Title

Association of long-term patterns of depressive symptoms and attention/executive function among older men with and without human immunodeficiency virus

Journal

Journal of NeuroVirology, 23(4)

ISSN

1355-0284

Authors

Armstrong, Nicole M
Surkan, Pamela J
Treisman, Glenn J
et al.

Publication Date

2017-08-01

DOI

10.1007/s13365-017-0527-y

Peer reviewed

HHS Public Access

Author manuscript

J Neurovirol. Author manuscript; available in PMC 2017 September 30.

Published in final edited form as:

J Neurovirol. 2017 August ; 23(4): 558–567. doi:10.1007/s13365-017-0527-y.

Association of long-term patterns of depressive symptoms and attention/executive function among older men with and without human immunodeficiency virus

Nicole M. Armstrong[1], **Pamela J. Surkan**[2], **Glenn J. Treisman**[3], **Ned C. Sacktor**[4], **Michael R. Irwin**[5,6], **Linda A. Teplin**[7], **Ron Stall**[8], **Eileen M. Martin**[9], **James T. Becker**[10], **Cynthia Munro**[4], **Andrew J. Levine**[11], **Lisa P. Jacobson**[1], and **Alison G. Abraham**[1,12]

[1]Departments of Epidemiology, Johns Hopkins University Center on Aging and Health, Johns Hopkins Bloomberg School of Public Health, 2024 E. Monument Street, Baltimore, MD 21205, USA

[2]International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[3]Departments of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[4]Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[5]Cousins Center for Psychoneuroimmunology, UCLA Semel Institute for Neuroscience, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

[6]Departments of Psychiatry and Biobehavioral Sciences, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

[7]Departments of Psychiatry and Behavioral Sciences and Medicine: Infectious Diseases, Feinberg School of Medicine, Chicago, IL, USA

[8]Departments of Behavioral and Community Health, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

[9]Department of Psychiatry, Rush University Medical Center, Chicago, IL, USA

[10]Psychiatry, Psychology, and Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

[11]Neurology, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

[12]Department of Ophthalmology, Johns Hopkins School of Medicine, Baltimore, MD, USA

Abstract

Correspondence to: Nicole M. Armstrong.

Electronic supplementary material The online version of this article (doi:10.1007/s13365-017-0527-y) contains supplementary material, which is available to authorized users.

Compliance with ethical standards The study protocol was approved at all collaborating institutions' IRBs, and participants provided written informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

Older HIV-infected men are at higher risk for both depression and cognitive impairments, compared to HIV-uninfected men. We evaluated the association between longitudinal patterns of depressive symptoms and attention/executive function in HIV-infected and HIV-uninfected men aged 50+ years to understand whether HIV infection influenced the long-term effect of depression on attention/executive function. Responses to the Center for Epidemiologic Studies—Depression scale and attention/executive function tests (Trail Making Test Part B and Symbol Digit Modalities Test) were collected semiannually from May 1986 to April 2015 in 1611 men. Group-based trajectory models, stratified by HIV status, were used to identify latent patterns of depressive symptoms and attention/executive function across 12 years of follow-up. We identified three depression patterns for HIV-infected and HIV-uninfected men (*rare/never* 50.0 vs. 60.6%, *periodically depressed* 29.6 vs. 24.5%, *chronic high* 20.5 vs.15.0%, respectively) and three patterns of attention/executive function for HIV-infected and HIV-uninfected men (*worst-performing* 47.4 vs. 45.1%; *average* 41.9 vs. 47.0%; *best-performing* 10.7 vs. 8.0%, respectively). Multivariable logistic regression models were used to assess associations between depression patterns and worst-performing attention/executive function. Among HIV-uninfected men, those in the *periodically depressed* and chronic high depressed groups had higher odds of membership in the worst-performing attention/executive function group (adjusted odds ratio [AOR] = 1.45, 95% CI 1.04, 2.03; AOR = 2.25, 95% CI 1.49, 3.39, respectively). Among HIV-infected men, patterns of depression symptoms were not associated with patterns of attention/executive function. Results suggest that HIV-uninfected, but not HIV-infected, men with chronic high depression are more likely to experience a long-term pattern of attention/executive dysfunction.

Keywords

Depression; Human immunodeficiency virus; Aging; Attention/executive function

Introduction

Depression is prevalent in older community-dwelling adults, with 26% reporting depressive symptoms (Substance Abuse and Mental Health Services Administration 2011). Depression can elevate risk of disability, hospitalizations, comorbidities, cognitive impairment, and death (Almeida et al. 2012; Ariyo et al. 2000; Broadhead et al. 1990; Snowden et al. 2015).

The relationship between depressive symptoms and cognitive impairment has been extensively studied in older adults (Andreescu et al. 2008; Graziane et al. 2016). Depressive symptoms are risk factors for cognitive impairment (Barnes et al. 2006; Saczynski et al. 2010; Rosenberg et al. 2010). Graziane et al. (2016) found that those with moderate-grade depressive symptoms were at high risk of persistently lower cognitive function over a 5-year period. While the relationship between depressive symptoms and cognitive deficit in older adults is established, the effect of depression on cognitive function in vulnerable populations, such as persons living with HIV (PLWH), has not been well described.

More than half of PLWH today in the USA are aged 50 years and older (Mahy et al. 2014). Many are living longer without AIDS-related complications as a result of highly active antiretroviral therapy (HAART) (Goodkin et al. 2001) but are at increased risk for age-

related comorbidities (Guaraldi et al. 2011; Vance et al. 2011). Moreover, HIV-infected individuals have twice the risk of major depressive disorder, compared to HIV-uninfected individuals (Ciesla and Roberts 2001). The estimated prevalence of depression in PLWH varies from 22% (Campos et al. 2008) to 71% (Savetsky et al. 2001). Depression is a risk factor for both HIV viral load increase and CD4 T cell count decline, indicating that depression may act to enhance viral replication or suppress immune function in PLWH (Horberg et al. 2008; Ironson et al. 2005).

Cognitive impairment affects up to 52% of middle-aged PLWH (Heaton et al. 2010), compared with 16–19% of HIV-uninfected adults (Heaton et al. 2011). Cognitive decline is independently associated with aging (Plassman et al. 2010; Sachdev et al. 2012) and HIV infection (Heaton et al. 2011), such that increasing age and HIV severity both add substantially to the burden of cognitive impairment among PLWH (Wendelken and Valcour 2012). In PLWH, a history of chronically low CD4 T cell count predicts cognitive impairment (Heaton et al. 2011) indicating one pathway whereby depression may increase the risk of cognitive impairment among PLWH (Kiecolt-Glaser and Glaser 2002). Additionally, depression increases the risk for medication non-adherence, leading to poorer viral suppression and cognitive impairment (Gonzalez et al. 2011).

One domain of cognitive function that may be particularly susceptible to the effect of HIV and depression is executive function, a set of higher-order cognitive processes including attention, inhibitory control, and working memory. Early changes in executive function may predict mild cognitive impairment (Albert et al. 2001; Petersen et al. 2001) and contribute to difficulties in daily functioning (Heaton et al. 2004). HIV is associated with executive dysfunction (Reger et al. 2002), a characteristic of HIV-related neurocognitive impairment (Dawes et al. 2008).

To elucidate the association between depression and attention/executive dysfunction among PLWH, we used data from a cohort of HIV-infected and HIV-uninfected older men who have sex with men (MSM) with up to 12 years of serial assessments on depressive symptoms and attention/executive function. By classifying participants by long-term patterns of depressive symptoms and attention/executive function, we examined whether specific longitudinal patterns of depressive symptoms were associated with patterns of worse attention/executive function by HIV status. We hypothesized that associations of depression patterns with worse attention/executive function would be more pronounced in HIV-infected MSM than in HIV-uninfected MSM.

Methods

Research participants

The study was conducted within the Multicenter AIDS Cohort Study (MACS), a prospective study of the natural history of HIV infection among MSM that started in 1984 (Kaslow et al. 1987). Study design, eligibility criteria, and recruitment have been described previously (Kaslow et al. 1987). In brief, participants ($N = 7338$) underwent structured interviews and physical exams every 6 months. For the present study, we restricted the data set to those aged 50 and older ($N = 6981$), to coincide with the onset or exacerbation of depressive

symptoms and cognitive decline in most populations (Ganguli 2009). Follow-up time was contributed from May 1986 to April 2015.

To assure robust modeling of long-term patterns, we further restricted to HIV-infected and HIV-uninfected participants with at least five visits (2.5 years) of follow-up data at which both depressive symptoms and executive function were measured, given that a minimum of three assessments are needed for trajectory estimation (Murphy et al. 2015; Nagin and Odgers 2010). HIV serostatus was treated as time-varying with seroconverters contributing to both HIV-infected and HIV-uninfected trajectories. The study protocol was approved at all collaborating institutions' IRBs, and participants provided written informed consent.

Depressive symptoms

Depressive symptoms were assessed via the Center for Epidemiologic Study—Depression scale (CES-D), a 20-item self-report measure of depressive symptom severity experienced during the past week (Radloff 1977). A CES-D score ≥16 was used to define the presence of mild clinically relevant depressive symptoms (Radloff 1977) at each semiannual visit.

Measures of attention/executive function

Attention/executive function was assessed semiannually from study inception, using the performance on two cognitive tests as indicators of the construct: the number of symbol-digit pairs from the Symbol Digit Modalities Test (SDMT) (Smith 1968) and the completion times from the Trail Making Test (TMT) (Reitan 1958). The TMT Part A and SDMT assess information processing. The TMT Part B has a set-shifting component, which indexes attention/executive function. We used the difference in completion times of TMT Parts B and A to obtain an assessment of executive function, since both measures encompass psychomotor functioning (Corrigan and Hinkeldey 1987; Drane et al. 2002; Sanchez-Cubillo et al. 2009).

Z-scores were calculated for attention/executive function and standardized to the baseline visit using the baseline test-specific mean and standard deviation (SD) across all MACS participants (Becker et al. 2014; Selnes and Miller 1994). Then, the test-specific *z*-scores for each visit were summed and re-standardized such that the interpretation of the domain-specific *z*-score would be one SD change in the baseline score (Rawlings et al. 2014).

Covariates

Fixed covariates included baseline age, race, college education, enrollment cohort, and cumulative years of efavirenz and rilpivirine use. Enrollment cohort adjusts for socioeconomic differences and cART era exposure differences between enrollment waves (Walensky et al. 2006). Efavirenz and Rilpivirine cause depressive symptoms (Panel on Antiretroviral Guidelines for Adults and Adolescents), and efavirenz may lead to susceptibility to cognitive impairment (Jin et al. 2016).

Time-varying covariates included hypertension, dyslipidemia, illegal drug use, heavy alcohol use, viral load, and low CD4 count. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Dyslipidemia was defined as either a

fasting total cholesterol ≥200 mg/dL, low-density lipoprotein >40 mg/dL, triglycerides ≥150 mg/dL, or use of lipid-lowering medication with self-report of a previous diagnosis. Both were absorbent states, such that the individual was assumed to always have the condition after meeting the definition. Illegal drug use and heavy alcohol use (heavy/binge drinking vs. none/low/moderate drinking) were reported for the 6 months period prior to the study visit. Viral load was log-transformed, and low CD4 count was defined as <200 vs. ≥200 cells/mm^3 (US Department of Health and Human Services).

Trajectory group membership for depressive symptoms and attention/executive function

To identify distinct trajectory patterns of depressive symptoms and attention/executive function, we used a latent group-based dual trajectory modeling approach under the assumption that the sample is drawn from a discrete set of subpopulations, each one having a distinct trajectory pattern, to approximate an underlying continuous distribution with a complex structure (Graziane et al. 2016; Jones and Nagin 2007; Jones et al. 2001; Nagin and Odgers 2010; Nagin and Tremblay 2001).

First, we modeled depressive symptoms and attention/executive function data separately to find the best-fit group-based univariate trajectory models. The optimal number of trajectory classes and functional form (linear or polynomial) were determined. Criteria for the determination of best fit were average posterior probability of trajectory group membership >0.7 for all trajectory groups, smallest Bayesian information criteria, presence of at least 5% of participants in each trajectory group, and the odds of correct classification >5.0 (Nagin and Tremblay 2001).

For depressive symptoms, a logit model was used to describe the probability of clinically significant depressive symptoms at each visit up to 12 years. This model was adjusted for time-varying covariates to estimate the highest membership probability in depression trajectory groups. For attention/executive function, a censored normal model was used to describe attention/executive function *z*-scores over time.

Next, we jointly estimated the proportion of the sample belonging to each attention/executive function trajectory group by depression trajectory groups in a dual trajectory model of depressive symptoms and attention/executive function.

Statistical analysis

We characterized the sample at the baseline visit using means and percentages. We also compared baseline depressive symptoms and attention/executive function *z*-scores between included vs. excluded participants, stratified by HIV status, to evaluate whether the requirement of at least 2.5 years of data led to a non-representative sample in terms of the distribution of depression and cognitive status. The baseline visit was the first visit with available data occurring at or after age 50.

After assigning group membership for long-term depressive symptoms and attention/executive function, multivariable logistic regression models were used to determine if moderate/high depression groups were associated with worst attention/executive functioning. Models were adjusted for baseline covariates only, as the depression group

membership estimation included all time-varying covariates. A p value <0.05 guided statistical interpretation. Analyses with model fit were done using R 3.1.2 and SAS version 9.4, and all other analyses were completed using Stata version 13.1 (Jones and Nagin 2007; R Core Team 2015; SAS Institute Inc. 2002–2004; StataCorp 2013).

Sensitivity analysis

We repeated all methods to define class membership using a CES-D ≥20 (Lyness et al. 1997) and an alternate definition of depressive symptoms that allowed either CES-D ≥16 or current antidepressant use to see if inferences remained the same. The alternate definition was used in lieu of adjustment for depression treatment, as antidepressant use is both a cause and a consequence of depression status. Thus, adjustment could introduce bias.

Results

Sample characteristics

There were 669 HIV-infected and 942 HIV-uninfected older MSM who met eligibility criteria. There were no differences in baseline depressive symptoms and attention/executive function z-scores among included and excluded HIV-uninfected MSM (ps > 0.05). Among included and excluded HIV-infected MSM, we found differences in mean z-scores of attention/executive function (p = 0.03), but no differences in baseline depressive symptoms (p = 0.44) and the univariate association between depressive symptoms and attention/executive function z-scores (ps > 0.05).

Demographic characteristics

Baseline sample characteristics are shown in Table 1. HIV-infected MSM were more likely to be younger; have recent illegal drug use, diabetes, hypertension, and hyperlipidemia; report more baseline depressive symptoms; and be on antidepressant treatment longer than HIV-uninfected MSM (all ps < 0.01). HIV-infected MSM were less likely to be Caucasian and college-educated as well as belong to post-2000 enrollment waves (all ps < 0.01). Also, HIV-infected MSM had fewer visits completed than HIV-uninfected MSM (p < 0.01).

Table 1 shows the characteristics by depression trajectory. The mean baseline age, race, and illegal drug use differed by depression trajectory groups among HIV-uninfected MSM (all ps < 0.01) but did not differ among HIV-infected MSM (all ps > 0.05). College education, antidepressant use, post-2000 enrollment wave, and mean number of completed visits (all ps < 0.01) differed by depression trajectory groups between HIV-infected and HIV-uninfected MSM. Baseline diabetes, hypertension, and dyslipidemia did not differ by depression trajectory groups between HIV-infected and HIV-uninfected MSM (all ps > 0.05).

Trajectory group membership for depression and attention/executive function

The optimal univariate trajectory model fit for depression and executive dysfunction was achieved when three trajectory groups for both were specified (Supplementary Tables 1 and 2). The three patterns for HIV-infected MSM were rare/never (50.0%), periodically depressed (29.6%), and chronic high (20.5%). The three patterns for HIV-uninfected MSM were rare/never (60.6%), periodically depressed (24.5%), and chronic high (15.0%) (Fig. 1).

Among HIV-infected MSM, the three attention/executive function groups were worst-performing (47.4%), average (41.9%), and best-performing (10.7%) (Fig. 2). Similarly, among the HIV-uninfected MSM, the three attention/executive function groups were worst-performing (45.1%), average (47.0%), and best-performing (8.0%) (Fig. 2).

Relationships of trajectories between depressive symptoms and attention/executive function

We examined the proportion of individuals in each depression group who were assigned to the worst-performing attention/executive function trajectories (Supplementary Table 2). The *chronic high* depressed group for both HIV-infected and HIV-uninfected samples had the highest percent membership in the *worst-performing* attention/executive function group (52.4, 60.1%). The *rare/never* depressed group from HIV-infected and HIV-uninfected samples had the highest percent membership in the *best-performing* attention/executive function group (12.7, 8.5%) (Supplementary Table 2).

Associations of depression trajectory groups and worst-performing attention/executive function group

We used logistic regression models to examine the association between worst-performing attention/executive function group membership and the depression group membership with and without baseline covariate adjustment. Best-performing and average attention/executive function groups were combined because of a small sample in the best-performing group. Among HIV-infected MSM, MSM belonging to the chronic high depressed (OR 1.13, 95% CI 0.74, 1.73) and the periodically depressed (odds ratio [OR] 1.09, 95% confidence interval [CI] 0.75, 1.59) groups were not associated with the odds of worst-performing attention/executive function, as compared to the rare/never depressed group (Table 2). Among HIV-uninfected MSM, MSM belonging to either chronic high depressed groups (OR = 2.25, 95% CI 1.49, 3.39) or periodically depressed (OR = 1.45, 95% CI 1.04, 2.03) had higher odds of belonging to the worst-performing attention/executive function group, as compared to the rare/never depressed group (Table 2).

Sensitivity analyses

After determining the best-fitting trajectory model based on a logit distribution when using CES-D ≥20, we found three depressive symptom classes for both samples (Supplementary Tables 1 and 2, Supplementary Fig. 1). In both samples, the magnitudes were similar (Supplementary Table 3).

As an additional analysis, we included antidepressant use with CES-D at each visit to broaden the definition of depressive symptoms for the group membership. When we examined the association of the depressive symptom trajectory groups with worst-performing attention/executive function group, inferences did not change (Supplementary Table 4).

Discussion

Our findings suggest that there are three depressive symptom trajectory patterns (rare/never, periodically depressed, and chronic high) and three attention/executive function trajectory patterns (worst-performing, average, and best-performing) among older HIV-infected and HIV-uninfected MSM. Among HIV-infected MSM, there was no association between the depressive symptom trajectory groups and worst-performing attention/executive function group. We expected that HIV-infected MSM in the chronic high depressed group would have higher odds of worst-performing group membership compared to HIV-infected MSM in the rare/never depressed group, but our results do not support this hypothesis. Among HIV-uninfected MSM, compared to the rare/never depressed group, those in the periodically depressed and chronic high depressed group have higher odds of worst-performing attention/executive function group membership. This result suggests that depressive symptoms are related to impairments in attention/executive function in older adults without HIV infection, which is consistent with other studies (Butters et al. 2004; Kommer et al. 2013).

The lack of an association between depressive symptom trajectory groups and attention/executive function trajectory groups among HIV-infected MSM could be explained in several ways. First, HIV-infected MSM had more cumulative years on antidepressant therapy and elevated baseline depressive symptoms than HIV-uninfected MSM. HIV-infected MSM appear to be aggressively treated and receive more follow-up care, which may mitigate any long-term impact on cognition. Similar results were found when we used a stringent threshold for the CES-D for depression trajectories.

Secondly, HIV-infected MSM had greater baseline cognitive deficits. We found that HIV-infected MSM had significantly fewer pairs on the SDMT than HIV-uninfected MSM at baseline. HIV-infected MSM may already be experiencing some non-specific baseline cognitive deficits, as compared to HIV-uninfected MSM, and thus, effects of depression may have already occurred prior to entry into our study.

Lastly, the impact of depression on attention/executive function among HIV-infected may be relatively small compared to the effect of other HIV-related factors, resulting in an inability to detect its contribution.

Main strengths of the study were repeated measures of depressive symptoms and attention/executive function collected semiannually since 1984. Substantial follow-up is needed in the HAART era to detect changes in sensitive indicators of HIV-related cognitive impairment (Sacktor et al. 1996; Sacktor et al. 2010; Cole et al. 2007). Cognitive performance diminishes slightly as we age, so long-term follow-up of neuropsychological measures may detect changes (Salthouse 1996). The study also had a large sample of an aging at-risk population in which risk for depression and cognitive function deficit is expected to be relatively high, providing an ideal platform for characterizing depression and attention/executive patterns longitudinally.

There were several study limitations. First, older participants tended to be from the first enrollment wave of MACS. This may introduce survivorship bias, meaning that those in earlier enrollment waves are different from those in later enrollment waves. This may lead to

questionable generalizability to the current HIV-infected population (Becker et al. 2009; Becker et al. 2014; Sacktor et al. 2010). Another limitation is the lack of clinical interview for depression diagnosis. To overcome this limitation, we assessed face validity of depression trajectory classifications, by showing that the baseline CES-D scores and proportion on antidepressants increased as the severity of depressive symptom trajectories increased. Moreover, there may be unmeasured confounders, such as social support, which may affect inferences.

These results suggest the importance of screening for depressive symptoms in older HIV-uninfected MSM. Assessment of depressive symptoms up to 12 years after age 50 showed that those with chronic high depression were more likely to have worse attention/executive function among HIV-uninfected men. We did not find added impact of HIV and depression on attention/executive function among HIV-infected men.

Further studies are required to determine if similar results are present in HIV-infected women and HIV-infected individuals acquiring HIV infection through different risk factors. MACS only consists of MSM, representative of one vulnerable population. Injection drug users represent another vulnerable population at risk for depression, HIV infection, and cognitive impairment. If similar patterns emerge, then depression might not be a major contributor to executive dysfunction among HIV-infected individuals. However, HIV-uninfected individuals appear to be at great risk of executive dysfunction if they are severely depressed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank all MACS participants and Alden Gross and Ms. Natalie Kelso for their expertise.

Funding This study was supported by the National Institutes of Health (1R03MH10396-01). An additional source of support for MACS included the Center for AIDS Research, Johns Hopkins University (P30AI094189). NMA was supported by fellowship from the Epidemiology and Biostatistics of Aging Training Grant (5T32AG000247).

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS): MACS (principal investigators): Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels), U01-AI35040; University of Pittsburgh (Charles Rinaldo), U01-AI35041; and the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR001079 (JHU ICTR) from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

Role of funder/sponsor The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH), Johns Hopkins ICTR, or NCATS. The MACS website is located at http://aidscohortstudy.org/.

References

Albert M, Moss M, Tanzi R, Jones K. Preclinical prediction of AD using neuropsychological tests. JINS. 2001; 7:631–639. [PubMed: 11459114]

Almeida OP, Alfonso H, Flicker L, Hankey GJ, Norman PE. Cardiovascular disease, depression and mortality: the Health in Men Study. Am J Geriatr Psychiatry. 2012; 20:433–440. [PubMed: 21422905]

Andreescu C, Chang C, Mulsant B, Ganguli M. Twelve-year depressive symptom trajectories and their predictors in a community sample of older adults. Int Psychogeriatr. 2008; 20:221–236. [PubMed: 18234145]

Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A, Furberg CD, Group CHSCR. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Circulation. 2000; 102:1773–1779. [PubMed: 11023931]

Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Arch Gen Psychiatry. 2006; 63:273–279. [PubMed: 16520432]

Becker J, Kingsley L, Mullen J, Cohen B, Martin E, Miller E, Ragin A, Sacktor N, Selnes O, Visscher B, for Multicenter AIDS Cohort Study. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology. 2009; 73:1292–1299. [PubMed: 19841381]

Becker J, Kingsley LA, Molsberry S, Reynolds S, Aronow A, Levine AJ, Martin E, Miller EN, Munro CA, Ragin A, Sacktor N, Selnes OA. Cohort profile: recruitment cohorts in the neuropsychological substudy of the Multicenter AIDS Cohort Study. Int J Epidemiol. 2014:1–11.

Broadhead W, Blazer D, George L, Tee C. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA. 1990; 264:2524–2528. [PubMed: 2146410]

Butters M, Whyte E, Nebes R, Begley A, Dew M, Mulsant B, Zmuda M, Bhalla R, Meltzer C, Pollock B, Reynolds C, Becker J. The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry. 2004; 61:587–595. [PubMed: 15184238]

Campos L, Guimaraes M, Remien R. Anxiety and depression symptoms as risk factors for non-adherence to antiretroviral therapy in Brazil. AIDS Behav. 2008; 14

Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. Am J Psychiatry. 2001; 158:725–730. [PubMed: 11329393]

Cole M, Margolick J, Cox C, Li X, Selnes O, Martin E, Becker J, Aronow H, Cohen B, Sacktor N, Miller E, for Multicenter AIDS Cohort Study. Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. Neurology. 2007; 69:2213–2220. [PubMed: 17914066]

Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. J Clin Psychol. 1987; 43:402–409. [PubMed: 3611374]

Dawes S, Suarez P, Casey CY, Cherner M, Marcotte TD, Letendre S, Grant I, Heaton RK, the HNRC Group. Variable patterns of neuropsychological performance in HIV-1 infection. J Clin Exp Neuropsychol. 2008; 30:613–626. [PubMed: 18608689]

Drane DL, Yuspeh RL, Huthwaite JS, Klingler LK. Demographic characteristics and normative observations for derived-trail making test indices. Cogn Behav Neurol. 2002; 15:39–43.

Ganguli M. Depression, cognitive impairment and dementia: why should clinicians care about the web of causation? Indian J Psychiatry. 2009; 51:S29–S34. [PubMed: 21416013]

Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J Acquir Immune Defic Syndr. 2011; 58doi: 10.1097/QAI.0b013e31822d490a

Goodkin K, Wilkie F, Concha M, Hinkin C, Symes S, Baldewicz T, Asthana D, Fujimura R, Lee D, Mv Z, Khamis I, Shapshak P, Eisdorfer C. Aging and neuro-AIDS conditions and the changing spectrum of HIV-1-associated morbidity and mortality. J Clin Epidemiol. 2001; 54:S35–S43. [PubMed: 11750208]

Graziane JA, Beer JC, Snitz BE, Chang C-CH, Ganguli M. Dual trajectories of depression and cognition: a longitudinal population-based study. Am J Geriatr Psychiatry. 2016; 24:364–373. [PubMed: 26560510]

Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, Berti A, Rossi E, Roverato A, Palella F. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011; 53:1120–1126. [PubMed: 21998278]

Heaton R, Marcotte T, Mindt M, Sadek J, Moore D, Bentley H, McCutchan J, Reicks C, Grant I. The impact of HIV-associated neuropsychological impairment on everyday functioning. JINS. 2004; 10:317–331. [PubMed: 15147590]

Heaton R, Clifford D, Franklin D, Woods S, Ake C, Vaida F, Ellis R, Letendre S, Marcotte T, Atkinson J, Rivera-Mindt M, Vigil O, Taylor M, Collier A, Marra C, Gelman B, McArthur J, Morgello S, Simpson D, McCutchan J, Abramson I, Gamst A, Fennema-Notestine C, Jernigan T, Wong J, Grant I, For the CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75:2087–2096. [PubMed: 21135382]

Heaton R, Franklin D, Ellis R, McCutchan J, Letendre S, LeBlanc S, Corkran S, Duarte N, Clifford D, Woods S, Collier A, Marra C, Morgello S, Mindt MR, Taylor M, Marcotte T, Atkinson JH, Wolfson T, Gelman B, McArthur J, Simpson D, Abramson I, Gamst A, Fennema-Notestine C, Jernigan T, Wong J, Grant I, For the CHARTER and HNRC Groups. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neuro-Oncol. 2011; 17:3–16.

Horberg M, Silverberg M, Hurley L, Towner W, Klein D, Bersoff-Matcha S, Weinberg W, Antoniskis D, Mogyoros M, Dodge W, Dobrinich R, Quesenberry C, Kovach D. Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients. J Acquir Immune Defic Syndr. 2008; 47:384–390. [PubMed: 18091609]

Ironson G, O'Cleirigh C, Fletcher M, Laurenceau J, Balbin E, Klimas N, Schneiderman N, Solomon G. Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. Psychosom Med. 2005; 67:1013–1021. [PubMed: 16314608]

Jin J, Grimmig B, Izzo J, Brown L, Hudson C, Smith A, Tan J, Bickford P, Giunta B. HIV non-nucleoside reverse transcriptase inhibitor efavirenz reduces neural stem cell proliferation in vitro and in vivo. Cell Transplant. 2016; 25:1967–1977. [PubMed: 28836850]

Jones B, Nagin D. Advances in group-based trajectory modeling and an SAS procedure for estimating them. Sociol Methods Res. 2007; 35:542–571.

Jones B, Nagin D, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. Sociol Methods Res. 2001; 29:374–393.

Kaslow R, Ostrow D, Detels R, Phair J, Polk B Jr, C R. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. 1987; 126:310–318. [PubMed: 3300281]

Kiecolt-Glaser JK, Glaser R. Depression and immune function. J Psychosom Res. 2002; 53:873–876. [PubMed: 12377296]

Kommer TN, Comijs H, Aartsen M, Huisman M, Deeg D, Beekman A. Depression and cognition: how do they interrelate in old age? Am J Geriatr Psychiatry. 2013; 21:398–410. [PubMed: 23498387]

Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients: a comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. Arch Intern Med. 1997; 157:449–454. [PubMed: 9046897]

Mahy M, Autenreith CS, Stanecki K, Wynd S. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. AIDS. 2014; 28:S453–S459. [PubMed: 25222641]

Murphy R, Hagaman A, Reinders I, Steeves J, Newman A, Rubin S, Satterfield S, Kritchevsky S, Yaffe K, Ayonayon H, Nagin D, Simonsick E, Penninx B, Harris T, For the Health ABC Study. Depressive trajectories and risk of disability and mortality in older adults: longitudinal findings from the Health, Aging, and Body Composition Study. J Gerontol A Biol Sci Med Sci. 2015:1–8. [PubMed: 24534516]

Nagin D, Odgers C. Group-based trajectory modeling in clinical research. Ann Rev Clin Psychol. 2010; 6:109–138. 10.1146/annurev.clinpsy.121208.131413.: 109–138. [PubMed: 20192788]

Nagin D, Tremblay R. Analyzing developmentary trajectories of distinct but related behaviors: a group-based method. Psychol Methods. 2001; 6:18–34. [PubMed: 11285809]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 30 Dec 2016

Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001; 58:1985–1992. [PubMed: 11735772]

Plassman BL, Williams JW Jr, Burke J, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med. 2010; 153:182–193. [PubMed: 20547887]

R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing; Vienna: 2015.

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.

Rawlings AM, Sharrett AR, Schneider ALC, Coresh J, Albert M, Couper D, Griswold M, Gottesman RF, Wagenknecht LE, Windham BG, Selvin E. Diabetes in midlife and cognitive change over 20 years: the Atherosclerosis Risk in Communities Neurocognitive Study. Ann Intern Med. 2014; 161:785–793. [PubMed: 25437406]

Reger M, Welsh R, Razani J, Martin D, Boone K. A meta-analysis of the neuropsychological sequelae of HIV infection. JINS. 2002; 8:410–424. [PubMed: 11939699]

Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills. 1958; 8:271–276.

Rosenberg PB, Mielke MM, Xue Q-L, Carlson MC. Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. Am J Geriatr Psychiatry. 2010; 18:204–211. [PubMed: 20224517]

Sachdev P, Lipnicki D, Crawford J, Reppermund S, Kochan N, Trollor J, Draper B, Slavin M, Kang K, Lux O, Mather K, Brodaty H, the Memory and Ageing Study Team. Risk profiles of subtypes of mild cognitive impairment: the Sydney Memory and Ageing Study. JAGS. 2012; 60:24–33.

Sacktor N, Bacellar H, Hoover D, Nance-Sproson T, Selnes O, Miller E, Pan GD, Kleeberger C, Brown A, Saah A, McArthur J. Psychomotor slowing in HIV infection: a predictor of dementia, AIDS, and death. J Neuro-Oncol. 1996; 2:404–410.

Sacktor N, Skolasky RL, Cox C, Selnes O, Becker JT, Cohen B, Martin E, Miller EN. Longitudinal psychomotor speed performance in human immunodeficiency virus-seropositive individuals: impact of age and serostatus. J Neuro-Oncol. 2010; 16:335–341.

Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf P, Au R. Depressive symptoms and risk of dementia: the Framingham Heart Study. Neurology. 2010; 75:35–41. [PubMed: 20603483]

Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychol Rev. 1996; 103:403–428. [PubMed: 8759042]

Sanchez-Cubillo I, Perianez J, Adrover-Roig D, Rodriguez-Sanchez J, Rios-Lago M, Tirapu J, Barcelo F. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J Int Neuropsychol Soc. 2009; 15:438. [PubMed: 19402930]

SAS Institute Inc. SAS 9.1.3. SAS Institute Inc; Cary: 2002–2004.

Savetsky J, Sullivan L, Clarke J, Stein M, Samet J. Evolution of depressive symptoms in human immunodeficiency virus-infected patients entering primary care. J Nerv Ment Dis. 2001; 189:76–83. [PubMed: 11225690]

Selnes, OA., Miller, EN. Development of a screening battery for HIV-related cognitive impairment: the MACS experience. In: Grant, I., Martin, A., editors. Neuropsychology of HIV infection. Oxford University Press Inc; New York: 1994. p. 176-187.

Smith, A., editor. The symbol-digit modalities test: a neuropsychologic test of learning and other cerebral disorders. Special Child Publications; Seattle: 1968.

Snowden MB, Atkins DC, Steinman LE, Bell JF, Bryant LL, Copeland C, Fitzpatrick AL. Longitudinal association of dementia and depression. Am J Geriatr Psychiatry. 2015; 23:897–905. [PubMed: 25441056]

StataCorp. Stata Statistical Software: Release 13. StataCorp LP: College Station; 2013.

Services DoHaH. , editor. Substance Abuse and Mental Health Services Administration. The treatment of depression in older adults: depression and older adults: key issues. Center for Mental Health Services, Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services. US Department of Health and Human Services AIDS.gov; 2011.

Vance D, Mugavero M, Willig J, Raper J, Saag M. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. J Assoc Nurses AIDS Care. 2011; 22:17–25. [PubMed: 20471864]

Walensky R, Paltiel A, Losina E, Mercincavage L, Schackman B, Sax P, Weinstein M, Freedberg K. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006; 194:11–19. [PubMed: 16741877]

Wendelken LA, Valcour V. Impact of HIVand aging on neuropsychological function. J Neuro-Oncol. 2012; 18:256–263.

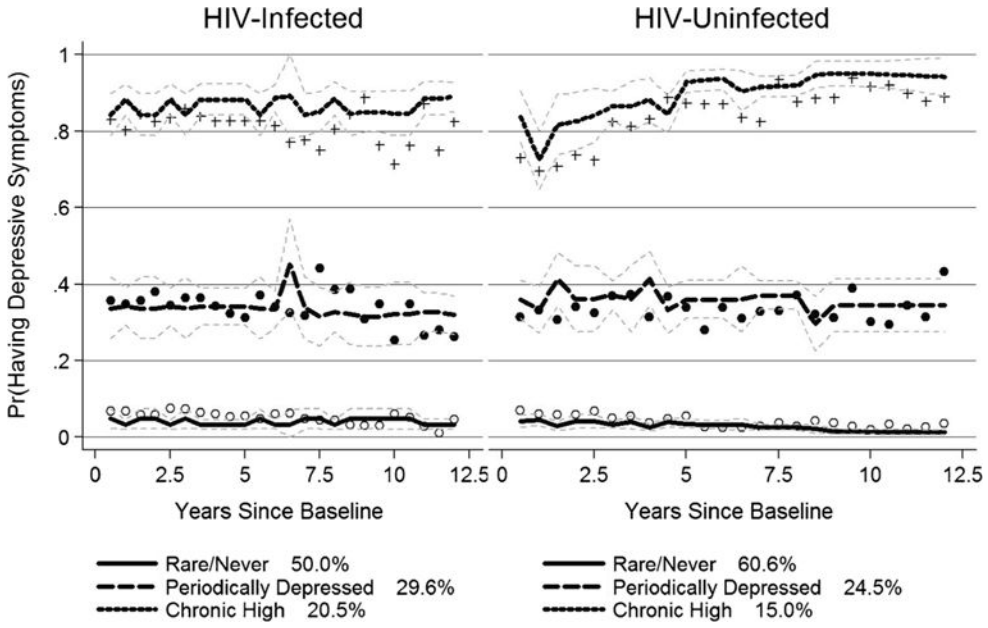

Fig. 1.

Depressive symptom trajectory groups and years since baseline visit using a logistic regression group-based trajectory model by HIV status. The trajectory models were adjusted by time-varying covariates, such as hypertension, dyslipidemia, illegal drug use, heavy alcohol use, low CD4 count (HIV-infected men only), and viral load (HIV-infected men only). Cutoff of CES-D was 16 and above for each visit since baseline

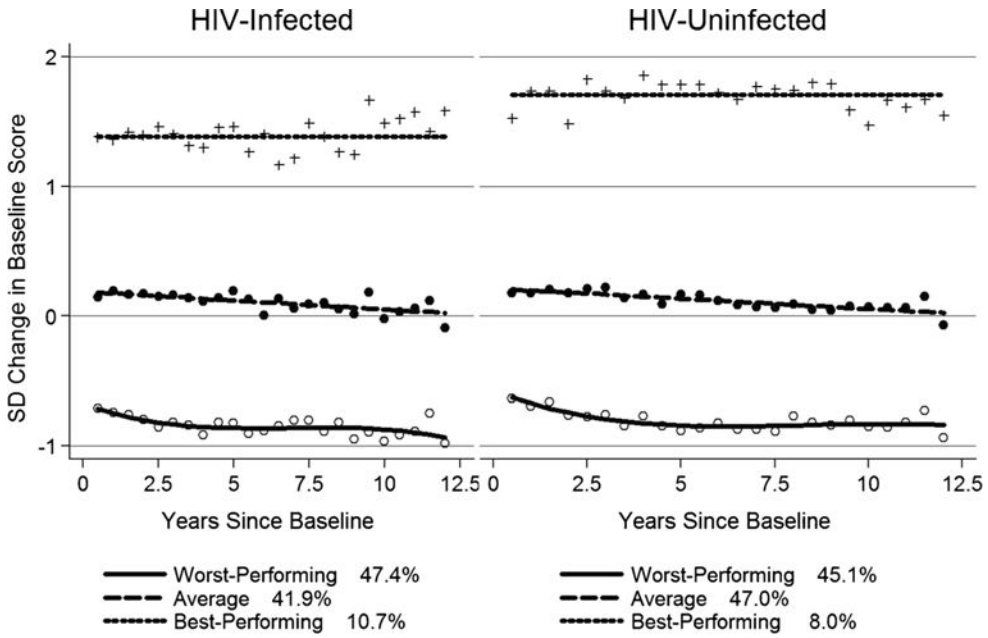

Fig. 2.

Trajectories of *z*-scores of attention/executive function and years since baseline visit using censored normal group-based trajectory models

J Neurovirol. Author manuscript; available in PMC 2017 September 30.

Table 1

Characteristics of the participants, overall and by depressive symptom trajectory group

Baseline characteristics	HIV+ (*N* = 669)	HIV− (*N* = 942)	*p*	HIV-infected				HIV-uninfected			
				Depressive symptom trajectory classes				Depressive symptom trajectory classes			
				Rare/never *N* = 378	Periodically depressed *N* = 180	Chronic high *N* = 138	*p*	Rare/never *N* = 642	Periodically depressed *N* = 184	Chronic high *N* =116	*p*
Age, mean (SD)	50.9 (2.44)	52.2 (3.7)	<0.01	50.9 (2.5)	50.9 (2.4)	50.9 (2.4)	0.99	52.6 (4.1)	51.3 (2.5)	51.4 (2.6)	<0.01
Caucasian, *n* (%)	474 (70.9)	796 (84.5)	<0.01	281 (74.3)	127 (70.6)	90 (65.2)	0.12	565 (88.0)	148 (80.4)	83 (71.6)	<0.01
College education, *n* (%)	356 (53.2)	637 (67.7)	<0.01	218 (74.3)	99 (56.6)	55 (41.0)	<0.01	454 (71.2)	122 (66.7)	61 (53.5)	<0.01
Diabetes, *n* (%)	45 (6.7)	30 (3.2)	<0.01	27 (13.6)	11 (9.8)	7 (9.3)	0.48	21 (7.6)	6(6.7)	3 (4.5)	0.67
Hypertension, *n* (%)	443 (66.2)	552 (58.6)	<0.01	213 (69.8)	129 (73.7)	101 (74.8)	0.47	337 (65.2)	131 (71.2)	84 (72.4)	0.16
Dyslipidemia, *n* (%)	535 (80.0)	613 (65.1)	<0.01	280 (86.7)	149 (85.1)	106 (78.5)	0.09	397 (75.0)	131 (71.2)	85 (73.3)	0.58
Antidepressants, *n* (%)	145 (21.7)	192 (20.4)	0.09	46 (13.0)	40 (22.9)	59 (43.7)	<0.01	92 (14.4)	50 (27.2)	50 (43.1)	<0.01
CES-D score, mean (SD)	13.3 (9.7)	11.5 (8.6)	<0.01	8.6 (5.6)	14.1 (7.9)	24.7 (10.4)	<0.01	8.3 (5.5)	14.7 (7.5)	24.5 (10.3)	<0.01
Cohort 2000 and after, *n* (%)	373 (55.8)	756 (80.3)	<0.01	234 (61.9)	93 (51.7)	67 (48.6)	<0.01	534 (83.2)	137 (74.5)	85 (73.3)	<0.01
TMT A, mean (SD)	24.0 (10.8)	24.8 (10.1)	0.16	23.1 (10.1)	23.9 (10.2)	26.5 (12.8)	<0.01	24.9 (10.2)	22.8 (7.8)	27.1 (12.4)	<0.01
TMT B, mean (SD)	55.9 (32.8)	54.0 (25.6)	0.22	53.0 (29.6)	54.6 (33.4)	65.3 (38.4)	<0.01	54.0 (25.4)	50.0 (21.5)	61.0 (31.3)	<0.01
Number of pairs, SDMT, *n* (%)	52.7 (12.9)	54.3 (11.8)	0.01	53.6 (12.4)	53.5 (13.4)	49.2 (13.1)	<0.01	54.6 (11.5)	55.3 (11.8)	51.2 (12.7)	<0.01
Years on antidepressants, mean (SD)	3.0 (4.4)	2.6 (4.5)	<0.01	1.6 (2.9)	3.5 (4.4)	5.0 (5.0)	<0.01	1.7 (3.5)	3.5 (4.9)	5.5 (5.9)	<0.01
Recent illegal drug use, *n* (%)	369 (54.8)	397 (42.4)	<0.01	198 (53.2)	93 (53.4)	78 (60.9)	0.29	249 (39.6)	87 (46.0)	61 (50.8)	0.04
Heavy drinking, *n* (%)	148 (22.0)	219 (23.4)	0.45	77 (20.7)	31 (17.8)	40 (31.3)	0.01	143 (22.8)	43 (22.8)	33 (27.5)	0.52
Low CD4 count, *n* (%)	53 (7.9)	–	–	30 (8.1)	16 (9.2)	7 (5.5)	0.48	–	–	–	–
Viral load(in 1000), mean (SD)	17.0 (5.7)	–	–	21.7 (68.0)	14.2 (47.2)	7.3 (17.2)	0.04	–	–	–	–
Years on efavirenz, mean (SD)	3.5 (4.7)	–	–	3.5 (4.8)	3.8 (4.7)	3.1 (4.4)	0.39	–	–	–	–
Years on rilpivirine, mean(SD)	0.1 (0.3)	–	–	0.1 (0.4)	0.1 (0.4)	0.1 (0.3)	0.97	–	–	–	–
Number of completed semiannual visits, mean (SD)	10.2 (7.8)	11.0 (8.3)	<0.01	9.2 (6.2)	8.9 (6.1)	8.2 (5.7)	<0.01	9.4 (6.4)	9.6 (6.2)	8.8 (5.9)	<0.01

TMT A and TMT B were measured by completion times in seconds. Diabetes was defined as a fasting glucose greater than or equal to 126 mg/dL or self-report of a previous clinical diagnosis with medication. Viral load was measured in 1000 cells/mL; low CD4 count was <200 vs. 200+ cells/mm^3. Years on antidepressants, efavirenz, and rilpivirine represent cumulative years on these drugs. Recent drug use is defined as use of any of the following drugs in the last 6 months: phencyclidine, depressants, ethyl, gamma-hydroxybutyric acid, speed balls, opiates/heroin, stimulants, erectile dysfunction drugs, cocaine, alkyl nitrites, or marijuana. *p* values represent *p* values of the differences among the categories

SD standard deviation, *CES-D* Centers for Epidemiologic Studies-Depression Scale, *TMT* Trail Making Test, *SDMT* Symbol Digit Modalities Test

Table 2

Unadjusted and adjusted logistic regression models comparing depressive symptom trajectory group adjusted for time-varying covariates to worst-performing trajectory groups for attention/executive function by HIV status

	HIV-infected		HIV-uninfected	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Depression group				
Rare/never	REF	REF	REF	REF
Periodically depressed	1.12 (0.79, 1.60)	1.09 (0.75, 1.59)	*1.44 (1.04, 1.99)*	*1.45 (1.04, 2.03)*
Chronic high	1.28 (0.86, 1.91)	1.13 (0.74, 1.73)	*2.39 (1.61, 3.56)*	*2.25 (1.49, 3.39)*
Baseline age		1.02 (0.95, 1.10)		*1.07 (1.03, 1.11)*
College education		*0.64 (0.46, 0.88)*		*0.74 (0.55, 0.98)*
Race		0.70 (0.46, 1.07)		*0.62 (0.38, 0.99)*
Cumulative years on efavirenz		0.98 (0.95, 1.02)		–
Cumulative years on rilpivirine		0.76 (0.45, 1.26)		–
Post-2000 enrollment wave		0.88 (0.59, 1.29)		1.15 (0.74, 1.78)

Time-varying covariates included hypertension, dyslipidemia, illegal drug use, heavy alcohol use, low CD-4 count (only for HIV-infected men), and log-transformed viral load (only for HIV-infected men). Depressive symptoms were defined using a cutoff point of 16 or greater on the CES-D. All italic odds ratios indicate significance at *p* value less than 0.05. Cohort is defined as enrollment waves occurring prior to 2000 vs. enrollment waves occurring after 2000

OR odds ratio, *CI* confidence interval