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# Neurocognitive impairment in HIV-infected individuals with previous syphilis

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## Summary

Cognitive impairment is common in HIV-infected individuals, as is syphilis. *Treponema pallidum*, the bacterium that causes syphilis, invades the central nervous system early in disease. We hypothesized that HIV-infected patients with a history of syphilis or neurosyphilis would have more cognitive impairment than HIV-infected individuals without these infections. Eighty-two of 1574 enrollees in CHARTER, a prospective, observational study, had reactive serum rapid plasma reagin (RPR) tests. They were matched to 84 controls with non-reactive RPR by age, gender, ethnicity and HIV risk factor. Participants underwent comprehensive neuropsychological (NP) evaluations. RPR results were confirmed and serum fluorescent treponemal antibody absorption (FTA-ABS) test reactivity determined at a central laboratory. Sera from 101 of 166 participants were FTA-ABS reactive, indicating past or current syphilis. Among the 136 individuals without confounding conditions, compared with patients who had never had syphilis, those with prior syphilis had a greater number of impaired NP test domains (1.90 SD [1.77] versus 1.25 [1.52], $P$ = 0.03), a higher global deficit score (0.47 [0.46] versus 0.31 [0.33], $P$ = 0.03), and more were

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impaired in the NP learning domain (36 [42.9%] of 84 versus 13 [25.0%] of 52, $P = 0.04$). These effects of prior syphilis remained after controlling for education and premorbid intelligence.

### Keywords

HIV; AIDS; sexually transmitted infection; Treponema pallidum; syphilis; neurocognitive impairment; neurosyphilis; central nervous system

## INTRODUCTION

In 2000, the rate of infectious syphilis in the USA was the lowest since reporting began in 1941. However, since 2001, the number of cases of syphilis in the USA has increased steadily. Between 2001 and 2010, the rates of primary and secondary syphilis more than doubled. In 2010, 67% of primary and secondary syphilis cases reported to the Centers for Disease Control and Prevention occurred in men who have sex with men (MSM).[1] HIV is particularly common in men who have sex with men (MSM) with syphilis,[2] and MSM who use methamphetamine are more likely to have syphilis than non-users.[3]

*Treponema pallidum* spp *pallidum* (hereafter termed *T. pallidum*), the bacterium that causes syphilis, invades the central nervous system (CNS) early in the course of infection. Viable organisms or their DNA or RNA can be identified in cerebrospinal fluid (CSF) from patients with primary and secondary syphilis.[4,5] CNS invasion is of particular concern in patients also infected with HIV, in whom clearance of the organism from the CNS may be impaired.[6,7] Asymptomatic neurosyphilis, defined as CSF abnormalities consistent with neurosyphilis in a neurologically asymptomatic patient, occurs in about one-quarter of HIV-infected patients with syphilis.[4] However, no study has investigated cognitive function in HIV-infected patients with ‘asymptomatic’ neurosyphilis. The current study was conducted to test the hypothesis that HIV-infected patients with a history of syphilis or neurosyphilis would have more cognitive impairment than HIV-infected individuals without these infections.

## METHODS

### Study participants

CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) is a prospective, observational study conducted at six USA research clinics: Johns Hopkins University, Baltimore, MD; The Mount Sinai School of Medicine, New York, NY; University of California, San Diego, CA (UCSD); University of Texas, Galveston, TX; University of Washington, Seattle, WA and Washington University, St Louis, MO. Institutional Review Boards at each site approved this research and each subject gave written informed consent to participate.

CHARTER participants undergo a comprehensive neuromedical, psychiatric and neuropsychological evaluation at study entry that includes collection of CSF and a serum rapid plasma reagin (RPR) test performed at the local study site. We identified 82 patients among 1574 enrollees who had a reactive serum RPR test result determined at the local site.

These cases were matched to 84 controls by age (±2 years), gender, ethnicity and HIV risk factor.

## Neuropsychological assessment

Participants underwent a 2–2.5 hour comprehensive neuropsychological test battery, covering seven major cognitive domains sensitive to HIV-associated cognitive dysfunction: (1) speed of information processing (Wechsler Adult Intelligence Scale [WAIS]-III Digit Symbol and Symbol Search subtests, Trail Making Test Part A), (2) learning (Hopkins Verbal Learning Tests Revised [HVLT-R] learning trials, Brief Visuospatial Memory Test Revised [BVMT-R] learning trials), (3) recall (HVLT-R delayed recall, BVMT-R delayed recall), (4) executive function (Wisconsin Card Sorting Test [64-item version], Trail Making Test Part B), (5) verbal fluency (Controlled Oral Word Association Test [F-A-S letters], Category Fluency [animals]), (6) attention and working memory (WAIS-III Letter-Number Sequencing, Paced Auditory Serial Addition Test-50), and (7) motor function (Grooved Pegboard Test, dominant and non-dominant hands).[8] The Reading subtest of the Wide Range Achievement Test (Third Edition) (WRAT-III) was administered as an index of premorbid verbal intelligence. Briefly, neuropsychological test scores were corrected for age, education, gender and ethnicity, as appropriate, and summary scores were determined for each domain; performance for each domain also was coded as impaired or unimpaired.[9] A clinical rating algorithm was used to classify presence or absence of overall neurocognitive impairment (global impairment), which required presence of at least mild impairment in two or more ability domains.[9] A single observer determined whether confounding conditions could explain, on their own, neurocognitive impairment. Examples of such confounding conditions include major depressive disorder with psychotic features, traumatic brain injury without return to work or school, developmental delay or learning disability with inability to perform some activities of daily living, and severe liver disease with hepatic encephalopathy.[10]

## Laboratory methods

Sera and CSF were sent to a single research laboratory. Serum RPR and fluorescent treponemal antibody absorbed (FTA-ABS) tests, and CSF Venereal Disease Research Laboratory (VDRL) tests (only in samples from participants with reactive serum FTA-ABS tests; CSF was missing for one participant) were performed using standard methods.[11] Compared with the serum RPR test results from the individual study sites, 15 fewer samples tested in the central research laboratory were RPR-reactive. Two samples were non-reactive at the study sites but reactive at the central laboratory. Four samples from the study sites were RPR-reactive but FTA-ABS non-reactive, consistent with a biological false-positive (BFP) result. There were no BFP results when considering the RPR results from the central laboratory.

Because cases and controls had been matched based on the serum RPRs collected at the sites, we confirmed the accuracy of our matching using the serum RPR results obtained at the central research laboratory. There were no statistically significant differences in age, gender, ethnicity or HIV risk factor between those with a reactive and non-reactive serum

RPR test at the central research laboratory. For the purposes of subsequent analysis, only the serological results obtained from the central research laboratory were considered.

Plasma and CSF HIV RNA concentrations were determined by reverse transcriptase polymerase chain reaction ultrasensitive assay (lower limit of quantitation 50 copies/mL; Amplicor, Roche Diagnostic Systems, Indianapolis, IN, USA) at the CHARTER coordinating centre laboratory at UCSD. Current CD4 was measured by flow cytometry at the local sites. Participants were asked to recall their lowest prior (nadir) CD4.

### Statistical methods

Subjects with major confounding conditions were excluded from the analysis of neuropsychological test performance.[8] Descriptive statistics are reported as mean (SD), median (interquartile range), and number (*N*) (%). Prior to all statistical testing, the data, either raw or transformed, were reviewed to establish that parametric test assumptions were valid. Shapiro–Wilk tests were used to test for normality. If assumptions were not valid, non-parametric methods were used when available. Associations between continuous variables were assessed using Pearson's or Spearman's correlation tests. For categorical variables, Pearson's chi-square or Fisher's exact tests were applied. Associations between continuous and categorical variables were determined by *t*-tests or Wilcoxon rank sum tests. Linear or logistic regression was used for multivariable analyses. *P* values $<0.05$ were considered to be statistically significant. No adjustments were made for multiple comparisons.

## RESULTS

### Participant characteristics

Not surprisingly, some sera from patients who were RPR non-reactive were FTA-ABS reactive. Overall, sera from 101 patients were FTA-ABS reactive, indicating that these individuals had syphilis at some time in the past. We did not have information on date of syphilis diagnosis and thus hereafter refer to these patients as having prior or past syphilis. Among the 94 patients with prior syphilis and available treatment information, only two reported that they had prior syphilis but had not been treated. However, 23 patients with reactive serum FTA-ABS tests gave no history of prior syphilis or its treatment.

### Neurocognitive function

Thirty patients had major confounding conditions that could explain, regardless of syphilis history or HIV infection, neurocognitive impairment, and they were excluded from the analysis. The proportion of patients with past syphilis did not differ between those patients with and without major confounding conditions (data not shown). Of the 136 patients included in the subsequent analysis, 52 had never had syphilis and 84 had past syphilis based on serum FTA-ABS reactivity (Table 1). Despite the fact that our original matching was based on serum RPR reactivity rather than FTA-ABS reactivity and did not take into account confounding conditions, patients with and without past syphilis who did not have major confounding factors were well matched (Table 1).

Compared with participants without prior syphilis, those with prior syphilis had a greater number of impaired neuropsychological test domains (1.90 [1.77] versus 1.25 [1.52], $P$ = 0.03) and a higher global deficit score (GDS) (0.47 [0.46] versus 0.31 [0.33], $P$ = 0.03), and a higher proportion of individuals were impaired in the neuropsychological learning domain (hereafter termed learning impairment) (36 [42.9%] of 84 versus 13 [25.0%] of 52, $P$ = 0.04). The two groups did not differ significantly on current depressive symptoms (as measured by the Beck Depression Inventory-II total score), WRAT-III score, years of education or performance on the other six cognitive domains. Compared with patients with documented syphilis treatment, patients with serological evidence of syphilis but no history of syphilis treatment did not have more impaired neurocognitive domains, worse GDS or greater prevalence of learning impairment. In addition, among patients with past syphilis, CSF HIV RNA concentrations, reactive serum RPR or, among those with a reactive serum RPR, serum RPR titers were not significantly associated with number of impaired neurocognitive domains, GDS or learning impairment.

Despite no difference in WRAT-III or years of education between those without and with prior syphilis, we repeated the above analyses taking these two variables into account due to their demonstrated importance in neurocognitive function. Taking into account WRAT-III and years of education in separate models, the number of impaired domains, GDS and proportion of patients with learning impairment remained higher in those with previous syphilis (for number of impaired domains, partial-$r$ 0.21, $P$ = 0.02 when adjusted for WRAT-III and partial-$r$ 0.18, $P$ = 0.04 with education; for GDS, partial-$r$ 0.21, $P$ = 0.02 after adjustment for WRAT-III and partial-$r$ 0.18, $P$ = 0.04 with education; for learning impairment partial-$r$ 0.20, $P$ = 0.02 when controlled for WRAT-III and partial-$r$ 0.17, $P$ = 0.04 with education).

Compared with participants who reported never using methamphetamine, a significantly higher proportion of individuals who had a history of methamphetamine use had learning impairment (21 [55.3%] of 38 versus 27 [27.8%] of 97, $P$ = 0.003). Similarly, compared with current non-users, a higher proportion of current methamphetamine users had learning impairment (8 [72.7%] of 11 versus 40 [32.3%] of 124, $P$ = 0.007). Among patients who had ever used methamphetamine ($N$ = 34), there was no significant relationship between learning impairment and reported age of first methamphetamine use, cumulative quantity, duration of use or days since last use (data not shown). Similarly, among current methamphetamine users ($N$ = 9), the reported quantity of methamphetamine used within the previous 30 days had no significant association with learning impairment.

The relationship between prior syphilis and learning impairment remained significant after taking into account history of methamphetamine use (odds ratio [OR] = 2.61, 95% confidence interval [CI]: 1.19–6.10, $P$ = 0.02), and there was a marginally significant association between prior syphilis and learning impairment when current methamphetamine use was taken into account (OR 2.12, 95% CI: 0.98–4.75, $P$ = 0.055). There was no significant relationship between number of impaired cognitive domains, GDS or learning impairment and plasma or CSF HIV RNA concentrations.

### Syphilis, neurosyphilis and CSF abnormalities

There was no significant association between past syphilis and CSF or plasma HIV RNA or CSF white blood cells (WBCs). Six of 100 patients with a reactive serum FTA-ABS test had a reactive CSF-VDRL, which is consistent with either a current or a past diagnosis of neurosyphilis. Treatment history was available for five of the six and disclosed that all five had been previously treated. Despite small numbers, among those with serological evidence of past syphilis, compared with patients with a non-reactive CSF-VDRL, patients with a reactive CSF-VDRL had higher CSF WBCs (17 [3–40] cells/μL versus 2 [1–6] cells/μL, $P$ = 0.02), higher CSF HIV RNA (3.32 [2.24–4.29] log copies/mL versus 1.70 [1.70–2.07] log copies/mL, $P$ = 0.001) and higher plasma HIV RNA (4.15 [2.36–5.32] log copies/mL versus 2.55 [1.70–4.28] log copies/mL, $P$ = 0.047). We found no significant relationship between a reactive CSF-VDRL and current or nadir CD4+ T-cell counts, and there was no significant relationship between the number of impaired neuropsychological test domains, GDS or proportion of patients with learning impairment and reactive CSF-VDRL or CSF WBCs.

## DISCUSSION

We conducted a case-control study of neurocognitive impairment in HIV-infected individuals enrolled in CHARTER with and without serological evidence of past syphilis. CHARTER participants are routinely screened for active syphilis with serum RPR but not with treponemal tests like the serum FTA-ABS test. Our cases were originally defined as having reactive serum RPR tests and they were matched to participants with non-reactive serum RPR tests. We subsequently found that many of our RPR-negative patients had reactive serum FTA-ABS tests, indicating prior recognized or unrecognized syphilis. This finding is not surprising. Syphilis is common among HIV-infected individuals, particularly in men who have sex with men.[12,13] While serum RPR may serorevert after syphilis therapy, this is rarely the case with serum FTA-ABS, which generally remains reactive for life.[14] Because we sought to identify the impact of prior syphilis on cognitive function, we chose to include individuals with reactive serum FTA-ABS tests but non-reactive serum RPR tests in our case group. We also restricted our analysis to individuals who did not have major confounding conditions that could explain neurocognitive impairment regardless of prior syphilis or HIV infection. Despite these deviations from our initial plan, our cases and controls were well matched. We found that HIV-infected patients with past syphilis performed more poorly on a comprehensive neuropsychological test battery than HIV-infected patients who had never had syphilis. Differences in performance were largely independent of years of education, premorbid intelligence as assessed by the WRAT-III and methamphetamine use. There was no difference in performance in those patients with evidence of past syphilis who currently had a reactive compared with a non-reactive serum RPR.

One previous study has examined the relationship between syphilis and cognition. Wallace *et al.*[15] tested cognitive function in HIV-infected and -uninfected patients with and without a history of syphilis or gonorrhoea, and found that performance was significantly impaired in HIV-infected patients who ever had either sexually transmitted infection (STD); similar findings were not seen in the HIV-uninfected group. The association with syphilis was

expected based on an *a priori* hypothesis. However, the association with gonorrhoea was difficult to explain, particularly because participants with and without a history of either STI had equivalent education. Our study differs from this previous study in several respects. We were able to exclude individuals with confounding conditions, addressed the concomitant impact of methamphetamine use, and were able to include CSF measures in our analysis. Because few of our patients reported prior gonorrhoea, we were not able to test for an association between cognitive impairment and this STI (data not shown).

Despite small numbers, we found that, compared with patients with a non-reactive CSF-VDRL, patients with a reactive CSF-VDRL, which is indicative of neurosyphilis, had higher CSF HIV RNA concentrations. In a recent report, de Almeida *et al.*[16] found that, among a sample of HIV-infected patients with detectable plasma HIV RNA, those with neurosyphilis had higher CSF HIV RNA concentrations than HIV-infected subjects with syphilis but not neurosyphilis (uncomplicated syphilis) and HIV-infected patients who had never had syphilis. The authors were able to use multivariable models to demonstrate that the increases in CSF HIV RNA concentration in patients with neurosyphilis were independent of plasma HIV RNA and CSF WBC concentrations. Because only six of our participants had laboratory evidence of neurosyphilis, we were not able to perform similar analyses.

*Treponema pallidum* invades the CNS in a large proportion of patients with syphilis and may go unnoticed. One possible explanation for our observation of poorer neurocognitive function in HIV-infected patients with prior syphilis is that CNS *T. pallidum* infection stimulates ingress of HIV-infected T-cells, which could directly augment CNS infection, tissue injury and cognitive dysfunction. T-helper cells are likely recruited to the CNS to control local *T. pallidum* infection.[17] Alternatively, CNS *T. pallidum* infection could augment ongoing CNS HIV infection by upregulation of inflammatory cytokines such as interleukin-10 and tumour necrosis factor (TNF)-alpha; plasma levels of both these cytokines decrease after treatment of uncomplicated syphilis.[18] Moreover, patients with early syphilis have increases in plasma HIV RNA concentrations that decline after syphilis treatment.[19–22]

In support of the above hypotheses, Arendt *et al.*[23] found that HIV-infected patients with cerebral toxoplasmosis as their AIDS-defining diagnosis were more likely to develop HIV-associated dementia than matched patients with *Pneumocystis* pneumonia as their AIDS-defining diagnosis, at more than 14 months after diagnosis. Similarly, Levine *et al.*[24] performed detailed neurocognitive assessments in HIV-infected patients with previous CNS opportunistic infections, including cryptococcal meningitis, toxoplasmosis and progressive multifocal leukoencephalopathy, and compared their performance with that of HIV-infected controls. All patients were taking combination antiretroviral therapy. Compared with controls, patients with previous CNS infections, particularly those with CNS toxoplasmosis, performed significantly more poorly on the neuropsychological test battery.

In our study, cognitive impairment was seen in individuals without and with evidence of CNS *T. pallidum* infection based on CSF-VDRL reactivity or CSF pleocytosis. An alternative hypothesis is that systemic *T. pallidum* infection leads to an inflammatory response that indirectly augments the detrimental cognitive effects of already established

CNS HIV infection. *In vitro* studies support the concept that acute systemic inflammation can accelerate the progression of neurodegenerative disease and ageing via activation of primed microglial cells (reviewed in ref.[25]). In addition, there is precedent for such a scenario in Alzheimer's disease. Holmes *et al.*[26] showed that among 269 assessable community dwelling patients with Alzheimer's disease, compared with those without acute systemic inflammatory events, patients with acute systemic inflammatory events had increases in serum TNF-alpha and had a two-fold increased rate of cognitive decline over six months.

Our study has limitations, which should be noted in interpreting our data. CHARTER focuses on neurological, neuropsychological and neuromedical consequences of HIV. Thus the historical information on syphilis is not collected prospectively, and is based on self-report. We did not have information on previous syphilis stage or specific treatment, and the number of subjects with neurosyphilis was small. Based on the epidemiology of syphilis in the USA,[1,2] we assume that HIV was acquired before syphilis, but the opposite could be true in some individuals. As noted above, our eventual choice of cases and controls differed from our initial plan. Nonetheless, our results are in keeping with those of past studies and extend beyond previous work by excluding individuals with confounding conditions, and including comprehensive neurocognitive assessments, consideration of recreational drug use and CSF measures in the same analyses. To better understand the individual contributions of syphilis and HIV to cognitive impairment in HIV-infected patients, future work should include study of HIV-infected and -uninfected individuals with and without syphilis and neurosyphilis, and in those with syphilis, should examine the impact of its treatment.

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## REFERENCES

1. [last checked 30 September 2012] See http://www.cdc.gov/std/stats10/syphilis.htm
2. Buchacz K, Klausner JD, Kerndt PR, et al. HIV incidence among men diagnosed with early syphilis in Atlanta, San Francisco, and Los Angeles, 2004–2005. J Acquir Immune Defic Syndr. 2008; 47:234–240. [PubMed: 18340654]
3. Wong W, Chaw JK, Kent CK, Klausner JD. Risk factors for early syphilis among gay and bisexual men seen in an STD clinic: San Francisco, 2002–2003. Sex Transm Dis. 2005; 32:458–463. [PubMed: 15976605]
4. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis. 2004; 189:369–376. [PubMed: 14745693]
5. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. N Engl J Med. 1997; 337:307–314. [PubMed: 9235493]
6. Taylor MM, Aynalem G, Olea LM, He P, Smith LV, Kerndt PR. A consequence of the syphilis epidemic among men who have sex with men (MSM): neurosyphilis in Los Angeles, 2001–2004. Sex Transm Dis. 2008; 35:430–434. [PubMed: 18446083]
7. Walter T, Lebouche B, Miailhes P, et al. Symptomatic relapse of neurologic syphilis after benzathine penicillin G therapy for primary or secondary syphilis in HIV-infected patients. Clin Infect Dis. 2006; 43:787–790. [PubMed: 16912958]

8. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75:2087–2096. [PubMed: 21135382]
9. Woods SP, Rippeth JD, Frol AB, et al. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. J Clin Exp Neuropsychol. 2004; 26:759–778. [PubMed: 15370374]
10. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789–1799. [PubMed: 17914061]
11. Larsen, SA.; Pope, V.; Johnson, RE.; Kennedy, EJ, Jr. A Manual of Tests for Syphilis. 9th edn.. Washington, DC: American Public Health Association; 1998.
12. Chesson HW, Heffelfinger JD, Voigt RF, Collins D. Estimates of primary and secondary syphilis rates in persons with HIV in the United States, 2002. Sex Transm Dis. 2005; 32:265–269. [PubMed: 15849526]
13. Pathela P, Braunstein SL, Schillinger JA, Shepard C, Sweeney M, Blank S. Men who have sex with men have a 140-fold higher risk for newly diagnosed HIV and syphilis compared with heterosexual men in New York City. J Acquir Immune Defic Syndr. 2011; 58:408–416. [PubMed: 21857351]
14. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev. 1995; 8:1–21. [PubMed: 7704889]
15. Wallace MR, Heaton RK, McCutchan JA, et al. Neurocognitive impairment in human immunodeficiency virus infection is correlated with sexually transmitted disease history. Sex Transm Dis. 1997; 24:398–401. [PubMed: 9263360]
16. de Almeida SM, Bhatt A, Riggs PK, et al. Cerebrospinal fluid human immunodeficiency virus viral load in patients with neurosyphilis. J Neurovirol. 2010; 16:6–12. [PubMed: 20132081]
17. Marra CM, Castro CD, Kuller L, et al. Mechanisms of clearance of *Treponema pallidum* from the CSF in a nonhuman primate model. Neurology. 1998; 51:957–961. [PubMed: 9781512]
18. Knudsen A, Benfield T, Kofoed K. Cytokine expression during syphilis infection in HIV-1-infected individuals. Sex Transm Dis. 2009; 36:300–304. [PubMed: 19265730]
19. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. Aids. 2004; 18:2075–2079. [PubMed: 15577629]
20. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. Sex Transm Dis. 2006; 33:143–148. [PubMed: 16505739]
21. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. J Acquir Immune Defic Syndr. 2007; 44:356–359. [PubMed: 17159654]
22. Jarzebowski W, Caumes E, Dupin N, et al. Effect of early syphilis infection on plasma viral load and CD4 cell count in human immunodeficiency virus-infected men: results from the FHDH-ANRS CO4 cohort. Arch Intern Med. 2012; 172:1237–1243. [PubMed: 22826097]
23. Arendt G, von Giesen HJ, Hefter H, Neuen-Jacob E, Roick H, Jablonowski H. Long-term course and outcome in AIDS patients with cerebral toxoplasmosis. Acta Neurol Scand. 1999; 100:178–184. [PubMed: 10478582]
24. Levine AJ, Hinkin CH, Ando K, et al. An exploratory study of long-term neurocognitive outcomes following recovery from opportunistic brain infections in HIV+ adults. J Clin Exp Neuropsychol. 2008; 30:836–843. [PubMed: 18608693]
25. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol. 2008; 84:932–939. [PubMed: 18495785]
26. Holmes C, Cunningham C, Zotova E, et al. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009; 73:768–774. [PubMed: 19738171]

## Table 1

Characteristics of 136 participants included in the neurocognitive analyses

| | Prior syphilis *N* = 84 | No prior syphilis *N* = 52 | All *N* = 136 |
|---|---|---|---|
| **Characteristics** | | | |
| Female | 21 (25.0%) | 11 (21.2%) | 32 (23.5%) |
| Age, years | 41.6 (8.9) | 41.0 (9.9) | 41.4 (9.3) |
| Education, years | 12.7 (2.6) | 12.4 (2.0) | 12.6 (2.4) |
| Race/ethnicity | | | |
| Hispanic | 12 (14.3%) | 2 (3.9%) | 14 (10.3%) |
| White | 23 (27.4%) | 18 (34.6%) | 41 (30.1%) |
| African American | 49 (58.3%) | 32 (61.5%) | 81 (59.6%) |
| HIV risk factor | | | |
| MSM | 43 (51.2%) | 28 (54.9%)* | 71 (52.6%) |
| Heterosexual | 41 (48.8%) | 23 (45.1%)* | 64 (47.4%) |
| Injection drug use | 10 (11.9) | 10 (19.2%) | 20 (14.7%) |
| Estimated duration of HIV infection in years | 9.7 (6.6)† | 8.6 (6.1) | 9.2 (6.4) |
| Currently taking ARVs | 54 (64.3%) | 35 (67.3%) | 89 (65.4%) |
| Ever taken ARVs | 67 (79.8%) | 45 (86.5%) | 112 (82.4%) |
| Current CD4, cells/μL | 462 (324)† | 444 (252) | 455 (298) |
| Nadir CD4, cells/μL | 264 (263)‡ | 202 (156) | 240 (229) |
| Log plasma HIV RNA, copies/mL | 2.53 (1.70–4.28) | 2.65 (1.70–4.15) | 2.57 (1.70–4.23) |
| Log CSF HIV RNA, copies/mL | 1.70 (1.70–2.31)† | 1.70 (1.70–2.81) | 1.70 (1.70–2.50) |
| Currently using methamphetamine | 8 (9.6%)† | 3 (5.8%) | 11 (8.1%) |
| Ever used methamphetamine | 21 (25.3%)† | 17 (32.7%) | 38 (28.1%) |
| WRAT-III | 93.1 (14.0) | 90.3 (15.3) | 92.0 (14.5) |

MSM = men who have sex with men; CSF = cerebrospinal fluid; ARV = antiretroviral therapy; WRAT-III = Wide Range Achievement Test, Third Edition Results are expressed as *N* (percent), mean (standard deviation) and median (interquartile range)

*$N = 51$

†$N = 83$; one subject whose urine toxicology screen was positive for methamphetamine but who reported that he had never used methamphetamine was not included in the methamphetamine using group

‡$N = 82$