

This is a post-peer-review, pre-copyedit version of an article published in *AIDS Care*. The final authenticated version is available online at: <http://dx.doi.org/10.1080/09540121.2016.1191614>

Fialho, R., Pereira, M., Bucur, M., Fisher, M., Whale, R., & Rusted, J. (2016). Cognitive impairment in HIV and HCV co-infected patients: A systematic review and meta-analysis. *AIDS Care*, 28(12), 1481-1494. doi:10.1080/09540121.2016.1191614

## **Abstract**

Cognitive impairment has been well documented in HIV and hepatitis C virus (HCV) mono-infections. However, in the context of HIV/HCV co-infection the research is more limited. The aim of this systematic review was to describe the characteristics of cognitive impairment in HIV/HCV co-infection and to examine the differences in cognitive performance between HIV/HCV and HIV and HCV mono-infected patients. Of the 437 records initially screened, 24 papers met the inclusion criteria and were included in the systematic review. Four studies were included in the meta-analysis. Most studies indicated that HIV/HCV co-infected patients had a higher level of cognitive impairment than HIV mono-infected patients. Meta-analysis also indicated that HIV mono-infected patients had a significantly lower global deficit score than co-infected patients. The results also indicated that co-infected patients were more likely to be impaired in information processing speed than HIV mono-infected patients. These findings can be challenged by biasing factors such as the small number of included studies, heterogeneity of the samples, and a large diversity of methodological procedures. Future research with consistent and comprehensive neuropsychological batteries and covering a greater diversity of risk factors is needed, in order to clarify the effects of both viruses on cognitive function and the mechanisms that underlie these effects. Because cognitive impairments may pose significant challenges to medication adherence, quality of life and overall functioning, such knowledge may have important implications to the planning and implementation of effective interventions aimed at optimising the clinical management of these infections.

**Keywords:** cognitive impairment, HIV/HCV co-infection, meta-analysis, systematic review.

## Introduction

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) have been individually associated with cognitive impairment. Despite the era of combination antiretroviral therapy, the incidence of HIV-associated neurocognitive disorders (HAND) in milder and mild forms, defined respectively as asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), has remained stable but still prevalent (Letendre, 2011; Simioni et al., 2010). There is evidence indicating that cognitive impairment occurs in a substantial proportion (15-50%) of HIV-infected patients (Schouten, Cinque, Gisslen, Reiss, & Portegies, 2011). Cognitive impairment has been associated with disease stage (Woods, Moore, Weber, & Grant, 2009), poor adherence to treatment, HCV infection and other comorbid conditions such as substance use and mental illness (Anand, Springer, Copenhaver, & Altice, 2010; Cysique et al., 2009; Martin-Thormeyer & Paul, 2009). Abnormalities in the neurocognitive profile of HAND have been shown in executive function, memory, information processing speed, attention/working memory, motor skills, language/verbal fluency and sensoriperception (Grant, 2008; Woods et al., 2009). The prevalence of HIV-associated cognitive impairment is high even in patients with undetectable HIV RNA. The cause of this remains unclear, although there is evidence that immune activation, neuroinflammation, genetic and behavioural factors may have an important role (Hong & Banks, 2015; Simioni et al., 2010).

In hepatitis C, the rates of cognitive impairment described range from 0% to 82% (Hilsabeck, Perry, & Hassanein, 2002), and several studies demonstrated evidence of cognitive impairment across a variety of domains. Particularly, attention, concentration, working memory, executive function and psychomotor speed have been shown to be the cognitive domains most likely to be impaired (Perry, Hilsabeck, & Hassanein, 2008; Posada et al., 2009). Several risk factors for cognitive impairment in HCV have been identified. Among these, history of alcohol and drug misuse (Foster, Goldin, & Thomas, 1998), depression (Fontana et al., 2005), severity of liver disease (Hilsabeck et al., 2002; Letendre et al., 2005) and high levels of pro-inflammatory cytokines (Gershon, Margulies Gorczynski, & Heathcote, 2000) were the most consistent. Despite the complexity of mechanisms and associated risk factors, investigations of cognition in viral hepatitis have one common finding of

greater disease severity being associated with more significant cognitive impairment (Córdoba et al., 2003).

Among HIV/HCV co-infected patients, the rates of cognitive impairment are less well-defined, although it appears prevalent (Hilsabeck, Castellon, & Hinkin, 2005; Hinkin, Castellon, Levine, Barclay, & Singer, 2008; Martin-Thormeyer & Paul, 2009). Existing literature suggests that the presence of co-infection with both viruses leads to greater cognitive deficit than in mono-infection, though with a different pattern of cognitive impairment (Letendre et al., 2005; Martin et al., 2004). The aim of this systematic review and meta-analysis was to bring more clarity to this area by analysing the differences on cognitive domains between HIV/HCV co-infection and HIV and HCV mono-infections, as well as to describe the characteristics of cognitive impairment in HIV/HCV co-infected patients.

## **Methods**

### **Information sources and search strategy**

The Cochrane Central Registered of Control Trials Library, SCOPUS, Medline, PsycINFO and ScienceDirect were systematically searched for records from the earliest data available online to April 2014. Each database was searched separately using the following key terms “*cognitive impairment*” AND “*HIV HCV co-infection*”, where AND was the Boolean operator. The search was supplemented with information from references lists of the eligible articles, conferences abstracts, and contact with the key academics in the field of cognitive impairment and HIV/HCV. The selection was limited to publications written in English. The study was designed according to the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

### **Eligibility criteria**

Study inclusion criteria were: (1) type of studies: prospective experimental studies concerning cognitive aspects in co-infection with HIV and HCV; retrospective cohort studies with data collected from previous medical records on cognitive domains; (2) Participants: individuals diagnosed with HIV/HCV co-infection and individuals with HIV and HCV mono-infection; (3) interventions: no intervention and all interventions, including HCV treatment. No description of intervention was necessary, as this review did not aim to compare intervention between groups; (4) primary outcome

measures: any cognitive outcome measure described in the HIV/HCV co-infected group.

### **Data extraction**

Two authors (RF and MB) independently reviewed references from electronic and non-electronic sources and selected the relevant studies. Data extraction was conducted independently (by RF and MB) and reviewed by the lead author. Disagreements were resolved by consensus. Information on the following items was extracted from each study: year of publication, design, sample size, and population characteristics (e.g., gender, age, clinic stage of HIV and HCV, past and/or current intravenous drug use (IDU), and domains and measures of cognitive impairment). If the full-text article did not provide sufficient data, the authors of the studies were contacted for clarification or additional data. Risk of bias assessment was undertaken on each selected study. A checklist was created based on a quality assessment instrument, and included the following items: aims explicitly stated, selection and representativeness of the sample, inclusion/exclusion criteria, measures clearly identified, data adequately reported, and discussion addressing cognitive outcomes (Higgins & Green, 2011).

### **Primary outcomes**

Data were extracted to address all cognitive domains available. For the meta-analysis, the global deficit score (GDS) was also extracted, which was defined as a unitary global score representing overall neuropsychological tests performances. Each individual cognitive test score was converted to T-scores demographically corrected (for education, age and gender) (Rempel et al., 2013; Letendre et al., 2005; Sun, Abadjian, Rempel, Monto, & Pulliam, 2013). The meta-analyses were performed for: (a) the studies that provided a GDS score; and (b) the studies that reported specific neurocognitive domains.

### **Data analysis**

Meta-analyses quantifying the differences in cognitive impairment between co-infected and mono-infected groups were performed using the Review Manager software (RevMan; version 5.2, The Cochrane Collaboration, 2012). The meta-analysis was carried out for continuous variables using inverse variance with standardised mean differences (SMD) and 95% confidence intervals (CI). Heterogeneity was assessed using  $\chi^2$  and  $I^2$  tests, with an  $I^2$  more than 50% being regarded as

substantial heterogeneity (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). If significant heterogeneity was identified, a random-effects model was adopted.

## Results

### Study selection

The study selection process is described in Figure 1. Briefly, the electronic search identified 434 records. Three additional records were identified by non-electronic methods of searching. After the removal of duplicates and of the initial screening (application of the pre-defined inclusion criteria and of PICO parameters), 40 full-text articles were assessed for eligibility. After full-text reading, 16 studies were further excluded, and 24 studies were included in the systematic review. Four studies (16.7%) were included in the meta-analysis process.

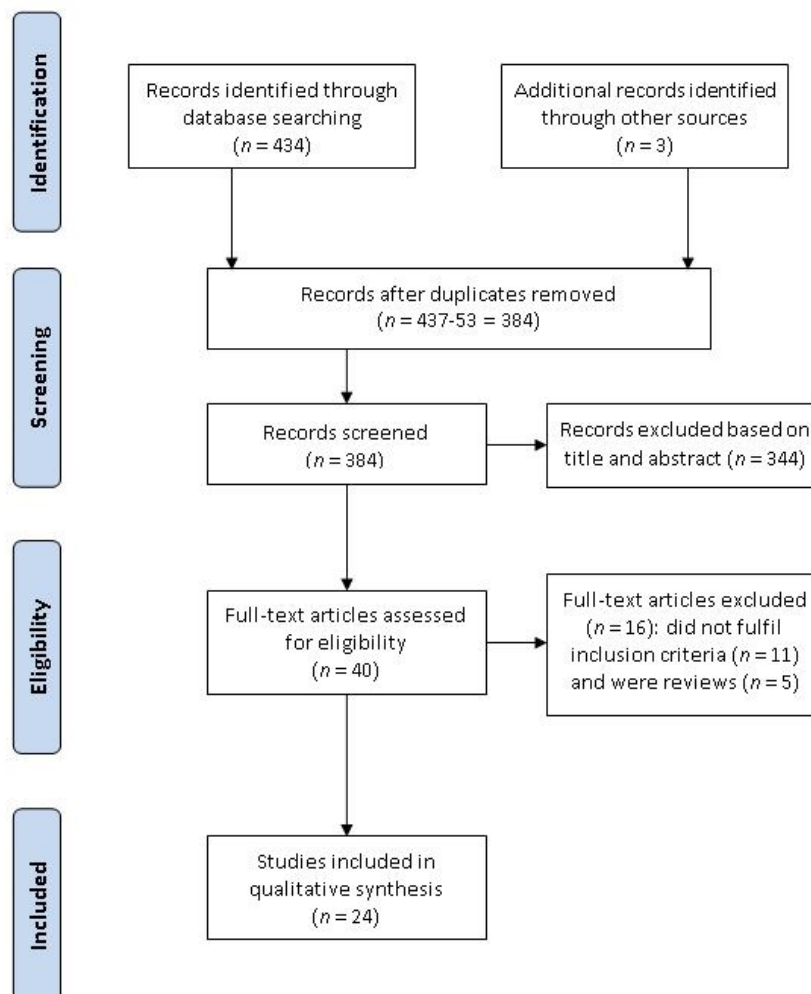


Figure 1. Flow diagram outlining the study selection process

A low risk of bias was observed when considering the identification of aims, inclusion and exclusion criteria, the procedures associated with how outcomes were determined, reporting of relevant results, and discussion addressing cognitive outcomes. However, bias was found, most notably in relation to the selection of participants (e.g., a systematic difference between the characteristics of groups that were compared was identified), which limited their representativeness.

### **Study characteristics**

The 24 studies of this systematic review included a total of 5,674 participants from 6 countries (one study from Australia, Canada, Italy and Germany, three studies from the UK; and 17 studies from the USA). Selected studies were published between 2004 and 2013. Study designs were largely cross-sectional ( $n = 14$ , 58.3%) and cohort ( $n = 8$ , 33.3%), and included a comparison between co-infected and HIV mono-infected groups ( $n = 14$ , 54.2%). The majority of studies included both male and female participants and two studies included only female participants (Crystal et al., 2012; Richardson et al., 2005). The proportion of male participants ranged from 56.2% (von Giesen et al., 2004) to 100% (Martin et al., 2004; Rempel et al., 2013; Sun et al., 2013; Winston et al., 2010). Regarding the clinical stage, 22 studies included participants in HCV chronic stage. In relation to HIV stage, the majority of studies included HIV-infected participants who were chronic and clinically stable ( $n = 16$ ). General characteristics of included studies are described in Table 1.

[Insert\_Table\_1]

### **Cognitive impairment**

#### *Qualitative synthesis of findings*

Regarding cognitive impairment, the existing literature has produced inconsistent findings. Overall, most studies reported that the HIV/HCV co-infected patients were generally more impaired than HIV and HCV mono-infected patients and controls (Cherner et al., 2005; Ciccarelli et al., 2013; Clifford, Evans, Yang, & Gulick, 2005; Devlin et al. 2012; Hinkin et al., 2008; Letendre et al., 2005; Martin et al., 2004; Parsons et al., 2006; Rempel et al., 2013; Ryan et al., 2004; Sun et al., 2013; Vivinhatanaporn et al., 2012; von Giesen et al., 2004). Other studies found no differences on cognitive performance between HIV/HCV and HIV mono-infected groups (Aronow, Weston, Pezeshki, & Lazarus, 2008; Thiyagarajan et al., 2010), between HIV/HCV and HCV mono-infected

groups (Clifford et al., 2009; Perry et al., 2005), and between HIV/HCV and both HIV and HCV mono-infected groups (Thein et al., 2007). A qualitative synthesis of the relevant findings is presented in Table 2.

[Insert\_Table\_2]

### Meta-analyses

Among the studies that measured the GDS (Letendre et al., 2005; Rempel et al., 2013; Sun et al., 2013), the meta-analysis revealed statistically significant differences between groups (SMD = 0.56, 95% CI: 0.36, 0.75,  $p < .00001$ ). Specifically, the results indicated that HIV/HCV co-infected groups were more globally impaired than HIV mono-infected groups. No significant heterogeneity among studies was detected (Figure 2). Due to overlapping samples of the two studies that compared HIV/HCV co-infected and HCV mono-infected groups, the meta-analysis was not performed.

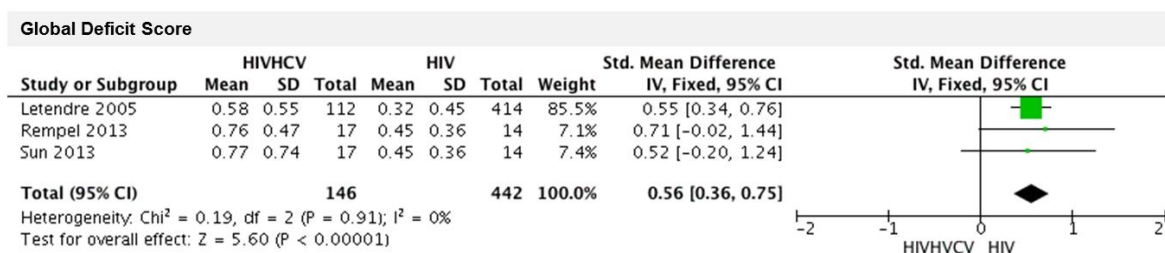


Figure 2. Forest plot of meta-analysis of differences between HIV/HCV co-infected and HIV mono-infected patients in GDS. Abbreviations: SD, standard deviation; CI, confidence interval

In order to explore the existence of differences between HIV/HCV co-infection and HIV and HCV mono-infections on specific cognitive domains, data from each specific domain were also combined and SMD differences with 95%CI were performed. In the meta-analysis, two studies were included (Devlin et al., 2012; Rempel et al., 2013). The forest plots of the assessed cognitive domains are presented in Figures 3 and 4.

Regarding verbal fluency, significant heterogeneity in the meta-analysis was detected ( $I^2 = 61\%$ ;  $p = .11$ ). Consequently, a random effects model meta-analysis was adopted. No significant difference between comparison groups was found (SMD = - 0.08, 95%CI: -0.25, 0.42,  $p = .63$ ). The meta-analysis of the two studies assessing information processing speed indicated that the HIV/HCV

group was more likely to report impairment in this domain than the HIV mono-infected group (SMD = -0.47, 95% CI: -0.81, -0.14,  $p = .006$ ). In relation to working memory and attention, the meta-analysis revealed no differences between HIV/HCV co-infected and HIV mono-infected groups (SMD = -0.00, 95% CI: -0.34, 0.33,  $p = .98$ ). No significant heterogeneity among studies was detected in these two domains.

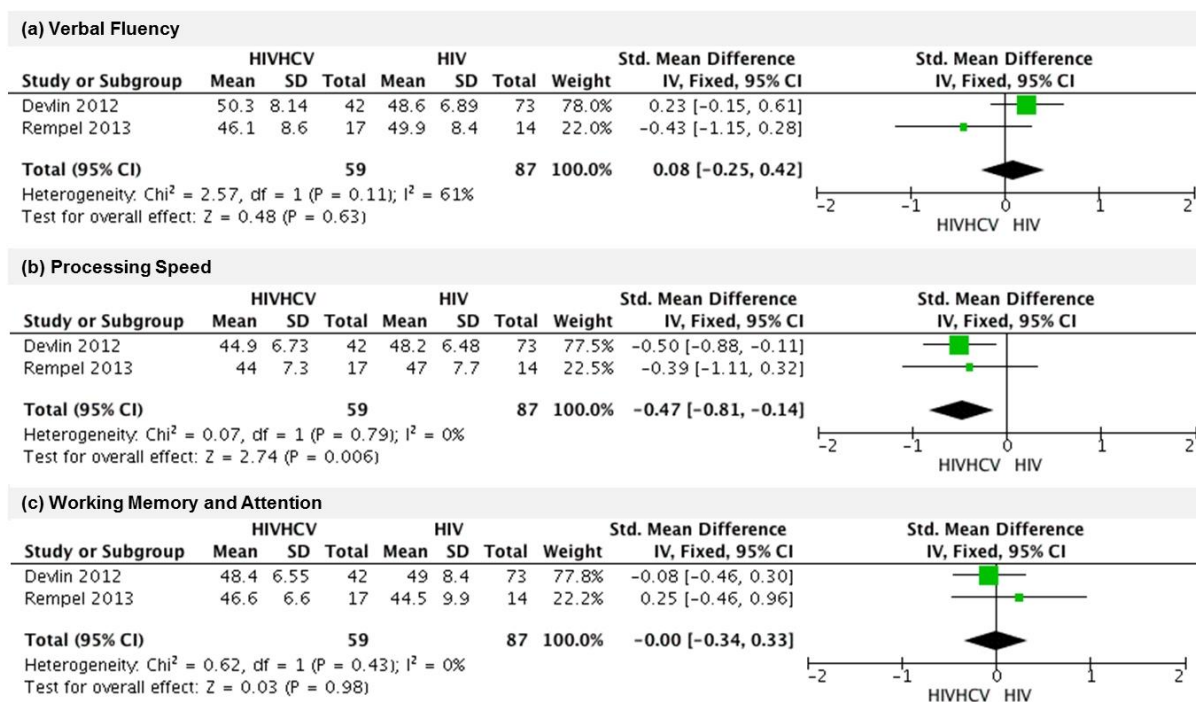


Figure 3. Forest plots of meta-analyses of differences in (a) verbal fluency, (b) processing speed; and (c) working memory and attention between HIV/HCV co-infected and HIV mono-infected patients.

Abbreviations: SD, standard deviation; CI, confidence interval

Regarding the comparison between HIV/HCV co-infected and HCV mono-infected patients, no significant differences were found in relation to verbal fluency (SMD = -0.15, 95% CI: -0.64, 0.33,  $p = .53$ ), information processing speed (SMD = -0.09, 95% CI: -0.57, 0.40,  $p = .72$ ) and working memory and attention (SMD = 0.34, 95% CI: -0.15, 0.82,  $p = .17$ ). No significant heterogeneity among studies was detected in these three domains.



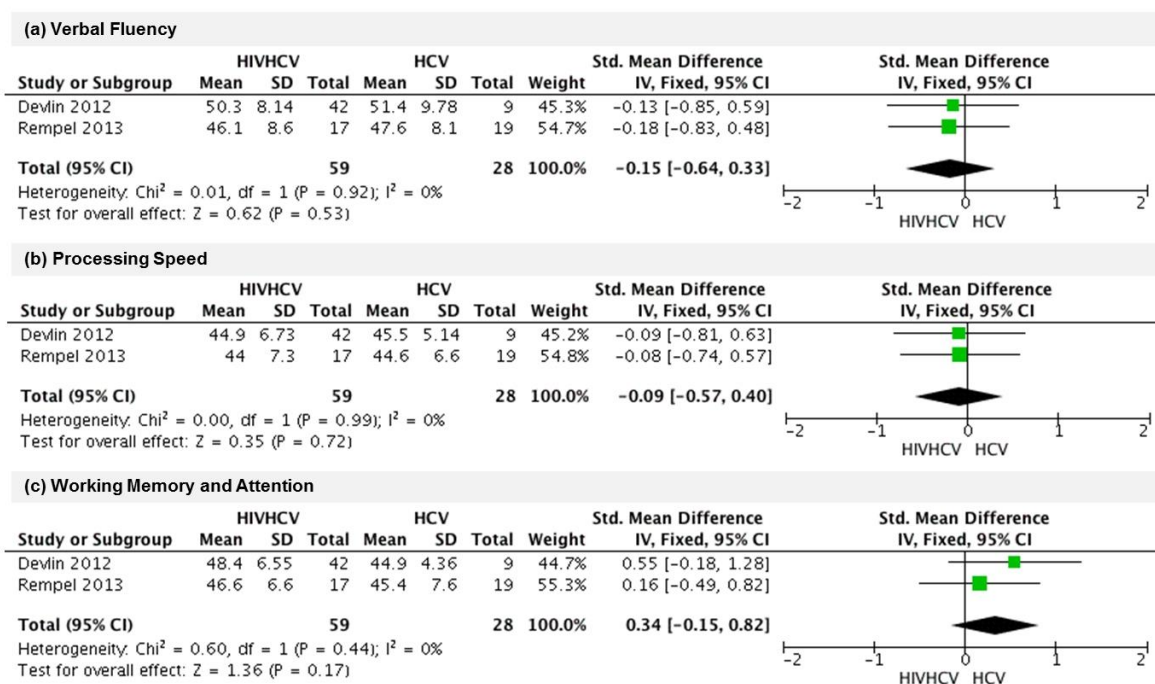


Figure 4. Forest plots of meta-analyses of differences in (a) verbal fluency, (b) processing speed; and (c) working memory and attention between HIV/HCV co-infected and HCV mono-infected patients.

Abbreviations: SD, standard deviation; CI, confidence interval

## Discussion

The aim of this systematic review was to explore the differences in cognitive impairment in co-infection with HIV and HCV, being to our knowledge the first to do so. The main contribution of this meta-analytic review is the ascertainment of the magnitude of cognitive impairment among co-infected patients, in comparison with HIV and HCV mono-infected patients. This is particularly relevant for co-infected patients, as cognitive deficits can translate into significant functional consequences, such as patients' difficulties in carrying out a range of important daily routines, which may compromise the adherence to complex treatments for HIV and hepatitis C, difficulties in remembering important information regarding the management of their disease(s), as well as reduced quality of life.

The findings of this meta-analysis indicate that HIV/HCV co-infection is more reliably associated with GDS impairment than HIV mono-infection, reinforcing the conclusions of several individual studies (Ciccarelli et al., 2013; Hinkin et al., 2008; Letendre et al., 2005; Rempel et al.,

2013). The meta-analysis also shows that the co-infected group has significantly poorer information processing speed than the HIV mono-infected group. No differences were found between HIV/HCV co-infected and HCV mono-infected patients in the examined cognitive domains.

Our meta-analysis demonstrates that HIV/HCV patients were more impaired than HIV mono-infected patients on the GDS, which has been suggested to be a useful method to summarise results of neuropsychological assessment in HIV clinical practice (Carey et al., 2004). This finding may reflect differences in immune biomarkers in HIV or HCV mono-infected patients compared to HIV/HCV patients (Kushner et al., 2013; Rempel et al., 2013) and suggest that the presence of HCV may have a greater impact in cognitive impairment in individuals co-infected with HIV, particularly when compared with HIV mono-infected patients. Indeed, some studies reported that HIV/HCV co-infection was an important predictor of neurocognitive impairment, attributing the difference to the adverse effect of HCV on cognition mediated by HCV viral load (Letendre et al., 2005; Sun et al., 2013), monocyte activation (Rempel et al., 2013), plasma inflammatory cytokine levels (Cohen et al., 2011) or the additive effects of both virus on specific brain sites (Hilsabeck et al., 2005). In HIV-infected patients, HCV replication in the brain has been demonstrated in the frontal cortex, white matter and basal ganglia (Letendre et al., 2007). The acute HCV stage is characterized by an active HCV replication in the brain and has been associated with cognitive impairment in HIV/HCV (Winston et al., 2010). It has also been shown that HCV core protein activates human glia and potentiates HIV-associated neurotoxicity (Vivithanaporn et al., 2010). Among HIV/HCV patients, in a study examining the white matter integrity, Stebbins and colleagues (2007) found a trend toward lower fractional anisotropy (FA) and a significant increase in mean diffusivity (MD) (lower FA and higher MD values typically refer to reduced neuronal integrity; Martin-Thormeyer & Paul, 2009), therefore suggesting brain compromise among co-infected patients. However, as noted by the authors, a positive history of substance abuse was also common in the sample, which may have influenced the results. This seems to be particularly relevant to justify the lack of differences between HIV/HCV and HCV mono-infected groups. Indeed, in the studies included in the meta-analysis, the participants of both groups had significant rates of drug abuse (> 63%) and lifetime substance dependence. Thus, we cannot exclude the fact that this higher proportion of participants with history of drug misuse, which

has been consistently associated with cognitive impairment (Martin-Thormeyer & Paul, 2009) may also have influenced our findings.

In relation to cognitive impairment in HIV, potential influencing factors may be incomplete viral suppression in the central nervous system (CNS) of HIV-infected patients, increased age, poor CNS penetration of some antiretroviral drugs, time of antiretroviral exposure, presence of drug resistance and psychiatric comorbidities (Ciccarelli et al., 2013; Nightingale et al., 2014; Rosca, Rosca, Chirileanu, & Simu, 2011; Woods et al., 2009). It is also noteworthy that persistent cognitive impairment in HIV-infected stable patients is generally attributed to inflammatory influences. An association between inflammation, characterised by high levels of plasma cytokines, and cognitive impairment has been shown in HIV/HCV (Cohen et al., 2011). Moreover, cytokines are involved in neurodevelopmental processes (McAfoose & Baune, 2009). Another mechanism involved in cognitive impairment is immunosuppression; particularly, nadir CD4<sup>+</sup> T-cells have been suggested to be an indicator of cognitive decline. For example, ANI has been associated with an increased risk for earlier development of symptomatic HAND (Grant et al., 2014). The authors of this study also noted that those patients with ANI had evidence of lower nadir CD4<sup>+</sup> T-cells and were more likely to develop everyday life problems.

Overall, the diverse findings abovementioned are noteworthy and represent important advances in understanding the mechanisms underlying cognitive deficits in HIV and HCV mono-infections. However, as the CNS may be compromised by these comorbid medical conditions via additive or synergistic processes, the field of HIV/HCV co-infection and the study of joint mechanisms in cognitive impairment would still benefit from additional research.

This review also indicates that the HIV/HCV group reported more impairment in information processing speed than the HIV mono-infected group. Information processing speed describes the ability to rapidly process serial cognitive operations; when impaired, information processing speed interferes negatively with other cognitive processes due to the reduction of available information needed and the limited time for task execution (Salthouse, 1996). Earlier studies have reported impairment in this domain as a cognitive marker of HIV-associated dementia, reflecting its broad impact on cognitive flexibility (Becker & Salthouse, 1999). An association between HCV chronic

infection and impairment in processing speed has been also reported (Cherner et al., 2005; Vigil et al., 2008). A possible explanation for greater impairment in the co-infected patients may be the higher risk of neurotoxicity due to CNS insults by both viruses in fronto-striatal areas. Particularly, high levels of HIV have been found in the basal ganglia (notably the substantia nigra) and fronto-cortical areas (Kumar, Borodowsky, Fernandez, Gonzalez, & Kumar, 2007), and it has been shown that fronto-striatal neuronal circuitry mediates processing speed (e.g., Fellows, Byrd, & Morgello, 2014; Kumar, Ownby, Waldrop-Valverde, Fernandez, & Kumar, 2011; Salthouse, 1996). Additionally, there is evidence that fronto-striatal circuits are rich in dopaminergic activity and it is hypothesised that dopamine depletion exacerbates processing speed impairment in HIV (Kumar et al., 2011).

Some limitations in this review should be acknowledged. First, the literature search was restricted to articles written in English. Second, only few studies with consistent measurement methods were identified. The lack of the consistency in the cognitive domains and measures, as well as the inability to compile a GDS from the information supplied, resulted in a rather small number of studies included in the meta-analysis. Methodological differences between the studies should also be noted, including the great heterogeneity of the samples' characteristics, the relatively small sample sizes, the predominance of studies with cross-sectional design and the large variability of cognitive measures and domains. Although the inclusion of studies of varying quality is common in most meta-analyses, these biasing factors are noteworthy and require some caution in the interpretation of the cumulative results. Studies on neurocognitive complications of HIV/HCV (as in the general HIV context) are essentially based on studies involving men, and women are still under-represented in neuropsychological studies. Moreover, it is notable that most studies were conducted in the USA (17 out of 24), and very limited research has been conducted in other settings where these diseases are more widespread.

Illicit drug use causes deficits in cognition and in combination with mental health disorders and social/behavioural factors may exacerbate cognitive impairment (Gill & Kolson, 2014; Martin-Thormeyer & Paul, 2009). The variability of age across studies may also affect the classification and rate of patients classified as cognitively impaired. It is possible that HIV-related cognitive impairment reported in this study may be impacted by either advanced age (Rempel et al., 2013; Sun et al., 2013)

or by the emergence of cognitive decline due to AIDS indicator conditions (Letendre et al., 2005). Another relevant factor relates to cognitive reserve, which has been demonstrated to modulate cognitive impairment (Stern, 2003), and that has been shown to be protective factor of cognitive impairment, both in HIV (Foley et al., 2012; Morgan et al., 2012; Vázquez-Justo, Piñón, Vergara-Moragues, Guillén-Gestoso, & Pérez-García, 2014) and HCV (Sakamoto et al., 2013). In future research, it will be important to include appropriate controls/comparison groups, longitudinal follow-up of cohorts with repeated measures, comprehensive neuropsychological batteries, as well as social and behavioural factors and levels of cognitive reserve that may increase the prevalence of cognitive impairment. This will be a significant opportunity to determine whether these effects are independent or additive, to identify similarities and differences in the neuropsychological patterns of HIV/HCV co-infected and HIV and HCV mono-infected patients, as well as to clarify the discrepancies of the prevalence rates of cognitive impairment reported in the literature.

In conclusion, HIV and HCV infections have detrimental effects on neurocognitive function, which in turn may have a significant impact on patients' quality of life and overall functioning, adherence to treatments, and management of risk behaviours. Patients with HIV and HCV usually present several cofactors, where interactions and cumulative effects may well increase their vulnerability to cognitive impairment. Therefore, biological, behavioural and social risk factors that could influence cognitive dysfunction need to be defined more accurately and will require special clinical attention. Moreover, with greater understanding of cognitive dysfunction, new avenues for treatment and prevention can be developed, as this knowledge may contribute to improve disease(s) management and optimise medication adherence, to facilitate treatment decision-making, to reduce risk behaviours and, ultimately, to maximise the patients' health outcomes.

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Table 1. Characteristics of the 24 studies included in the systematic review: study design, sample size, age of participants and clinical stage of HIV and HCV infections

Authors, Year	Study design	Sample size (N)		Sample characteristics (Age) <sup>a</sup>						Clinical stage	
		HIV/ HCV	HCV	HIV	Control s	HIV/HCV	HCV	HIV	Controls	HIV	HCV
Aronow et al., 2008	Cross sectional	31		128		NA		42.6 (7.8)		Late-stage HIV infection	Chronic
Cherner et al., 2005	Cross sectional	83		347		40.9 (7.3)		36.3 (9.3)		Chronic	Chronic
Ciccarelli et al., 2013	Cross sectional	50	50	50		48 (45-53) <sup>b</sup>	48 (42-52) <sup>b</sup>	48 (42-55) <sup>b</sup>		Clinically stable	Chronic
Clifford et al., 2005	Cross sectional	30		234		40.27 (7.75)		38.05 (8.63)		Clinically stable	Chronic
Clifford et al., 2009	Retrospective	249		310		NA		NA		Clinically stable	Chronic
Cohen et al., 2011	Cohort	9		21	34	NA		NA	46.0 (15.9)	Clinically stable	Chronic
Crystal et al., 2012	Cohort	184	42	721	392	47.8 (6.3)	45.9 (8.2)	38.3 (8.8)	36.1 (9.8)	All stages	Chronic
Devlin et al., 2012	Cross sectional	42	9	73	63	NA	NA	45.4 (9.48)	NA	Clinically stable	Chronic
Garvey et al., 2012	Case-control study	24		57		41 (36-44) <sup>b</sup>		47 (39-56) <sup>b</sup>		Clinically stable	Acute
Hinkin et al., 2008	Cohort	35		83		44.7 (8.4)		42.5 (8.3)		HIV in several HAND stages	Chronic
Letendre et al., 2005	Cross sectional	112		414		42		37		Chronic	Chronic
Martin et al., 2004	Cross sectional	28	20	39	69	45.2 (4.2)	44.9 (4.3)	41.6 (5.0)	40 (10.6)	Clinically stable	Chronic
Morgello et al., 2005	Cohort	67		116		NA		NA		Advanced stage	Chronic

Parsons et al., 2006	Cohort	20		45		42.8 (4.9)		40.0 (6.8)		All stages	Chronic
Perry et al., 2005	Cohort	29	47			43.90 (10.27)	47.28 (7.21)			Clinically stable	Chronic
Rempel et al., 2013	Cross sectional	17	19	36	28	54.5 (5.2)	56.6 (4.5)	NA	NA	Clinically stable	Chronic
Richardson et al., 2005	Cross sectional	70	27	75	48	39.6 (6.5)	37.3 (9.2)	33.8 (7.2)	33 (8.6)	Chronic	Chronic
Ryan et al., 2004	Cross sectional	67		49		45.1 (7.2)		41.9 (7.2)		Advanced stage	Chronic
Sun et al., 2013	Cross sectional	17	19	14	28	54.5 (5.2)	56.6 (4.5)	51.6 (7.2)	53.2 (6.0)	Clinically stable	Chronic
Thein et al., 2007	Cross sectional	15	19	30	30	35.5 (7.0)	42.2 (6.5)	34.7 (7.4)	34.8 (8.2)	Clinically stable	Chronic
Thiyagarajan et al., 2010	Cross sectional	27		45		46 (8.0)		48 (11.0)		Clinically stable	Chronic
Vivithanaporn et al., 2012	Cohort	91		365		NA		NA		HIV in several HAND stages	Chronic
von Giesen et al., 2004	Cross sectional	43	44	43		38 (8.1)	43.2 (13.7)	37.4 (7.8)		AIDS and non-AIDS stage	Chronic
Winston et al., 2010	Cohort	10		10	10	40 (9.2)		39 (5.9)	32 (8.9)	Chronic	Acute

*Note:* SD = Standard deviation; HAND: HIV-Associated Neurocognitive Disorder; NA: Not available

<sup>a</sup> Unless indicated, data are presented as mean (SD or range); <sup>b</sup> Data is presented as Median (Interquartile range)

Table 2. Synthesis of findings on cognitive impairment of the 24 studies included in the systematic review

Authors, Year	Cognitive domains	Cognitive measures	Main results	Group more cognitively impaired
Aronow et al., 2008	Verbal fluency, speed of information processing, learning, memory, executive functions, attention and working memory.	Controlled Oral Word Association Test, Wechsler Adult Intelligence Scale (WAIS) III digit symbol and symbol search, letter number sequencing sub tests, Trail Making Test A/B, Hopkins Verbal Learning Test Revised, Brief Visuospatial Memory Test Revised, Wisconsin Card Sorting Test, Grooved Pegboard Test	The co-infected group was more impaired than the HIV mono-infected group.	HIV/HCV > HIV
Cherner et al., 2005	Learning, recall, attention/working memory, speed information processing, verbal fluency, motor ability, abstraction/problem solving	Wide Range Achievement Test-3, Controlled Word Association Test Letters F, A, S; Category Fluency Animals, Paced Auditory Serial Addition Task (PASAT), WAIS III Letter Number Sequencing, Digit Symbol and Symbol Search sub tests, Trail Making Test A/B, Stroop task interference, Heaton Story Memory Test, Hopkins Verbal Learning Test rev, Heaton Figure Memory Test, Brief Visuospatial Memory Test rev, Wisconsin Card Sorting Test, Halsted Category Test, Grooved Pegboard Test	HCV infection has an independent adverse effect on cognitive impairment performance. HIV/HCV co-infection status was a predictor of global impairment.	NA
Ciccarelli et al., 2013	Memory, attention, executive functions, speed of psychomotor processing and language	Rey auditory verbal learning test, Stroop test, Trail Making Test A/B, WAIS R digit symbol, Grooved Pegboard Test and Letter Fluency	The HIV/HCV co-infected group showed lower neuropsychological performance (auditory verbal learning and letter fluency) than the mono-infected groups. The prevalence of minor cognitive impairment was significantly higher	HIV/HCV > HIV HIV/HCV > HCV



Clifford et al., 2005	Motor persistence, attention, response speed, visuomotor coordination, conceptual shifting/tracking	Trail Making Test A/B, Digit Symbol sub test from WAIS III	in HIV/HCV co-infected patients (54%) than in mono-infected groups. The HIV/HCV co-infected group performed worse on attention and psychomotor speed than HIV mono-infected group. There were no differences in the proportion of patients with neurological impairment (HIV/HCV: 33%; HIV: 25%).	HIV/HCV > HIV
Clifford et al., 2009	Attention and motor persistence	Trail Making Test A/B, WAIS R digit symbol test	There were no significant differences on cognitive performance between HIV mono-infected and HIV/HCV co-infected groups. The cognitive impairment was not exacerbated by HCV viral load.	HIV/HCV $\cong$ HIV
Cohen et al., 2011	Attention, executive function and psychomotor processing speed	Trail Making Test A/B, Stroop Test, Grooved Pegboard Test, WAIS-III Digit Symbol Coding, Letter Number sequencing and Symbol Search sub tests	The cognitive performance in HIV/HCV co-infection was associated with high levels of specific cytokines (IL-6, IL-16, MIP-1 $\beta$ ).	NA
Crystal et al., 2012	Speed information processing, perceptual motor ability and cognitive flexibility	Symbol Digit Modalities Test, Trail Making Test A/B, Stroop Test	HCV infection was not associated with cognitive status.	NA
Devlin et al., 2012	Speed of information processing, attention/working memory, executive functioning, learning,	Hopkins Verbal Learning Test – revised, Brief visuospatial memory test- revised, Controlled Oral Word Association Test, Stroop Color and Word Test, Trail Making Test A/B, Digit	No significant differences were found in cognitive performance between the study groups. HIV viral load and HIV/HCV co-	HIV/HCV $\cong$ HIV HIV/HCV $\cong$ HCV HIV/HCV $\cong$ Controls

	memory, verbal fluency and psychomotor speed	Symbol Coding, Symbol Search, Letter-number sequencing sub tests from WAIS III	infection were significant predictors of overall cognitive performance. HIV/HCV co-infection was associated with reduced processing speed, learning and memory.	
Garvey et al., 2012	Psychomotor function, identification, learning, working memory and executive function	CogState Battery	No significant differences were observed on overall cognitive tests between HIV mono-infected and HIV/HCV co-infected groups. The acute HIV/HCV co-infection was independently associated with poorer executive function scores. Disturbance of cerebral metabolites were poorer in the acute HIV/HCV group.	HIV/HCV $\cong$ HIV
Hinkin et al., 2008	Attention/working memory, speed of information processing, learning, memory, verbal fluency, abstract executive functioning, motor/psychomotor speed	A comprehensive battery of neuropsychological tests	The HIV/HCV co-infected group was significantly more likely to be globally cognitively impaired than was the HIV mono-infected group (63% vs. 43%). Learning and memory domains were the most impaired cognitive domains.	HIV/HCV > HIV
Letendre et al., 2005	Verbal fluency, attention and working memory, speed of information processing, learning, delayed recall, abstraction, problem solving and motor ability	Letter fluency, Category fluency, Paced Auditory Serial Addition Task and WAIS-III Letter Number Sequencing, Digit Symbol, Symbol Search sub tests and Trail Making Test A/B, Stroop Test, Heaton Story Memory Test and Hopkins Verbal Learning Test, Heaton Figure Memory Test, Brief Visuospatial Memory Test, Wisconsin Card Sorting Test, Halstead Category Test and Grooved Pegboard	The HIV/HCV co-infected group had worse cognitive performance, as measured by the GDS, which was independent of methamphetamine dependence. Higher HCV viral load was associated with neurocognitive impairment.	HIV/HCV > HIV

Martin et al., 2004	Executive functions, attention	Test Stroop Test	The HIV mono-infected group was impaired on the executive component of the Stroop task while the HCV mono-infected group presented overall slowed information processing.	NR
Morgello et al., 2005	Psychomotor speed, attention, memory, verbal fluency, executive function and premorbid cognitive function	Grooved Pegboard Test, Trail Making Test A/B, Digit Symbol, Symbol Search, Letter Number Sequencing, Paced Auditory Serial Addition Task, Hopkins Verbal Learning Test, Brief Visual Memory Test, Wisconsin Card Sorting Test, Wide Range Achievement Test-3	HIV/HCV co-infected patients were more likely to have previous history of drug misuse, greater impairment in executive function and meet diagnostic criteria for AIDS dementia when compared with the HIV mono-infected group.	HIV/HCV > HIV
Parsons et al., 2006	Attention/concentration, psychomotor speed, executive functioning, verbal memory, visual memory, motor functioning	Paced Auditory Serial Addition Task (PASAT), Stroop Test, Digit Symbol, Trail Making Test A/B, Auditory Verbal Learning Test, Complex Figure Test, Finger Tapping, Timed Gait	The co-infected group showed poorer visual memory and motor functioning than the HIV mono-infected group prior to antiretroviral therapy. Before cART, a greater percentage of co-infected patients performed poorly on the neuropsychology summary score (HIV/HCV: 50%; HIV: 20%). After being exposed for six months to antiretroviral therapy, no differences were found between groups.	HIV/HCV > HIV before cART HIV/HCV $\cong$ HIV after cART
Perry et al., 2005	Attention, concentration, psychomotor speed and working memory	Trail Making Test A/B, Symbol Digit Modalities test, WAIS-III symbol search sub test	No significant differences were found in cognitive performance between HIV/HCV co-infected and HCV mono-infected patients.	HIV/HCV $\cong$ HCV

			Greater fibrosis was associated with poorer cognitive status.	
Rempel et al., 2013	Attention, working memory, information processing speed, executive functions, motor ability, verbal fluency, visual and verbal learning	A comprehensive battery of neuropsychological tests	The HIV/HCV group was significantly more cognitively impaired than the HIV and HCV mono-infected groups. HIV/HCV co-infection was associated with a type 1 interferon monocyte activation profile that was correlated with cognitive impairment.	HIV/HCV > HIV HIV/HCV > HCV HIV/HCV > Controls
Richardson et al., 2005	Learning, recall, attention, mental flexibility and psychomotor speed	Color trails, WHO/UCLA Auditory Verbal Learning Test, Grooved Pegboard, Symbol Digit Modalities Test, Visual Reproduction subtest of the WAIS, Mental Alternations Test	HIV/HCV co-infected women had increased odds of cognitive impairment.	NR
Ryan et al., 2004	Psychomotor speed, attention, memory, verbal fluency, executive function and premorbid cognitive functioning	Trail Making Test A/B, Grooved Pegboard Test, Hopkins Verbal Learning Test, Brief Visual Memory Test Revised, Digit Symbol, Symbol search, Letter Number Sequencing, Controlled Oral Word Association Test, Wisconsin Card Sorting Test, Reading sub test of the Wide Range Achievement Test-3	The prevalence of impaired neuropsychological performance was equivalent in HIV/HCV (55%) and HIV mono-infected patients (53%). There was a trend however for co-infected patients perform poorly on neurocognitive tests. HIV/HCV co-infected patients performed worse on executive functioning and were more likely to present previous history of drug abuse than HIV and HCV mono-infected patients.	HIV/HCV $\cong$ HIV

Sun et al., 2013	General intellect, attention/working memory, information processing speed, executive function, fine motor skills, verbal fluency, visual learning memory, verbal learning memory	WAIS-III digit span, Brown Peterson 18,36, Symbol digit oral and written, Stroop word and color, Wisconsin Card Sorting Test, Grooved Pegboard Test, Finger Tapping, Controlled Oral Word Association Test, Brief Visuospatial Memory Test, California Verbal Learning Test	The rates of impairment based on GDS were higher in HIV/HCV co-infection (65%) than HCV mono-infection (42%), HIV mono-infection (29%) and controls (18%). HIV/HCV co-infection significantly increased the risk of cognitive impairment in patients with controlled HIV viral loads; HCV RNA in HCV mono-infection was correlated with worsening general cognitive scores but not in HIV/HCV co-infection.	HIV/HCV > HIV HIV/HCV > HCV HIV/HCV > Controls
Thein et al., 2007	Global cognitive function, psychomotor function, visual attention, executive function, learning and memory	National Adult Reading Test, Trail Making Test A/B, CogState battery	No significant difference in cognitive performance was found between study groups. The prevalence of impaired cognition was of 21% for HCV mono-infected patients and 6.7% for HIV-HCV co-infected patients.	HIV/HCV $\cong$ HIV HIV/HCV $\cong$ HCV HIV/HCV $\cong$ Controls
Thiyagarajan et al., 2010	Psychomotor function, nonverbal learning, visual and divided attention, visual learning, memory, working memory and executive functions. Screening test for HIV dementia	CogState, Prospective and Retrospective Memory Questionnaire, International HIV Dementia Scale (IHDS)	No significant differences in cognitive performance were observed between the groups. However, the HIV/HCV co-infected group reported significantly poorer IHDS scores than the HIV mono-infected group. The prevalence of cognitive impairment was of 11% for co-infected patients and of 22% for HIV mono-infected patients.	HIV/HCV $\cong$ HIV

Vivithanaporn et al., 2012	Memory, executive functions, psychomotor function, attention, concentration	Memorial Sloan Kettering Scale (MSK), Symbol Digit Modalities Test, Grooved Pegboard Test, Trail Making Test A/B	The HIV/HCV co-infected group showed a higher prevalence of multiple neurologic disorders compared with the HIV mono-infected group (60.4% vs. 46.6%). Symptomatic HIV associated neurocognitive disorders were more severe in the co-infected group.	HIV/HCV > HIV
von Giesen et al., 2004	Premorbid verbal intelligence, attention, working memory and screening test for HIV dementia	MWT-b and HIV Dementia Scale	The HIV/HCV co-infected group performed slower in reaction time. No significant differences were found on cognitive status among the groups.	HIV/HCV $\cong$ HIV HIV/HCV $\cong$ HCV
Winston et al., 2010	Associated learning, detection identification, congruent reaction, monitoring and one card learning	CogState battery	Abnormalities in cognitive functions were observed with monitoring domain being impaired and significant reductions in RBG mI/ Cr ratio in acute HIV/HCV co-infected group	HIV/HCV $\cong$ HIV

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*Note:* cART; combination antiretroviral therapy; NA: Not applicable; NR: Not reported