	Low	Precise	Consistent	Direct	Present	Yes	Small	Very low

**Details of the GRADE system has been provided in section 2.4.4.*

EF- Executive Function, ES- Effect Size, GRADE- Grading of Recommendations Assessment, Development and Evaluation system, HCV- Hepatitis C Virus, HIV- Human Immunodeficiency Virus, SIP- Speed of Information Processing, SOE- Strength of Evidence

Fig. 2. Effect Size (ES) distribution according to the study groups

As HIV infected individuals continue to live longer with ART, comorbidities will continue to pose significant challenges to the design, conduct and interpretation of neurocognitive studies. Hence future studies should effectively utilize guidelines and criteria such as AAN 2007 [9] that extensively delineates the contributions of comorbidities to neurocognitive function in HIV infected individuals.

5. CONCLUSION

Despite the heterogeneity from comorbidities and confounders in this meta-analysis, it is evident that HIV/HCV coinfected individuals are living with neurocognitive deficits that could exert profound negative influence on their lives. These findings could guide the design and conduct of larger studies as well as aid planning and implementation of medical, social and behavioral interventions that could shape and improve the lives of affected individuals.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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