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HIV, depression, and cognitive impairment in the era of effective antiretroviral therapy

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Abstract

Purpose of Review: Mental health disorders, especially depression, are prevalent among people living with HIV (PLWH) and are associated with cognitive impairment (CI) among HIV-uninfected (HIV) individuals. We conducted a comprehensive review of the link between depression and cognition among PLWH.

Recent Findings: Studies examining depression and cognition in PLWH report high rates of current (median=24%) and lifetime depression (42%). There is reliable evidence that depression is associated with overall CI among PLWH, and in the cognitive domains of processing speed, executive function, learning and memory, and motor function. Although few studies have examined the interaction between HIV serostatus and depression on CI, there is no evidence of a stronger association between CI and depression in PLWH compared to HIV− controls.

Summary: Depression is prevalent and reliably associated with CI in PLWH, with an overall pattern of domain-specific associations similar to that of HIV− individuals.

Keywords

HIV; Depression; Depressive Symptoms; Cognitive Impairment; HAND

Introduction

By 2030, the top two leading causes of burden of disease globally are projected to be HIV and depressive disorders[1]. The two disorders commonly co-occur; depression is the most common neuropsychiatric complication in persons living with HIV (PLWH) next to substance abuse[2, 3]. Depression is two- to three-times more common in PLWH versus the

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Conflict of Interest

The authors declare no conflicts of interest

Compliance with Ethics Guidelines

Human and Animal rights and Informed Consent

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general population [2–5]. Revised estimates from the only nationally representative study among PLWH in the United States (U.S.) found an 18.5% prevalence of major depressive disorder (MDD) over the preceding 12 months[2, 3], which was two- to three-times higher than the general U.S. population. U.S. cohort studies yield similarly high prevalence estimates[5, 6]. The Women's Interagency HIV study (WIHS), for instance, found that among women living with HIV the rate of current MDD based on diagnostic interview was 20% [4] versus 10% nationally, and the rate of lifetime MDD was 32.4% versus 22.9% nationally, respectively. Notably, the level of severity of depression was "serious" in 80% of women with MDD. Such studies indicate that depression is not only highly prevalent but also severe in PLWH.

Multiple factors contribute to the high prevalence of depression in PLWH[7]. These include the sadness and grief that come with initial diagnosis, the stress of living with a chronic illness, challenges of getting needed social support, and internalized stigma[8]. Additionally, PLWH have a high prevalence of psychosocial risk factors for depression including early life trauma, negative life events, violence exposure, financial instability, limited healthcare access, low education, and underemployment[9]. Behavioral risk factors such as substance and alcohol abuse and limited physical activity are also prevalent[4]. HIV-related clinical factors such as poor antiretroviral (ARV) adherence are linked to future depressive episodes, as are key risk factors observed in the general population, such as female sex, pre-existing mood disorders, and a family history of mood disorders[10].

The most serious complication of depression in PLWH is the two-fold increased risk of mortality[11], but cognitive impairment (CI) is also an important complication, one that is associated with decreased daily function[12–20] and quality of life[21–24]. Meta-analyses indicates that depression is associated with ARV non-adherence (r=0.19)[25–27]. Although depression is associated with medication non-adherence and decreased CD4 count, those clinical factors do not explain the relationship between depression and mortality[28]. Meta-analytic studies of HIV-uninfected (HIV−) individuals find that depression severity is most reliably associated with deficits in episodic memory, executive function, processing speed, and attention[29]. Importantly, these cognitive deficits persist in patients with remitted MDD[29]. Similarly, studies in PLWH show that depression is associated with deficits in those same domains[30–34], though that literature has not been comprehensively reviewed.

Prominent neurobiological features of depression contributing to cognitive symptoms include decreases in glucose metabolism in the prefrontal cortex (PFC)[35], and functional alterations of the anterior cingulate cortex (PFC subregion) and amygdala during performance of cognitive tasks[36–39]. In current models, functional alterations of the medial PFC and altered connectivity between medial PFC and limbic structures (i.e., amygdala, hippocampus, parahippocampal cortex), contribute to CI in MDD, and also disrupt cognition through effects on sympathetic arousal and glucocorticoid release[40, 41]. These functional brain alterations overlap in part with the HIV-associated alterations in brain circuitry[42]. Multiple neurobiological features of HIV infection, including chronic neuroinflammation, reduction of trophic factors, and alterations in dopamine and other neurotransmitters can contribute to depression in PLWH[43]. Mechanistically, neuroinflammation and impaired neurogenesis are key features of depression and HIV, and

are central contributors to CI[43–45]. Similarly, alterations in hypothalamic pituitary adrenal axis function can contribute to CI in depression and HIV[40, 41]. Depression can influence cognition function in PLWH indirectly through decreased adherence to medication.

Given the high prevalence of depression among PLWH and the robust link between depression, cognition, and brain health in HIV− individuals, we conducted a comprehensive review of the link between depression and cognition among PLWH. Specifically, we addressed the following questions: 1) In cross-sectional analyses, what is the relationship between depression and cognition among PLWH? 2) In longitudinal analyses, what is the relationship between depression and cognition among PLWH? 3) Does the association between depression and cognition differ between PLWH versus HIV− individuals?

Methods

Data for determining depression and cognition associations among PLWH were identified by searches in PubMED (June 2018) for titles/abstracts containing MeSH terms “depression,” “depressed,” “mood,” or “anxiety” combined with “cognition,” “cognitive,” “HIV-associated Neurocognitive Disorders (HAND),” “neurocognitive,” “neurocognition,” or “neuropsych,” combined with “HIV,” or “HIV-infected” with additional limits of “English Language,” “Humans,” and after 2000. Our search yielded 563 abstracts which were reviewed for the following inclusion criteria: 1) HIV sample size ≥95, 2) standard depression inventory with validated cutoff score indicating depression or use of a structured clinical interview to indicate MDD”, 3) cognition determined based on two or more validated neuropsychological tests, and 4) associations provided between depression and cognition. Based on abstract and article review, 41 articles met criteria. Publications in some cases reflect different analyses from the same cohort, but the individual papers from a given study report on varying cross-sectional and longitudinal subsets over different lengths of follow-up. Therefore, in some cases, we have included findings from one study reported in more than one paper (e.g., WIHS, Multicenter AIDS Cohort Study-MACS, CNS HIV Anti-Retroviral therapy Effects Research-CHARTER).

Study Selection

Tables 1 and 2 provides characteristics of the 41 selected articles meeting inclusion criteria. Of the 41 articles, 29 studies produced 35 cross-sectional and 12 longitudinal analyses. Samples sizes ranged from 95 to 2099 PLWH (median=254) and 49% were based on U.S.samples. An HIV− control group was included in 17 of 41 studies (41%), with control group sample sizes ranging from 18 to 1793 (median=74). The articles span 22 different countries and include 18,737 (14,362 PLWH), mostly male (70%) with an average age in most studies in the 40s. Of studies reporting on ARV use and/or undetectable HIV RNA, 71% of participants analyzed were on ARVs and 61% had undetectable HIV RNA.

Of the 41 studies assessing both depression and cognition in PLWH, 26 [30–32, 34, 46–67] included prevalence estimates of current depression (Figure 1A). Of the 26 studies, 22 (85%) measured depression via self-report questionnaires and the prevalence of current depression ranged from 6% to 41% (median=24.6%)[30, 31, 34, 46–51, 53–56, 58–63, 65–67]. Of the five studies measuring current MDD via structural clinical interviews, the prevalence of

current MDD ranged between 20% and 27% (median= 24.2%)[32, 52, 57, 63, 64] and lifetime MDD ranged from 26% to 50% (median=42%)[57, 63, 67, 68]. Nine of these 26 studies included controls and two of those studies reported and compared rates of depression between serostatus groups [47, 58].

Among the 41 studies measuring both depression and cognition in PLWH, 28 [34, 46, 48–52, 54, 55, 57–62, 65–67, 69–78] included the prevalence of CI (Figure 1B). Of the 28 studies, the prevalence of CI ranged from 11.7% to 88% (median=40.5%). Ten of these 28 studies included the prevalence of HAND stage[48–50, 54, 58, 60, 65, 67, 70, 75]. Asymptomatic neurocognitive impairment (ANI) ranged from 10% to 55% (median=30.5%), mild neurocognitive disorder (MND) from 5% to 31% (median=11%), and HIV-associated dementia (HAD) from 0% to 31% (median=3%).

In cross-sectional analyses, what is the relationship between depression and cognition among PLWH?—Thirty-one cross-sectional analyses examined the association between depression and cognition among PLWH[30–34, 46, 48–52, 54–59, 61, 63–67, 69, 70, 72, 74–76, 78, 79]. Seven of the 31 analyses excluded current depression from study participation[33, 49, 59, 65, 66, 75, 76]. All studies used similar statistical approaches (analysis of variance, regression).

Twenty of 31 cross-sectional analyses measured depression via questionnaires and CI. Of the 20 studies, 14 (70%) reported a significant association between depression and CI[31, 33, 34, 48–50, 55, 58, 66, 69, 70, 72, 75, 78], three studies (15%) missed statistical significance two at p=0.06 [54, 59] and one at p=0.11 [46], and three found no significant association[65, 74, 76](Table 1). One reported the prevalence of depression by each HAND category [49] using Frascati criteria[80]. After excluding individuals with severe depression, a depression rate of 17% was reported for those with normal cognitive function, 15% for ANI, 40% for MND, and 35% for HAD. Studies not excluding individuals with severe depression report higher rates of depression among those with HAD (58%)[75]. Similar findings are reported in studies comparing rates of depression across combined categories of MND and HAD versus ANI and normal[49, 50, 58]. Among the MND/HAD group 39% and 45% had depression versus 15% to 19% of those with ANI or no CI. In these studies, depression increased the odds of MND/HAD versus ANI and/or being unimpaired. Specifically, in adjusted analyses, PLWH with depression versus PLWH without depression, had a 1.4- to 3.1- fold increased odds of MND/HAD versus ANI/being unimpaired[49, 50, 58]. Although rates of depression are lower among PLWH on ARVs and/or virally suppressed, rates of depression remain higher among those with (16% to 35%) versus without CI (4% to 22%)[55, 66]. One study provided an adjusted estimate whereby depression was associated with a 1.5 fold increased odds of having CI versus no CI [48]. Of the three studies noting non-significant trends[46, 54, 59], one had a smaller sample size (n=103) and excluded participants with severe depression[59] thus possibly attenuating the true association. In contrast to most, but not all studies[48], the second study[54] showing a trend assessed CI with a computerized battery, CogState. ARV use in the third study[46] was lower (65%) than other studies, raising the possibility that the effects of active viremia overwhelmed any effect of depression. The three studies finding no association had smaller sample sizes[65, 74, 76] and ARV use in one was 0% [74].

Of the three cross-sectional analyses[52, 57, 67] assessing depression via a structured diagnostic interview in relation to CI, two reported that MDD was a significant predictor of CI[52, 67]. These two studies used the MINI-International Neuropsychiatric Interview[81] whereas the third study used the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders[57]. The two studies with estimates suggest that 28% to 46% of PLWH with CI have MDD compared to 19% to 32% with no CI[52, 57]. The one study providing an adjusted odds ratio indicated that PLWH with MDD have a 1.9 fold increased odds of CI versus non-depressed PLWH[52]. The other study demonstrating a significant association between depression and CI found almost a linear relationship[67]. Cognition was best in PLWH with no history of MDD, followed by those treated for one major depressive episode (MDE), then those with chronic effectively treated MDD, those with chronic MDD that was treated but recurrent, and then those with an active MDE who were not treated[67].

Across the 31 cross-sectional analyses in PLWH, 17 examined associations between depression and specific cognitive domains[30–34, 48, 51, 55, 56, 59, 61, 63, 64, 74, 76, 78, 79](Table 3). For processing speed, six [31–34, 48, 78] of twelve [51, 56, 61, 64, 74, 79] studies (50%) demonstrated an association with depression. For executive function, five [31, 32, 34, 56, 63] of eleven [30, 48, 51, 61, 74, 78](45%) demonstrated an association; for motor function, four [34, 55, 63, 78] of nine [31, 51, 56, 61, 74](44%); for learning and memory, five [30–32, 34, 61] of twelve [33, 48, 51, 61, 64, 74, 78](42%), for attention and working memory, three [34, 63, 79] of eight [30, 31, 48, 74, 78](38%). No study demonstrated links with fluency [31, 48, 51, 56, 61, 74] or visuospatial/visuoconstructive functions[56]. Different neuropsychological tests often went to each cognitive domain and not all studies categorized all tests similarly. For example, one study[33] included grooved pegboard, digit symbol, and Trail Making Test Part B as processing speed measures. While this domain was associated with depression, other studies typically categorized grooved pegboard as a test of motor function and Trail Making Test Part B as a test of executive function. Additionally, some treated cognition continuously whereas others examined CI.

In longitudinal analyses, what is the relationship between depression and cognition among PLWH?—Four studies[57, 67, 68, 77], all in either US or Australia, examined the relationship between depression and CI over time among PLWH (Table 2). Three were from CHARTER[57, 68, 77]; although it is unclear whether the participants from each study are independent. Two studies demonstrated an association between depression and CI[68, 77]. One study demonstrated that current MDD predicted decline to symptomatic HAND[68]. Specifically, current MDD was associated with a 3-fold increased risk of decline to symptomatic HAND (95%CI 1.56-5.77, p=0.001). A second study also demonstrated an association between lifetime MDD and CI [77]. Specifically, lifetime MDD was associated with almost a two-fold increase risk for cognitive decline (RR=1.7, p=0.01). For current depression measured continuously with the BID, there was a significant association with cognitive decline (p=0.005). However, for recent MDD (last 30 days) with a diagnostic interview, there was only a non-significant association with cognitive decline (RR=1.7, p=0.06). Of the two studies[53, 57] examining longitudinal associations between changes in depression and changes in domain specific cognitive decline, one study found a

significant association between depression and executive function and processing speed[53]. ARV use in the other study[57] was considerably lower (35%) than in other studies, again, raising the possibility that the effects of active viremia overwhelmed any effect of depression.

Does the association between depression and cognition differ between PLWH and HIV− individuals?

Cross-sectional analyses.—Seven studies examined the association between depression and cognition in samples of PLWH and HIV− controls[30, 47, 60, 62, 71, 73, 74]. Three of these studies did so in the combined sample[62, 71, 73] and demonstrated an association between depression and CI. Three studies examined depression and domain-specific cognitive function, and all studies examined these associations in the combined sample [30, 47, 60]. In WIHS, depression was associated with lower executive function, attention, learning, and memory[30]. In MACS, depression was associated with slower psychomotor speed; with a trend for memory[47]. In another study, depression was associated with slower psychomotor speed and motor function[60]. One study examined associations stratified by HIV− serostatus and found no significant associations but trends on motor in PLWH and fluency in HIV− controls[74]. One study examined the prevalence of CI and depression among PLWH versus HIV− individuals before and six months after initiating ARVs[62]. At both time points, the odds of having both CI and depression was significantly higher in PLWH (39% and 30%, respective time point) versus HIV− individuals (4% and 9%).

Longitudinal analyses.—Three, large-scale, multi-center, longitudinal analyses, including two in the MACS[82, 83] and one in WIHS[31], focused on the association between depression (CES-D ≥16) and cognition in combined samples of PLWH and controls. The largest MACS study included 2099 HIV+ and 1793 HIV− individuals, of who 21% were on ARVs and the standardized log10 viral load was on average 3.5 (SD=1.4)[83]. Participants performed tests of executive function, processing speed, attention and working memory, learning, memory, and motor function. A novel approach, mixed membership trajectory models, was used to characterize a few typical cognitive trajectories over time and to determine the probability of membership of each individual to those profiles. In this model, each individual did not necessarily belong exclusively to a membership category (profile) but rather had a weighted membership to each of the extreme profiles identified. Three distinct trajectories were identified including a “normal aging” profile (low probability of mild impairment until age 60), a “premature aging” profile (mild impairment starting at age 45-50), and an “unhealthy aging” profile (mild impairment in 20s and 30s). Notably, depression was a strong predictor of each participant’s closeness to each of the three trajectories. Specifically, depression increased closeness to the “unhealthy aging” profile (81% depressed) compared to both the “premature aging” (72% depressed) and “normal aging” (71% depressed) profiles (p’s<0.05). These estimates were not stratified by HIV-serostatus so it is unknown whether the combination of HIV-serostatus and depression increased closeness to the detrimental cognitive trajectories.

The second MACS study included 669 HIV+ and 942 HIV− men, with a mean age of 51.5 (SD=3.1) years, and only measured attention and executive function[82]. Depression and

cognitive profiles were examined using group-based dual trajectory modeling, an approach enabling the identification of distinctive trajectories for each outcome (depression and cognition) and then allowing the examination of the interrelationship of those two outcomes across the trajectory groups over time. Three patterns were identified for depression, those who rarely or never have depression (HIV+ 50%; HIV− 61%), those with periodic depression (30% HIV+; 25% HIV−), and those with chronic depression (HIV+ 21%, 15% HIV−). For cognition, three profiles were identified - worst performing (HIV+ 47%; 45%), average performing (HIV+ 42%, HIV− 47%), and best-performing (HIV+11%; HIV− 8%). Among both PLWH and HIV− individuals, the chronic high depressed group had the highest percent membership in the worst-performing attention/executive function group (52%, 60%, respectively) and the rare/never depressed group had the highest percent membership in the best-performing attention/executive function group (13%, 8%, respectively). In adjusted analyses, the association between depression and cognition was only significant among HIV − individuals (p's<0.05).

The WIHS study included 646 HIV+ (77% on ARVs; 52% HIV RNA undetectable) and 300 HIV− women, with a mean age of 45 (SD=9) years[31]. At the initial time point, 2, and 4 years later, seven cognitive domains were assessed including learning, memory, attention and working memory, processing speed, fluency, executive function, and motor function. Among PLWH, 32% had depression at one or two visits; 12% had depression at all visits (same percentages among HIV−). There was no cognitive domain in which the magnitude of change in performance over time depended on the combined influence of HIV-serostatus and depression. Rather, regardless of time, performance on attention and working memory depended on the combined influence of HIV-serostatus and depression (p=0.01). Similar to MACS[82], the interaction was driven by the HIV− and not the HIV+ individuals such that depression was associated with lower performance on this domain among HIV− (p<0.001) but not HIV+ women (p=0.12). Additionally, depression was associated with lower performance on global function (p<0.0001), memory (p=0.001), executive function (p<0.0001), psychomotor speed (p<0.0001), fluency (p=0.002), and motor function (p<0.0001) across time points.

Conclusion

Numerous studies have examined the association between cognition and depression in PLWH. The importance of considering this association is evident in the high rates of current and lifetime depression in these studies. Although rates of depression vary, the median rate for current depression was 24% in studies using self-report questionnaires[30, 31, 34, 46–51, 53–56, 58–63, 65–67] as well as in studies using structured diagnostic interviews[32, 52, 57, 63, 64]. Lifetime prevalence was on average 42%[57, 63, 67, 68]. The level of severity of MDD was examined in one study using structured diagnostic interviews and found to be "serious" in 80% of cases[4]. Thus, depression is an important and serious psychiatric comorbidity in PLWH.

There is reliable evidence that depression is associated with CI. Fourteen of 20 cross-sectional studies found a link between depression and CI[31, 33, 34, 48–50, 55, 58, 66, 69, 70, 72, 75, 78] and three studies (15%) noted trends in associations (p < .11)[46, 54, 59].

Studies using structured diagnostic interviews [52, 57, 67] also generally showed an association, except for one[57] where 35% of participants were on ARVs compared to other studies where more than 89% were on ARVs [52, 67]. The cognitive domains most reliably associated with depression across cross-sectional studies[30–34, 48, 51, 55, 56, 59, 61, 63, 64, 74, 76, 78, 79] were processing speed, executive function, learning and memory, and motor function, with many of the studies assessing those domains finding associations. Attention and working memory were associated with depression in 38% of cross-sectional studies.

Among the four longitudinal studies of the association between depression and cognition that did not include HIV− controls[57, 67, 68, 77] three were in CHARTER[57, 68, 77], one was in an Australian cohort[67], and of these two CHARTER studies[68, 77] found an association with depression. Although the Australian study found no overall association, certain aspects of depression including remission status, stability of MDD treatment, and severity of depression, were related to cognition[67]. The one CHARTER study that did not find a relationship excluded individuals with untreated MDD[76], whereas both of the CHARTER studies reporting a significant relationship did not indicate any exclusions based on MDD treatment. This raises the possibility that excluding for untreated MDD led to an underestimation of the general relationship between depression and CI. Indeed, CHARTER found evidence both that lifetime MDD predicted time to cognitive decline and conversely that the absence of lifetime MDD predicted cognitive improvement[77]. The other CHARTER study similarly demonstrated that current MDD was associated with a risk of decline to symptomatic HAND[68].

In longitudinal studies involving both PLWH and HIV− individuals, including all-male[82] and all-female cohorts[31], depression was associated with CI in PLWH and HIV− groups. In both cohorts, there were interactions between HIV serostatus and depression in select cognitive domains including attention/executive function, such that the associations were stronger or only significant in HIV− versus PLWH individuals. Thus, there is no evidence that PLWH are differentially susceptible to the negative associations between depression and CI. This appears true for women and men, because findings in WIHS and MACS are in agreement with the crosssectional studies which showed reliable associations with global function for PLWH and HIV− individuals. Additional studies of HIV+ women are needed, given that versus HIV+ men, HIV+ women have higher rates [84] of depression and more severe depressive symptoms[85–88].

Are depression-related cognitive deficits reversible in PLWH?

The observed association between depression and poor cognitive performance in PLWH may be (1) due to common biological pathways (e.g., neuroinflammation, dopaminergic alterations), (2) common psychosocial determinants (e.g., poverty, trauma, chronic stress); (4) common behavioral disorders (e.g., substance use, ARV nonadherence); (5) the causal influence of CI and related functional limitations on mood; (6) the causal influence of depression on CI and/or (7) the overlap between the signs and symptoms of CI and depression (e.g., psychomotor slowing, sleep disruption, poor nutrition) (see [7, 27, 29] for reviews). It is likely that all of these factors come into play, and that there is heterogeneity

among individuals in the factors leading to these associations. Nevertheless, given the significant mental health burden experienced by PLWH, it is worthwhile to consider how treating depression might influence cognition in PLWH.

A variety of interventions are reported to be effective in treating depression in PLWH. Psychotherapeutic interventions are particularly effective, especially those involving cognitive behavioral therapy (CBT)[89]. CBT is efficacious in improving depressive symptoms in depressed PLWH[90], including those with substance use disorders[91, 92]. These interventions can be delivered via phone with equivalent efficacy with face-to-face interventions[93, 94]. Antidepressants can also be efficacious in improving depressive symptoms among PLWH[95–97], though its effects in women, minorities, and low- to middle-income countries are unknown. Additionally, less is known about the effects of antidepressants on HIV outcomes (e.g., CD4 count, HIV RNA). Some studies report increased viral suppression and CD4 T cells among PLWH initiating antidepressants[98]. Most studies on the effects of antidepressants on depression were conducted before 2000, so our understanding of antidepressants on mental health is not fully characterized in the current era of ARVs where PLWH are also prescribed numerous concomitant non-ARV medications[99].

The studies examining the effectiveness of CBT or antidepressants in PLWH have not examined whether these depression treatments improve cognition. Instead these studies have primarily focused on the efficacy of these treatments, specifically CBT, on ARV adherence which was supported in the case in PLWH[90] but not among PLWH with substance use disorders[91]. Importantly, treating depression in HIV-uninfected individuals improves cognition[100–103].

Gaps in Knowledge and Opportunities

In general, the field of psychiatry has moved away from conceptualizing mental health and disorders as discrete diagnostic categories to being transdiagnostic brain disorders[104, 105], specifically in the Research Domain Criteria (RDoC) framework. This framework is based on the idea that fundamental dysfunctional neurobiological processes or neurobehavioral systems underlie multiple and often comorbid mental health disorders. The advantage of a transdiagnostic approach is that it provides promise in understanding the heterogeneity of mental health disorders, their comorbidities, and functional consequences. Additionally, this approach provides a strong foundation for the development of targeted interventions and treatments to improve mental health. Despite strong scientific evidence supporting the need for a transdiagnostic framework for understanding psychopathology, this approach has not been systematically applied to HIV.

Conclusion

In summary, depression is a highly prevalent disorder that is negatively associated with cognitive function in PLWH. Both a history of depression and current depression are associated with CI among PLWH. The pattern of associations between depression and domain-specific cognitive performance is similar to those reported in HIV− individuals. There remains gaps in knowledge about whether treating depression would improve CI in

PLWH and if so what mechanisms (e.g., direct neurobiological, indirect improvement through improved ARV adherence) might explain such improvements. Use of a transdiagnostic approach, which has well-characterized neurobiological substrates for different aspects of depression such as loss, negative valence, and anhedonia could inform this area of research. Thus, this area of research remains a priority and an area that may greatly benefit from utilizing a transdiagnostic approach.

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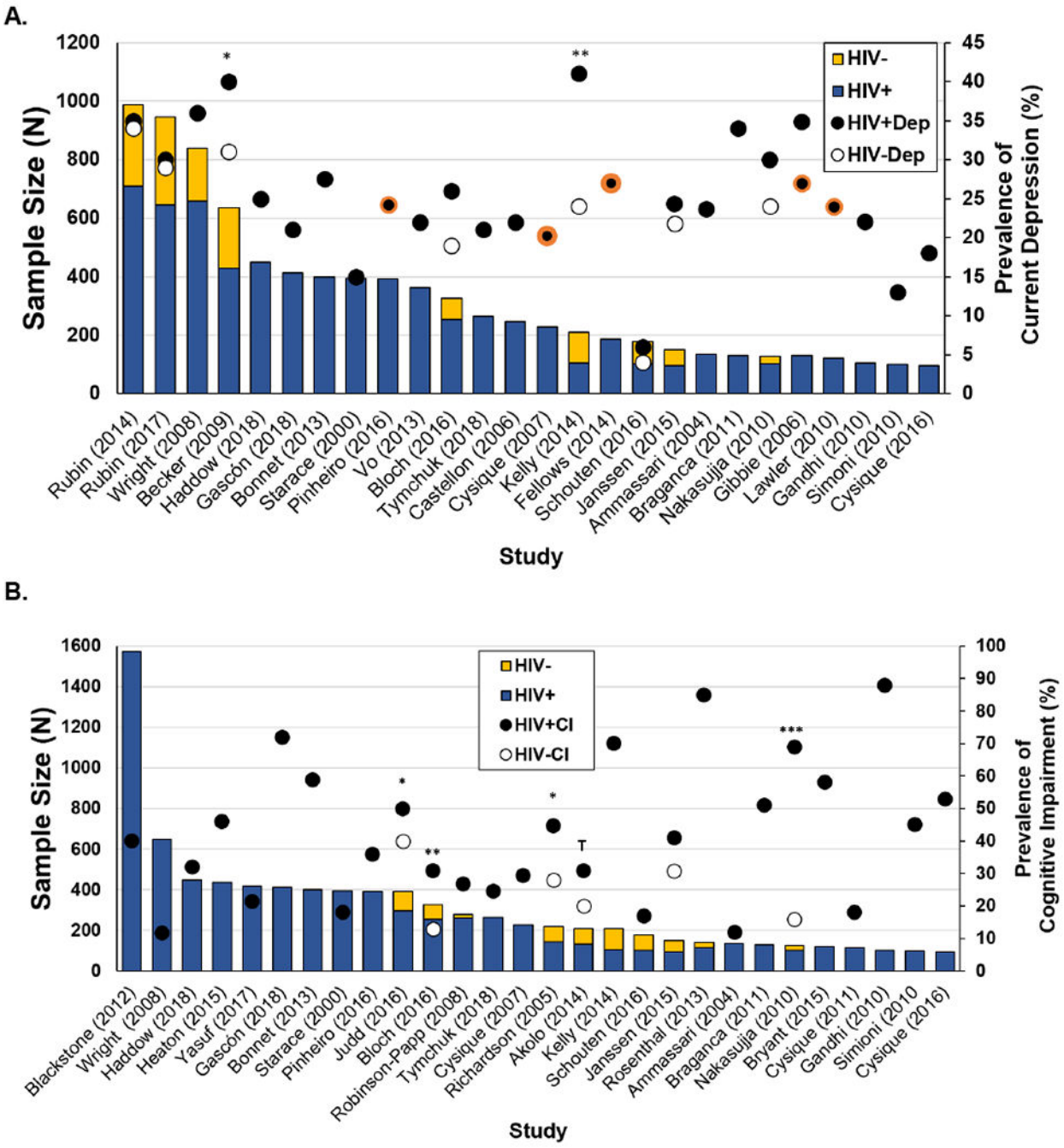

Figure 1.

In the context of studies assessing depression and/or cognitive impairment, (A) prevalence of elevated depressive (Dep) symptoms and (B) cognitive impairment among HIV-infected (HIV+) and/or HIV-uninfected (HIV−) individuals.

Note. *p<0.05; **p<0.01; ^{T}p<0.10; circles bordered in orange reflect depression being assessed using structural clinical diagnostic interviews whereas the remaining were assessed using self-report questionnaires

Table 1.

Cross-sectional studies included in the comprehensive review of the literature on the association between depression and cognitive function among people living with HIV (PLWH) in the era of effective antiretrovirals (ARVs).

Study	PLWH n	HIV− n	Country	Male (%)	Age range or mean/SD	On ARVs (%)	UDVL (%)	Depression Measure	Relationship between current depression & CI in PLWH
Blackstone (2012)[69] *CHARTER*	1574	-	US	76	44±8	86	59	BDI-II	**
Rubin (2014)[30] *WIHS*	708	278	US	0	44±7	65	51	CES-D ≥16	
Wright (2008)[46]	658	161	CN, FJ, GN, HH, KK, ID, MY, TH	59	35±9	65	-	CES-D ≥16	†
Becker (2009)[47] *MACS*	428	207	US	100	50±7	-	-	CES-D ≥16	
Haddow (2018)[48] *CIPHER*	448	-	DK, GB, IT	84	46	89	91	PHQ-9 ≥10	*
Yasuf (2017)[70]	418	-	NG	22	37±9	100	84	CES-D ≥16	**
Gascón (2018)[49] †	412	-	BR	68	45±11	100	84	BDI 13-19	***
Bonnet (2013)[50] *ANRS C03 Aquitaine*	400	-	FR	79	42-53	89	85	CES-D≥17♀; ≥23♂	***
Starace (2000)[51] *ICONA*	395	-	IT	68	35±8	74	-	MADRS >19	
Pinheiro (2016)[52]	392	-	BR	45	43±12	89	65	MINI-Plus	*
Judd (2016)[71] *AALPHI*	296	97	US	42	15-18	86	76	HADS	
Bloch (2016)[54]	254	72	AU	99	49±10	92	79	DASS-21>13	†
Shimizu (2011)[33] †// *Hawaii Aging with HIV*	285	-	US	84	Y: 35±5 O: 54±5	72	49	BDI	*
Tymchuk(2018)[55]	265	-	CA	89	47±10	93	-	PHQ-9 ≥10	*
Castellon (2006)[56]	247	-	US	-	37±8	-	-	BDI	
Richardson (2005)[73]	145	75	US	0	36±8	53	-	CES-D ≥16	

Study	PLWH n	HIV− n	Country	Male (%)	Age range or mean/SD	On ARVs (%)	UDVL (%)	Depression Measure	Relationship between current depression & CI in PLWH
WIHS									
Akolo (2014)[74]	133	77	NG	44	33±7	0	2	BDI	ns
Kelly (2014)[58]	106	103	MW	27	18-71	100	-	SRQ-20 ≥8	*
Fellows (2014)[32]	186	-	US	65	44±7	77	29	PRISM	
MHBB									
Schouten(2016)[59] †	103	74	NL	100	49-62	100	100	BDI 14-28	*T*
AGE$_h$IV									
Harrison (2017)[79] †	103	70	US	69	45±10	100	-	HADS	
Janssen (2015)[60]	95	55	NL	85	49±10	100	100	HADS	
Art-NeCo									
Rosenthal (2013)[75] †	114	38	US	69	45±8	100	59	BDI >16	***
NEAD/Oxidative Stress cohort									
Ammassari (2004)[61]	135	-	IT	64	19-64	100	-	MADRS	
ICONA									
Braganca (2011)[34]	130	-	PT	82	18-50	100	100	HAM-D≥10	***
Bryant (2015)[78]	120	-	US	64	45±9	82	71	CES-D	**
Lawler (2010)[64]	120	-	BW	50	37±6	98	80	PRIME-MD	
Cysique (2011)[76] †	116	-	AU	100	49±9	100	51	DASS	ns
Simioni (2010)[66] †	100	-	CH	72	47±9	100	100	HAD-D≥10	**

ns=not significant

* p<0.05

** p<0.01

*** p<0.001

T p=0.06 except Wright et al. p=0.11.

Country Codes: AU=Australia, BR=Brazil, BW=Botswana, CA=Canada, CH=Switzerland, CN=China, DK=Denmark, FJ=Fiji, FR=France, GB=Great Brittan, GN=Guinea, ID=Indonesia, IT=Italy, KH=Cambodia, MW=Malawi, MY=Malaysia, NG=Nigeria, NL=Netherlands, PT=Portugal, TH=Thailand, US=United States

Depression Measures: BDI=Beck Depression Inventory, CES-D=Center for Epidemiological Studies-Depression, CIDI=Composite International Diagnostic Interview, DASS=Depression, anxiety, stress scale, e-M.I.N.I=Electronic Mini International Neuropsychiatric Interview, HADS=Hospital Depression and Anxiety Scale, HAM-D=Hamilton Rating Scale for Depression, MADRS=Montgomery–Asberg Depression Rating Scale, MINI-Plus=MINI-International Neuropsychiatric Interview, PRIME-MD= *Primary Care Evaluation of Mental Disorders*, mood

module, PRISM=Psychiatric Research Interview for Substance and Mental Disorders, SCID=Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; SRQ-20=self-reporting questionnaire

Study Cohorts: AALPHI= Adolescents and Adults Living with Perinatal HIV Cohort, ANRS=French Agency of AIDS and Hepatitis Research, Art-NeCo=NeuroCognition in HIV-infected Patients on long term effective combination antiretroviral therapy; CHARTER=CNS HIV Anti-Retroviral Therapy Effects Research cohort, CIPHER=Cognitive Impairment in People with HIV in the European Region, ICONA=Italian Cohort Naïve Antiretrovirals research programme, MACS=Multicenter AIDS Cohort Study; MHBB=Manhattan HIV Brain Bank; NEAD=Northeast AIDS Dementia Cohort; WIHS=Women's Interagency HIV Study

Other: SD=standard deviation, UD VL=undetectable HIV RNA, CI=cognitive impairment

† studies excluded individuals either endorsing severe depression via questionnaire (e.g., BDI >19)(Gascón et al.), meeting criteria for major depression according to the Diagnostic and Statistical Manual of Mental Disorders (Simioni et al.), or had a self-reported history of severe affective disorders (Rosenthal et al.)

// Significant association in younger group only.

Table 2.

Longitudinal studies included in the comprehensive review of the literature on the association between depression and cognitive function among people living with HIV (PLWH) the era of effective antiretrovirals (ARVs).

Study	PLWH n	HIV− n	Country	Male (%)	Age range or mean/ SD	On ARVs (%)	UDVL (%)	Depression Measure	Relationship between current depression & CI in PLWH
Molsberry [83] *MACS*	2099	1793	US	100	40±9	21	-	CES-D≥16	
Armstrong [82] *MACS*	669	942	US	100	51±3	-	-	CES-D≥16	
Rubin (2017)[31] *WIHS*	646	300	US	0	45±9	77	52	CES-D≥16	**Avg
Heaton (2015)[77] *CHARTER*	436	-	US	80	44±8	70	41	CIDI, BDI	CIDI †/BDI **
Vo (2013) [53] *MACS*	362	-	US	100	35±8	-	-	CES-D ≥16	
Grant (2014)[68] *CHARTER*	347	-	US	82	44±8	68	41	CIDI	CIDI **
Robinson-Papp (2008)[72] *MHBB*	260	18	US	91	50±7	68	-	BDI	***B
Cysique (2007)[57] *CHARTER*	227	-	US	100	32±7	35	-	SCID	$_{ns}$B
Gandhi (2010)[65] † *NEAD/Oxidative Stress cohort*	104	-	US	72	47±6	100	-	BDI ≥16	$_{ns}$B
Gibbie (2006)[63]	129	-	AU	95	48	93	58	BDI≥14; SCID	
Nakasujja(2010)[62] 3 & 6 months	102	25	UG	27	30±6	0 100	0 -	CES-D≥16	
Cysique(2016)[67]	95	-	AU	98	56±8	100	98	e-M.I.N.I	***B

ns=not significant

* p<0.05

** p<0.01

*** p<0.001

^{T}p=0.06

Country Codes: AU=Australia, UG=Uganda; US=United States

Depression Measures: BDI=Beck Depression Inventory, CES-D=Center for Epidemiological Studies-Depression, CIDI=Composite International Diagnostic Interview, e-M.I.N.I=Electronic Mini International Neuropsychiatric Interview, HDS=Hospital Depression Scale, MINI-Plus=MINI-International Neuropsychiatric Interview, SCID=Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders

Study Cohorts: CHARTER=CNS HIV Anti-Retroviral Therapy Effects Research cohort, MACS=Multicenter AIDS Cohort Study, MHBB=Manhattan HIV Brain Bank; NEAD=Northeast AIDS Dementia Cohort; WIHS=Women's Interagency HIV Study

Other: SD=standard deviation, UD VL=undetectable HIV RNA, CI=cognitive impairment

†individuals self-reporting a history of severe affective disorders were excluded from study participation

^{B}longitudinal studies that included a cross-sectional analysis at baseline;

^{Avg}longitudinal studies that included a cross-sectional analysis collapsed over time

Table 3.

Relationship between current depression and domain specific cognitive performance in people living with HIV in the era of effective antiretrovirals (ARVs): Cross-sectional and longitudinal analyses.

Study	N	On ARVs (%)	Cognitive Domains						
			EF	FLU	ATT/WM	PS	LRN/MEM	VS	Motor
Cross-sectional									
Questionnaires									
Rubin (2014)[30] *WIHS*	708	65	†		†		*		
Rubin (2017)[31] *WIHS*	646	77	*	†	†	*	*		†
Haddow (2018)[48] *CIPHER*	448	89	ns	ns	ns	**	ns		
Starace (2000)[51] *ICONA*	395	74	ns	ns		ns	ns		ns
Shimizu (2011)[33] †// *Hawaii Aging with HIV*	285	72				*	ns		
Tymchuk (2018)[55]	265	93							*
Castellon (2006)[56]	247	-	*	ns		ns	*	ns	ns
Ammassari (2004)[61] *ICONA*	135	100	ns	ns		ns	ns		ns
Akolo (2014)[74]	133	0	ns	ns	ns	ns	ns		†
Braganca (2011)[34]	130	78	*		**	**	*		**
Bryant (2015)[78]	120	82	ns		ns	**	ns		*
Harrison (2017)[79] †	103	100			**	ns			
Diagnostic Interview									
Fellows (2014)[32] *MHBB*	186	77	**			*	*		
Gibbie (2006)[63] *B*	129	93	*		*				*
Lawler (2010)[64]	120	98				ns	ns		
Longitudinal									
Questionnaires									
Vo [53]	362	-	*		ns	***			

Study	N	On ARVs (%)	Cognitive Domains						
			EF	FLU	ATT/WM	PS	LRN/MEM	VS	Motor
MACS									
Diagnostic Interview									
Cysique (2007)[57]	227	35	ns	ns	ns	ns	ns		ns
CHARTER									

ns=not significant

*p<0.05

**p<0.01

***p<0.001, p's<0.08

Cognition: EF=executive function; FLU=Fluency; ATT/WM=attention and working memory; PS=processing speed; LRN/MEM=learning and memory; VS= visuospatial & visuoconstructive functions

†studies excluded individuals either meeting criteria for major depression according to the Diagnostic and Statistical Manual of Mental Disorders

‖Significant association in younger group only.

B=baseline assessment

Study Cohorts: CHARTER=CNS HIV Anti-Retroviral Therapy Effects Research cohort, ICONA=Italian Cohort Naïve Antiretrovirals research programme, MACS=Multicenter AIDS Cohort Study; MHBB=Manhattan HIV Brain Bank; WIHS=Women's Interagency HIV Study