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Persistent CSF but not plasma HIV RNA is associated with increased risk of new-onset moderate-to-severe depressive symptoms; a prospective cohort study

Edward R. Hammond[1,2] · Rosa M. Crum[1,2] · Glenn J. Treisman[2,3] · Shruti H. Mehta[1] · David B. Clifford[4] · Ronald J. Ellis[5] · Benjamin B. Gelman[6] · Igor Grant[7] · Scott L. Letendre[8] · Christina M. Marra[9] · Susan Morgello[10,11] · David M. Simpson[10] · Justin C. Mcarthur[1,3,12] · for the CHARTER Group

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Abstract Major depressive disorder is the most common neuropsychiatric complication in human immunodeficiency virus (HIV) infections and is associated with worse clinical outcomes. We determined if detectable cerebrospinal fluid (CSF) HIV ribonucleic acid (RNA) at threshold ≥50 copies/ml is associated with increased risk of depression. The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort is a six-center US-based prospective cohort with bi-annual follow-up of 674 participants. We fit linear mixed models ($N=233$) and discrete-time survival models ($N=154$; 832 observations) to evaluate trajectories of Beck Depression Inventory (BDI) II scores and the incidence of new-onset moderate-to-severe depressive symptoms (BDI≥17) among participants on combination antiretroviral therapy (cART), who were free of depression at study entry and received a minimum of three CSF examinations over 2496 person-months follow-up. Detectable CSF HIV RNA (threshold ≥50 copies/ml) at any visit was associated with a 4.7-fold increase in new-onset depression at subsequent visits adjusted for plasma HIV RNA and treatment adherence; hazard ratio (HR) = 4.76, (95 % CI 1.58–14.3); $P=0.006$. Depression (BDI) scores were 2.53 points higher (95 % CI 0.47–4.60; $P=0.02$) over 6 months if CSF HIV RNA was detectable at a prior study visit in fully adjusted models including age, sex, race, education, plasma HIV RNA, duration and adherence of CART, and lifetime depression diagnosis by Diagnostic Statistical Manual (DSM-IV) criteria. Persistent CSF but not plasma HIV RNA is associated with an increased risk for new-onset depression. Further research evaluating the role of immune activation and inflammatory markers may improve our understanding of this association.

Keywords Viral load · Cerebrospinal fluid · Psychiatry · Depression

✉ Edward R. Hammond
ehammond@jhu.edu

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[2] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, USA

[3] Department of Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[4] Department of Neurology, Washington University, St. Louis, MO, USA

[5] Department of Neurology, University of California, San Diego, CA, USA

[6] Department of Pathology, University of Texas, Medical Branch, Galveston, TX, USA

[7] Department of Psychiatry, University of California, San Diego, CA, USA

[8] Department of Medicine, University of California, San Diego, CA, USA

[9] Department of Neurology, University of Washington, Seattle, WA, USA

[10] Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[11] Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[12] Departments of Neurology and Pathology, Johns Hopkins University, Baltimore, MD, USA

Introduction

Major depressive disorder (MDD) is the most common neuropsychiatric disorder associated with HIV (Zanjani et al., 2007). In the USA, the lifetime prevalence of MDD in HIV remains high, estimated at between 22 and 45 % even with combination antiretroviral therapy (cART) use (Rabkin, 2008). Globally, MDD is a leading cause of disability-adjusted life years (DALYs) (Murray et al., 2013). Compared to the general US population with an estimated 9 % prevalence of depression (Centers for Disease Control and Prevention (CDC) 2010), persons with HIV bear some of the highest burden of depression-associated disability. MDD is associated with negative outcomes such as low productivity and medication non-compliance, and with comorbidities such as cardiovascular disease, stroke, diabetes, substance use, and suicidality (Sanchez-Gistau et al. 2012; Hees et al. 2013; Pacek et al. 2012; Grenard et al. 2011). MDD in HIV is associated with decreased adherence to cART, poor virologic outcomes, faster disease progression, increased hospitalization rates, and higher mortality (Kacanek et al., 2010; Cook et al., 2004).

There is increasing evidence implicating the activation of inflammatory pathways in MDD through innate and adaptive immune responses (Miller et al. 2009). Elevated levels of plasma and CSF pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1b are associated with MDD (Raison et al. 2009). Hepatitis C treatment with interferon has been shown to be associated with CNS inflammatory response and depression. Elevated pro-inflammatory cytokines are associated with the development of chronic diseases like diabetes and cardiovascular diseases (Miller et al. 2002; Wellen and Hotamisligil 2005), further suggesting a shared pathogenesis between MDD and chronic disease. Evidence suggests that a new diagnosis of HIV can lead to onset of depression (Jin et al., 2006), while the progression of HIV further increases the risk of MDD (Lyketsos et al. 1996). Furthermore, synergistic mechanisms between major MDD and HIV may be related to stress and immune dysfunction (Evans et al. 2002; Cruess et al., 2005), with HIV making MDD worse and MDD in turn leading to progression of HIV.

HIV replication creates an inflammatory environment through activation of the innate and adaptive immune systems (Boasso et al. 2008; Catalfamo et al. 2008). Chronic exposure to inflammatory mediators such as type I IFN is associated with dysregulation of T cell homeostasis mediated by homeostatic cytokines such as IL-7 and is linked to decreased HIV survival (Boasso et al. 2008; Herbeuval et al. 2005). Because HIV RNA levels are the main drivers of CD8 T cell proliferation (Catalfamo et al. 2008), coupled with increasing evidence on the role of inflammation in the pathogenesis of MDD, we hypothesized a priori that detectable levels of HIV RNA in the CSF would be associated with increased risk of depression. The study objectives were to determine if detectable CSF HIV RNA is associated with increased incidence of new-onset moderate-to-severe depressive symptoms and to evaluate the association between detectable CSF HIV RNA and trajectories of depression (BDI) scores. We utilized the data from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort, which uniquely affords bi-annual CSF examinations during follow-up.

Methods

Study design and participants

CHARTER is a six-center, US-based prospective, observational cohort study that started in 2004 and designed to comprehensively assess a demographically representative US population of individuals who are HIV-seropositive in clinical care. CHARTER aims to evaluate the changing presentation of HIV neurological complications in the context of cART (Heaton et al. 2010). There were no general exclusion criteria except for the inability to consent to participate in study assessments. Study sites include Johns Hopkins University, Baltimore, MD; Icahn School of Medicine at Mount Sinai, New York, NY; University of California, San Diego, CA; University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. The study was approved by the Institutional Review Board (IRB) or Western IRB for each study site and each participant provided written informed consent.

At study entry, 1561 CHARTER participants, of whom 1053 were currently on cART, underwent extensive evaluation including HIV and treatment history verified by medical records, physical examination, neuropsychiatric evaluation, neuropsychological testing lumbar puncture, and venipuncture (Heaton et al. 2010). Thereafter, 674 participants were selected if they agreed to undergo follow-up visits every 6 months as part of the longitudinal study component.

These analyses utilize data from the cohort of participants enrolled between 2004 and 2007 and followed through 2009 that were on cART and completed at least three study visits with CSF examination for HIV RNA (Heaton et al. 2010). To examine the effect of detectable CSF HIV RNA on trajectories of depressive symptoms assessed by the Beck Depression Inventory (BDI), we excluded four participants with missing MDD status and 31 participants with prevalent MDD based on Diagnostic Statistical Manual (DSM-IV) criteria assessed by the World Health Organization Composite International Diagnostic Interview (CIDI) (Kessler and Ustun 2004); ($N=223$, with 832 total observations). Because we were also interested in calculating the incidence of new-onset moderate-to-severe depressive symptoms (BDI ≥17), for those analyses, we excluded 69 participants with BDI scores ≥17, $N=154$.

Participants with prevalent MDD who were excluded had significantly higher mean baseline BDI scores, 26.3 (95 % CI 22.0–30.6), relative to those without prevalent MDD, 12.2 (95 % CI 10.9–13.6). There were no other differences in other covariates between participants excluded and those retained in our analysis.

Because the risk of new-onset depression associated with detectable CSF HIV RNA is unknown, we hypothesized from clinical experience that persons with detectable CSF HIV RNA would have at least a twofold increased risk of depression over 12 months compared to persons without detectable CSF HIV RNA. A study of 20 persons with detectable CSF HIV RNA and 100 with undetectable CSF HIV RNA (1:5 ratio) over 24-month follow-up would have 83 % power to detect a relative risk of 2.1 and reject the null hypothesis that the survival curves for persons with detectable CSF HIV RNA are equal to those without detectable CSF HIV RNA at type 1 error (α) = 0.05. Our study had sufficient statistical power to detect such a difference.

Measures

The principal outcome variable was new-onset moderate-to-severe depressive symptoms defined as BDI score ≥17, corresponding to a range of moderate-to-severe clinical depression (Aalto et al. 2012). We also examined trajectories of depression scores over time. The main exposure of interest was detectable CSF HIV RNA, threshold ≥50 copies/ml. CSF HIV RNA levels were measured at each 6-month follow-up visit and determined by commercial ultrasensitive reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostic Systems, Indianapolis, Indiana). Participants were included in these analyses if they completed a minimum of three CSF examinations. We defined persistence of CSF HIV RNA as a minimum of two CSF examinations positive for HIV RNA. Fixed covariates evaluated were patient demographics (age, sex, race, and years of education), self-reported duration of HIV seropositivity and nadir CD4+ T cell, lifetime history of DSM-IV MDD, and HCV seropositivity. We incorporated time-varying covariates assessed at 6-month intervals at each study visit, including cART regimen (protease inhibitor vs. non-nucleoside reverse transcriptase inhibitor-based regimen) and duration of cART regimen, CNS penetration effectiveness (CPE) score of cART which is an estimate of the extent to which antiretroviral drugs affect the CNS (Letendre et al. 2010), current CD4+ T cell count, plasma HIV RNA levels, cognitive impairment assessed by the Global Deficit Score (GDS) (Carey et al. 2004), a summary measure of the standardized comprehensive neurocognitive assessment, and medication adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire (Chesney et al. 2000). All participants included in these analyses were on cART, and changes in treatment regimen assessed at each study visit were captured by changes in CPE scores.

Statistical analysis

Population characteristics were examined using summary statistics. We conducted a complete case analysis of the 832 out of 892 (93.3 %) expected observations if all participants had completed each study visit. To examine the time-varying effect of detectable CSF HIV RNA, we fit discrete-time survival models to estimate hazard ratios between detectable CSF HIV RNA and new-onset moderate-to-severe depressive symptoms. Because protease inhibitor (PI)-based cART has been associated with decreased depression scores (Low-Beer et al. 2000), we examined interactions between lifetime MDD and cART regimen use. We also examined interactions between plasma HIV RNA and adherence to cART. Because relatively few endpoints were reached, we fit several discrete-time survival models, increasing the number of covariates adjusted in subsequent models.

To examine the trajectories of BDI scores over time, we fit linear mixed models with random intercepts and robust variance-covariance estimates of the model parameters (Laird and Ware 1982). We examined the effect of detectable CSF HIV RNA on BDI scores throughout follow-up by fitting interactions between follow-up time and CSF HIV RNA, as well as other covariates. Markov transition matrix was used to assess the transition probability for detectable CSF HIV RNA between study visits. We performed a Wald test to check the joint hypothesis that the coefficients of the interactions were significant. The best-fitting functional forms of each covariate were fit, performing collinearity checks and sensitivity analysis using BDI ≥ 14 (mild depressive symptoms) as outcome. Author ERH performed the statistical analysis with Stata Statistical Software: Release 12. (College Station, TX: StataCorp LP).

Results

The study population comprised 223 persons free of DSM-IV MDD at study entry. The mean age at entry was 44.8 years. Most were male (81.6 %), with 44.8 % Blacks, 39.5 % White, and 15.7 % Hispanic or other race (Table 1). At study entry, 32 (14.4 %) participants had detectable CSF HIV RNA at a threshold of ≥50 copies/ml, of which 28 (87.5 %) had detectable plasma HIV RNA compared to 4 (12.5 %) with undetectable plasma HIV RNA, $P < 0.001$. Participants with detectable CSF HIV RNA were younger, had higher plasma HIV RNA, more likely to be on PI-based and lower CPE cART regimen, and had <95 % medication adherence. Participants with detectable CSF HIV RNA were also more likely to

Table 1 Baseline characteristics of CHARTER study participants free of DSM-IV major depressive disorder by the presence of CSF HIV RNA (≥50 copies/ml) at study entry

	Total $N = 223$	CSF HIV RNA ≥ 50 copies/ml	
		Detectable $n = 32$ (14.4 %)	Undetectable $n = 191$ (85.6 %)
Characteristics			
Age, mean (SD) years	44.8 (7.4)	41.1 (8.3)	45.5 (7.0)**
Sex			
Male, *n* (%)	182 (81.6)	154 (80.6)	28 (87.5)
Race			
White	88 (39.5)	8 (25.0)	80 (41.9)
Black	100 (44.8)	18 (56.3)	82 (42.9)
Hispanic and other	35 (15.7)	6 (18.8)	29 (15.2)
Education, mean (SD) years	12.8 (2.3)	12.8 (1.7)	12.8 (2.3)
Log plasma RNA, mean (SD)	2.3 (1.0)	3.8 (1.1)	2.1 (0.8)***
Log CSF HIV RNA, mean (SD)	–	2.64 (0.76)	–
Current CD4, mean (SD) cells/mm^3	477.6 (288.1)	370.3 (270.3)	495.6 (287.7)
CD4 nadir, mean (SD)	145.2 (137.2)	140.7 (145.2)	146.0 (136.2)
CART regimen, *n* (%)			
PI	124 (55.6)	26 (81.3)	98 (51.3)
NNRTI	79 (35.4)	4 (12.5)	75 (39.3)
PI-NNRTI	11 (4.9)	1 (3.1)	10 (5.2)
Other	9 (4.0)	1 (3.1)	8 (4.2)*
CPE, mean (range)	7.7 (4–14)	7.2 (5–12)	7.8 (4–14)*
Adherence, *n* (%)[a]			
≥95	192 (86.1)	22 (68.8)	170 (89.0)
85–94	17 (7.6)	2 (6.2)	15 (7.9)
<85	14 (6.3)	8 (25.0)	6 (3.1)***
Current CART duration, mean (SD), months	18.1 (21.1)	13.6 (20.0)	18.8 (21.2)
Duration of HIV infection, mean (SD), months	139.6 (71.0)	113.0 (66.1)	144.0 (71.0)*
Lifetime DSM-IV depression, *n* (%)[b]	103 (46.2)	20 (62.5)	83 (43.5)*
Lifetime DSM-IV alcohol use disorder, *n* (%)[b]	62 (27.8)	8 (25.0)	54 (28.3)
Lifetime DSM-IV substance use disorder, *n* (%)[b]	73 (32.7)	5 (15.6)	68 (35.6)*
BDI score, mean (SD)	12.2 (10.2)	10.5 (9.0)	12.5 (10.3)
Cognition, GDS, mean (SD)	0.49 (0.47)	0.37 (0.40)	0.50 (0.48)
HCV positive, *n* (%)	63 (28.6)	5 (16.7)	58 (30.5)
History of opportunistic infection, *n* (%)	38 (44.7)	5 (45.5)	33 (44.6)

c ART combination antiretroviral therapy, *PI* protease inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *CPE* CNS penetration effectiveness score, *BDI* Beck Depression Inventory II, *GDS* Global Deficit Score

*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for difference comparing participants with detectable vs. undetectable CSF HIV RNA

[a] Adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire

[b] Lifetime depression, substance, and alcohol use disorder based on Diagnostic and Statistical Manual of Mental Disorders IV using the Composite International Diagnostic Interview (CIDI)

have experienced a previous lifetime depressive episode ($P = 0.05$). The prevalence of a lifetime depressive episode among the study population was 46.2 %. Persons with detectable CSF HIV RNA at baseline had detectable HIV RNA ≥50 copies/ml in 54.5 % of CSF examinations during follow-up. Participants with undetectable CSF HIV RNA at baseline had undetectable HIV RNA (<50 copies/ml) in 92.3 % of CSF examinations during follow-up. The Markov transition matrix probability that persons on cART with detectable CSF HIV RNA at prior visit would present with undetectable CSF HIV RNA at the next subsequent visit was 45.8 %.

Incidence and risk of new-onset moderate-to-severe depressive symptoms

The overall incidence of new-onset moderate-to-severe depressive symptoms over 2496 person-months of follow-up was 9.6 per 1000 person-months (95 % CI 6.1 to 14.3) (Table 2). When CSF HIV RNA was detectable, the incidence rate of new-onset moderate–to-severe depressive symptoms was 19.6 per 1000 person-months (95 % CI 8.8 to 43.6), compared to 8.2 per 1000 person-months when CSF HIV RNA was undetectable (Fig. 1).

The time-varying effect of detectable CSF HIV RNA was associated with more than four-fold increased risk of new-onset moderate-to-severe depressive symptoms adjusted for plasma HIV RNA and adherence to cART (adjusted HR 4.76, 95 % CI 1. 58 to 14.3); $P=0.006$ (Table 3). When further adjusted for lifetime DSM-IV MDD, lifetime DSM-IV alcohol and substance use disorder, cART regimen, adherence, duration of cART, and sex, age, and race, we observed similar associations between detectable CSF HIV RNA and increased risk of moderate-to-severe depressive symptoms (Table 3). There was no interaction between plasma HIV RNA and adherence.

Trajectories of Beck Depression Inventory (BDI) II scores

At study entry, mean BDI score for persons with detectable CSF HIV RNA was lower, although not significantly different, compared to when CSF HIV RNA was undetectable, 10.5 (SD 9.0) vs. 12.5 (SD 10.3), with adjusted mean difference of −2.99 (95 % CI −6.29 to 0.31), $P=0.08$ (Table 4a). However, throughout follow-up, BDI scores for persons with detectable CSF HIV RNA increased, whereas BDI scores decreased when CSF HIV RNA was undetectable in adjusted linear mixed models (Fig. 2, Table 4a). Unlike the findings for CSF HIV RNA, plasma HIV RNA (continuous and categorized <50, 50–199, 200–9999, ≥10,000 copies/ml) was not associated with an increase in BDI scores over time.

Detectable CSF HIV RNA measured at 6-month intervals was associated with increasing BDI scores over time (Table 4b). In linear mixed models, the presence of CSF HIV RNA at a prior study visit was associated with an increase in BDI of 2.5 points (95 % CI 0.47–4.60; $P=0.02$) during the subsequent 6 months after adjusting for age, sex, race, education, log plasma HIV RNA, nadir and current CD4 count, CPE2, current duration and adherence of cART, duration of HIV infection, lifetime DSM-IV MDD, DSM-IV substance and alcohol use disorder, depression diagnosis at prior study visit, cognitive impairment, and prior diagnosis of HCV infection.

Discussion

We found that persistent CSF HIV RNA (threshold of 50 copies/ml) is associated with over four-fold increase in new-onset moderate-to-severe depressive symptoms. Furthermore, persistent CSF HIV RNA is associated with an increase in BDI score, 2.5 points over 6 months. CSF rather than plasma HIV RNA is associated with new-onset moderate depression and worsening depression scores. These findings lend support to our a priori hypothesis that the presence of CSF HIV RNA is associated with increased depression in HIV.

At baseline, our study population had 12.2 % prevalence of DSM-IV MDD which when compared to HIV depression prevalence estimates of 22–45 % (Rabkin, 2008) is rather low, but is similar to that found in the MultiCenter AIDS Cohort Study (MACS) using the Center for Epidemiologic Studies Depression (CES-D) Scale (Lyketsos et al. 1996). This suggests that our study population was not at additional or higher risk of new-onset depression than the general HIV population. In this regard, our reported estimates of the association between detectable CSF HIV RNA and new-onset moderate-to-severe depressive symptoms may be conservative.

The evaluation of trajectories of BDI scores over time allows ascertainment of changes in mood along a continuum. The

Table 2 Incidence rates and cumulative incidence for new-onset moderate-to-severe depressive symptoms based on the Beck Depression Inventory (BDI score ≥17) by detectable CSF HIV RNA (≥50 copies/ml) and using discrete-time survival models ($N=154$)

New-onset moderate-to-severe depressive symptoms					
	No. of subjects at study entry (N)	Time at risk (person-months)	No. of events	Incidence rate (IR) per 1000 person-months	
				IR	95 % CI
Entire study cohort	154	2496	24	9.6	(6.4, 14.3)
CSF HIV RNA					
Undetectable	124	2190	18	8.2	(5.2, 13.0)
Detectable	30	306	6	19.6	(8.8, 43.6)

Markov transition matrix probability that persons on cART with detectable CSF HIV RNA at prior visit would present with undetectable CSF HIV RNA at the next subsequent visit is 45.8 %

Beck depression inventory II—depression severity scores 0–9, minimal; 10–16, mild; 17–29, moderate; 30–63, severe; CSF HIV RNA detectable at ≥50 copies/ml

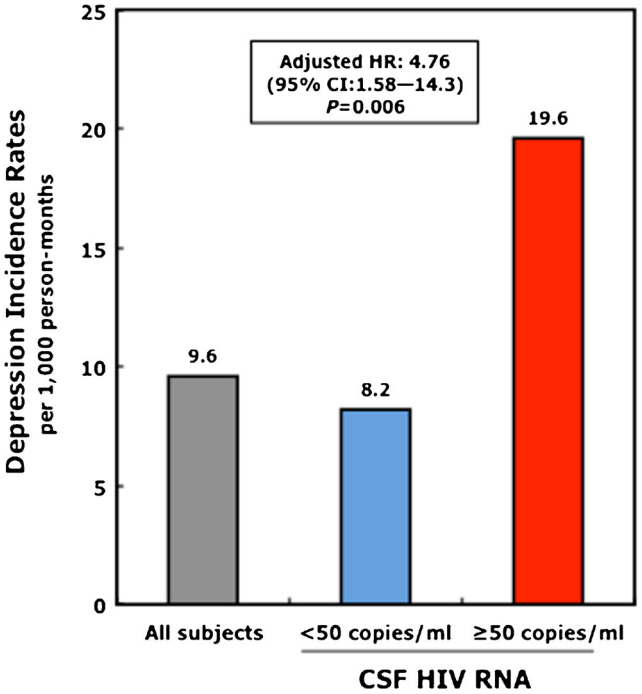

Fig. 1 Incidence rates (IR) for new-onset moderate-to-severe depressive symptoms assessed using the Beck Depression Inventory (BDI score ≥17) by detectable CSF HIV RNA (≥50 copies/ml) using discrete-time survival models. Incidence rates expressed per 1000 person-months. Adjusted HR = 4.76, 95 % CI 1.58–14.3; $P = 0.006$, adjusted for plasma HIV RNA and treatment adherence. CSF HIV RNA detectable at a threshold of ≥50 copies/ml. Depression assessed by Beck Depression Inventory II (BDI)—depression severity scores 0–9, minimal; 10–16, mild; 17–29, moderate; 30–63, severe

presence of HIV RNA in CSF is associated with an increasing BDI score over time. Of equal importance is our finding that undetectable CSF HIV RNA is associated with decreasing BDI scores over time (Fig. 2). Persistent over time, detectable CSF HIV RNA may be a cause of increasingly severe depression. Over the study period, there was 54.5 % transitional probability that persons with detectable CSF HIV RNA would present at a subsequent study visit with detectable CSF HIV RNA. Therefore, the likelihood that detectable CSF HIV RNA could have been misclassified due to false positive CSF HIV is reduced, more so because all patients were on cART.

We speculate that one mechanism for increased depression in HIV is HIV-induced CNS inflammation. This theory, though not yet evaluated in humans, may however be supported by evidence from animal studies in which intraventricular administration of HIV-1 Tat and HIV-1 gp120 has been associated with increased depressive-like behavior (Lawson et al. 2011; Barak et al. 2002).

Because depression is associated with increased risky behavior such as multiple lifetime sexual partners, sex when intoxicated by drugs or alcohol, sex for money or drugs, and decreased medication adherence, all of which increase the risk of HIV transmission (Hutton et al. 2004; Kacanek et al. 2010; High et al. 2012), it is important that clinicians and providers be aware of its association with detectable CSF HIV RNA. Unfortunately, mental health services for persons infected with HIV are still grossly unavailable in high-income countries, and much more so in mid-to-low income countries (High et al. 2012; Chander et al. 2006). Presently, there are no recommended guidelines for testing CSF in the management of HIV or for that matter depression in HIV. The European AIDS Clinical Society guidelines recommend CSF analysis for resistance patterns when neurocognitive impairment is detected (European AIDS Clinical Society 2012), but US guidelines do not address CSF monitoring. In a recent consensus report, the Mind Exchange Program recommends CSF testing for HIV RNA in persons with suspected or demonstrated neurocognitive impairment (Mind Exchange Working Group 2013).

The association between depression and persistent CSF HIV RNA may be bi-directional. In this study, we did not evaluate whether incident depression was associated with future loss of CSF virologic suppression, an unlikely finding given our

Table 3 Hazard ratios for the association between detectable CSF HIV RNA (≥50 copies/ml) and new-onset moderate-to-severe depressive symptoms based on the Beck Depression Inventory (BDI score ≥17) using discrete-time survival models displaying covariates adjusted for in various models ($N = 154$)

Model	Variables adjusted in model	HIV RNA compartment	Hazard ratio	95 % CI	*P* value
1	Unadjusted	CSF[b]	2.39	(0.98, 5.82)	0.06
		Plasma[c]	1.14	(0.78, 1.67)	0.51
2	Log plasma[a] HIV RNA/CSF[b] HIV RNA and adherence to cART	CSF	4.76	(1.58, 14.3)	0.006
		Plasma	0.81	(0.61, 1.08)	0.15
3	Fully adjusted model[a]	CSF	6.34	(1.74, 23.3)	0.005
		Plasma	0.82	(0.61, 1.23)	0.23

Beck depression inventory II—depression severity scores 0–9, minimal; 10–16, mild; 17–29, moderate; 30–63, severe

[a] Adjusted for log plasma HIV RNA, cART regimen, CNS penetration effectiveness score (CPE), adherence to cART, duration of cART, Lifetime Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) major depressive disorder, lifetime DSM-IV alcohol and substance use disorder, sex, age, and race

[b] Detectable CSF HIV RNA, ≥50 copies/ml

[c] Log plasma HIV RNA, per 10 RNA copies/ml; categorized plasma RNA <50, 50–199, 200–9999, ≥10,000 copies/ml

Table 4 Association between detectable CSF HIV RNA (≥50 copies/ml) and Beck Depression Inventory (BDI) scores over time; (A) longitudinal change in BDI scores, using adjusted linear mixed models with random intercept in persons without depression (DSM IV criteria) at baseline, and (B) cross-sectional effect of detectable CSF HIV RNA over time ($N = 223$)

(A)						
Time, months	Undetectable CSF HIV RNA			Detectable CSF HIV RNA		
	Coefficient[a]	(95 % CI)	*P* value	Coefficient[a]	(95 % CI)	*P* value
Baseline	*Ref*	–	–	−2.99	(−6.29, 0.31)	0.08
6	−1.67	(−3.11, −0.23)	0.02	3.72	(0.32, 7.13)	0.03
12	−2.72	(−4.41, −1.03)	0.002	3.72	(−0.03, 7.46)	0.05
18	−3.54	(−5.65, −1.42)	0.001	4.56	(0.71, 8.41)	0.02
24	−3.74	(−6.28, −1.20)	0.004	3.02	(−1.19, 7.22)	0.16
(B)						
Covariate	Unadjusted model estimates			Adjusted† model estimates		
	Coefficient[a]	95 % CI	*P* value	Coefficient[a]	95 % CI	*P* value
CSF HIV RNA						
Undetectable	*Ref*			*Ref*		
Detectable	0.51	(−1.16, 2.19)	0.55	2.52	(0.44, 4.60)	0.02*
Log plasma HIV RNA (per 10 RNA copies/ml)	0.53	(−0.29, 1.35)	0.21	−0.12	(−0.94, 0.70)	0.78

Beck depression inventory II—depression severity scores 0–9, minimal; 10–16, mild; 17–29, moderate; 30–63, severe

[a] Coefficient represents the longitudinal change in BDI scores from baseline with reference to persons without detectable CSF HIV RNA † Multivariate linear mixed models adjusted for log plasma HIV RNA, race, age, sex, education, nadir and current CD4 counts, CNS penetration effectiveness score (CPE), lifetime DSM-IV depression and depression at prior visit, lifetime DSM-IV alcohol and substance use disorder, years infected with HIV, cognitive impairment (Global Deficit Score; GDS), and prior diagnosis of HCV infection

approach. The present findings may suggest a clinical role both for monitoring depressive symptoms through valid and reliable assessment tools and for CSF viral load testing. Its value might include indicators for changes to cART regimen (including treatment intensification), discussions about adherence to medication, counseling aimed at reducing high-risk HIV behavior, and evaluation of antidepressant therapy. Depression in HIV can be effectively treated with psychotropic medication, psychological interventions, and by incorporating cognitive-behavioral components (Sherr et al. 2011). In persons with refractory HIV-associated depression, knowledge about the presence of CSF HIV RNA might become useful to guide treatment choices for both antidepressant and cART regimen.

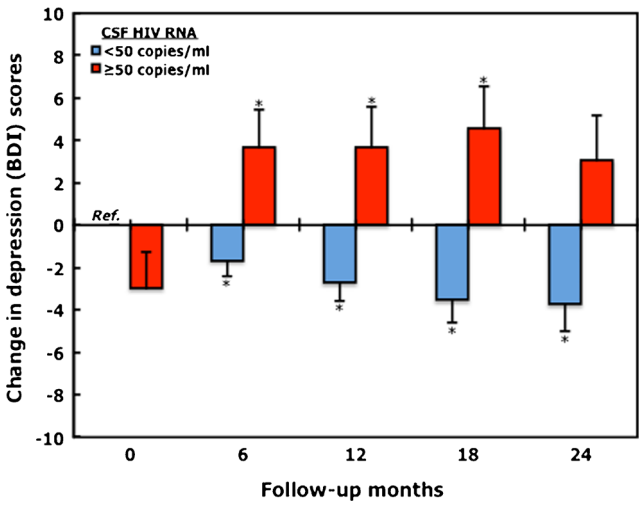

Fig. 2 Longitudinal effect of detectable CSF HIV RNA (≥50 copies/ml) on Beck Depression Inventory (BDI) scores using adjusted linear mixed models with random intercept in persons without depression (DSM IV criteria) at baseline. Change in depression (BDI) scores represents the longitudinal change in BDI scores from baseline with reference to persons without detectable CSF HIV RNA. *$P < 0.05$. Depression assessed by Beck Depression Inventory II (BDI)—depression severity scores 0–9, minimal; 10–16, mild; 17–29, moderate; 30–63, severe. Multivariate linear mixed model adjusted for log plasma HIV RNA, race, age, sex, education, nadir and current CD4 counts, CNS penetration effectiveness score (CPE), lifetime depression diagnosis, depression at prior study visit, years infected with HIV, cognitive impairment (Global Deficit Score; GDS), and prior diagnosis of HCV infection

Some limitations to our analyses need to be considered. First, although our prospective study is one of the largest available to assess CSF over time, because of the relatively low prevalence of participants at baseline with detectable CSF HIV RNA without MDD, we were unable to assess a dose-response association. Also, the measures of association we report for new-onset moderate-to-severe depressive symptoms have wide 95 % CIs. However, our study had sufficient statistical power to detect a difference in risk of depression by detectable CSF HIV RNA status. It is conceivable that higher levels of CSF HIV RNA may result in further increase in the incidence and severity of depressive symptoms. Second, we detected CSF HIV RNA at a threshold of 50 copies/ml. New ultrasensitive HIV RNA assays enable lower thresholds of HIV RNA detection and might allow refinement of our findings. Majority of the participants included in these analyses were male, which may make our findings a conservative estimate when applied to females, who may report more depressive

symptoms compared to males (Piccinelli and Wilkinson 2000). Although we accounted for the effect of lifetime substance and alcohol use disorder in these analyses, we did not evaluate the effect of current substance and alcohol use disorder because of the low diagnosis of current DSM-IV substance and alcohol use disorder, 0.9 and 0.8 %, respectively.

Strengths of our study include the availability of data from HIV participants with at least three CSF examinations during follow-up. This allowed us to harness the strength of longitudinal data analysis and robust statistical techniques, adequately accounting for correlations between repeated measures thereby providing robust estimates (Laird and Ware 1982). We utilized CSF HIV testing performed at each follow-up visit and incorporated its time-varying nature. We did not account directly for psychotropic medications received during follow-up. However, by adjusting for lifetime MDD and depression at a prior study visit, we indirectly accounted for antidepressant therapy effects any participants may have received. Although persons with a prior history of depression have an increased risk for new depression, we further restricted our analysis to persons free of MDD at baseline making it unlikely that our findings are a result of lifetime MDD.

We assessed depressive symptoms by the BDI, a validated tool with high content and construct validity (Aalto et al. 2012). By assessing outcomes at BDI score of ≥17, we captured moderate-to-severe depressive symptoms while excluding mild symptoms. Our approach results in less potential misclassification of depression and helps to ensure that our outcome is more likely to represent clinically relevant depressive disorder rather than distress symptoms associated with HIV. Furthermore, the use of the BDI allows depressive symptoms to be assessed on a continuum; enabling ascertainment of BDI changes over time and assessment of extreme BDI scores.

In conclusion, persistent CSF HIV RNA is associated with increased risk of new-onset moderate-to-severe depressive symptoms. Assessment of depressive symptoms using screening tools and techniques to determine which patients may benefit most from CSF testing may be beneficial. Because detectable plasma HIV RNA was not associated with depression even though patients with detectable CSF HIV RNA were more likely to have detectable plasma HIV RNA, persons with HIV presenting with persistent or worsening depression may benefit from CSF testing for HIV RNA, which may help guide HIV and depression treatment. We speculate that depression may be a surrogate of ongoing CNS inflammation and injury.

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