Structural brain alterations can be detected early in HIV infection

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ABSTRACT

Objective: Brain changes occurring early in HIV infection are not well characterized. The Chicago Early HIV Infection Study aimed to evaluate the presence and extent of structural brain alterations using quantitative MRI.

Methods: Forty-three HIV and 21 control subjects were enrolled. Mean length of infection was estimated as less than 1 year based on assay results. High-resolution neuroanatomical images were acquired. Automated image analysis was used to derive measurements for total brain, ventricular volume, and for tissue classes (total and cortical gray matter, white matter, and CSF). A separate image analysis algorithm was used to calculate measurements for individual brain regions. Cognitive function was assessed by neuropsychological evaluation.

Results: Reductions were quantified in total ($p = 0.0547$) and cortical ($p = 0.0109$) gray matter in the HIV group. Analysis of individual brain regions with a separate image analysis algorithm revealed consistent findings of reductions in cerebral cortex ($p = 0.042$) and expansion of third ventricle ($p = 0.046$). The early HIV group also demonstrated weaker performance on several neuropsychological tests, with the most pronounced difference in psychomotor speed ($p = 0.001$).

Conclusions: This cross-sectional brain volumetric study indicates structural alterations early in HIV infection. The findings challenge the prevailing assumption that the brain is spared in this period. Revisiting the question of the brain's vulnerability to processes unfolding in the initial virus-host interaction and the early natural history may yield new insights into neurologic injury in HIV infection and inform neuroprotection strategies. *Neurology*® 2012;79:2328–2334

GLOSSARY

ARV = antiretroviral; **MP-RAGE** = magnetization prepared rapid acquisition gradient echo.

HIV is widely disseminated throughout the body soon after transmission. Virus is detected first in lymph nodes and then in plasma within 5 days.[1] Although it has been established that viral invasion of the brain occurs early in infection,[2–4] possible changes during this period are not well characterized. Brain atrophy, white matter alterations, and injury to subcortical regions, such as basal ganglia, have been shown later in the course of infection.[5–7] Symptoms of brain involvement, such as cognitive deterioration, have been associated with increased risk of death[8,9]; however, the onset of neurologic injury has not been determined. A clearer understanding of the natural history of brain injury, particularly in the earliest stages, is therefore critical.

The Chicago Early HIV Infection Study was established to evaluate the presence and extent of brain injury using quantitative MRI. This report presents findings of a brain volumetric study designed to explore whether structural brain alterations can be detected early in the natural history of infection. Measurements were calculated for total brain, ventricular volume, and for tissue classes, including total gray matter, cortical gray matter, brain white matter, and CSF using SIENAX, an automated image analysis tool.[10] To examine localized changes, measurements

Supplemental data at www.neurology.org

Supplemental Data

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were derived for individual brain regions and landmarks using a separate algorithm, Freesurfer.[11] Cognitive function was assessed by neuropsychological evaluation.

METHODS Standard protocol approvals, registrations, and patient consents. The Northwestern University Institutional Review Board approved this investigation. All subjects provided written informed consent.

Table 1 Baseline characteristics of the Chicago Early HIV Infection cohort

	HIV (n = 43)	Controls (n = 21)	p Value
Age (mean years ± SD)	32.9 ± 9.8	31.4 ± 8.8	0.62
Gender (% male)	88	76	0.28
Race (% white)	63	76	0.24
Education (% college)	76	90	0.31
NART-R score	106.74 ± 10.2	111.264 ± 8.6	0.09
Substance use (past month)			
Alcohol (≥5 drinks)	25	8	0.24
Marijuana	13	2	0.07
Cocaine	3	0	0.55
Amphetamines	1	0	0.66
Glue or solvent sniffing	0	0	—
Heroin	0	0	—
Other	2	0	0.54
Clinical characteristics of the HIV participants			
CD4 cell count, cells/μL			
Mean ± SD	550 ± 254		
Range	162–1,282		
Plasma HIV RNA copies/mL (log_{10})			
Mean ± SD	3.17 ± 1.38		
ARV naive (n = 23)	3.54 ± 1.46		
Initiated on ARV (n = 20)	2.75 ± 1.18		
Regimen			
Efavirenz, emtricitabine, tenofovir (Atripla)	11		
Ritonavir, atazanavir, emtricitabine/tenofovir	3		
Ritonavir, atazanavir, tenofovir, abacavir	1		
Ritonavir, atazanavir, abacavir/lamivudine	1		
Ritonavir, darunavir, raltegravir	1		
Ritonavir, raltegravir, darunavir	1		
Raltegravir, emtricitabine/ tenofovir	1		
Unknown[a]	1		

Abbreviations: ARV = antiretroviral; NART-R = National Adult Reading Test-Revised; estimated full-scale IQ.
[a] One subject initiated on ARV had poor adherence and could not remember the regimen.

Participants. Forty-three HIV (38 men, 5 women; mean age: 32.9 ± 9.8 years) and 21 seronegative (16 men, 5 women; mean age: 31.4 ± 8.8 years) subjects were enrolled between March 2008 and July 2010. Exclusion criteria included chronic neurologic disorder, head injury, radiation/chemotherapy (prior month), uncontrolled seizure disorder, experimental drugs or vaccination within the past 15 days, mental condition involving inability to understand, chronic/active alcohol abuse, chronic/active drug abuse, pregnancy, opportunistic infection, cancer, medical condition (heart, liver, or kidney), or MRI contraindication. Demographic and clinical information is presented in table 1. HIV subjects were enrolled based on referrals from Infectious Disease and Sexually Transmitted Disease Clinics of Northwestern Memorial Hospital or through self-referral. Subjects with self-reported recent HIV infection were screened before study enrollment for an available prior negative test result or clinical history suggesting recent infection (e.g., symptoms consistent with acute HIV after unprotected high-risk sexual behavior or newly diagnosed HIV in a sexual partner). All infected subjects reported sexual transmission as the method of infection. Seronegative subjects were recruited from the same Chicago urban areas. HIV and seronegative groups did not differ in age, gender, racial composition, educational level (percentage of college), National Adult Reading Test–Revised scores,[12] or alcohol or drug use (table 1). IV drug use was not reported in either group. Blood samples were collected from all subjects. Serostatus was determined by ELISA and Western blot. An early infection assay was used to assess relative recency of infection (Blood Systems, San Francisco, CA). Fifteen subjects were within 6 months of initial infection, including 9 within 2 months (i.e., nonreactive: 95% confidence interval: 47–75 days). The mean length of infection was estimated to be approximately 1 year (mean: 367 days; 95% confidence interval: 258–495 days). Absolute CD4+ cell counts ranged from 162 to 1,282/mm^3 (mean: 550 ± 254.4/mm^3; median: 506/mm^3); plasma viral load (log_{10}) ranged from undetectable to 5.54 copies/mL (mean: 3.17 ± 1.38 copies/mL; median: 3.30 copies/mL). Plasma viral load was undetectable (<50 copies/mL) in 8 of the HIV subjects. Twenty-three HIV subjects were antiretroviral (ARV) naive. For the 20 who had initiated ARV treatment, CNS penetration-effectiveness rank was determined based on revised 2010 scaling.[13]

Magnetic resonance imaging. Imaging data were acquired on a single magnetic resonance scanner, a 3T MAGNETOM Tim Trio (Siemens, Erlangen, Germany) with maximum gradient slew rate, 200 mT/m/s, maximum gradient strength, 40 mT/m, using a 12-channel receive-only headcoil. Sagittal whole-brain magnetization prepared rapid acquisition gradient echo (MP-RAGE) images were acquired (repetition time/inversion time/echo time: 2300/900/2.91 milliseconds; flip angle: 9°; field of view: 256 × 256 mm; slice thickness: 1 mm; resolution: 1 × 1 mm; slices: 176). SIENAX (Oxford University, Oxford, UK) was used to calculate measurements for total brain and ventricular volume and for specific tissue classes (total gray matter, cortical gray matter, total white matter, and total CSF; table 2),which were normalized for individual differences in head size.[10] SIENAX first extracts a brain and skull image from the subject's structural MP-RAGE input image. The skull image is used to determine the registration scaling from subject space to standard space (MNI125). This scaling is then used in the affine-registration of the brain image to standard space. This process defines the volumetric scaling factor then used to normalize the brain volume. To avoid introducing error from blurring associated with registration,

Table 2 Brain volumetric measurements[a]

	HIV (n = 43)	Controls (n = 21)	t Test	p Value	ES
Overall brain volume	1,575,602 ± 105,871	1,607,367 ± 77,036.7	−1.22	0.23	0.33
Gray matter	893,076 ± 67,866.9	925,978 ± 54,840.7	−1.93	0.05[b]	0.51
Cortical gray matter	681,442 ± 57,275.2	712,101 ± 34,820.4	−2.25	0.01[b]	0.60
White matter	682,526 ± 64,713.6	681,389 ± 41,379.7	0.07	0.93	0.02
Ventricular volume	30,785 ± 11,128.4	28,301 ± 8,992.4	0.89	0.38	0.24

Abbreviation: ES = effect size: mean difference/common SD.
[a] Volumes in mm^3.
[b] Significant *p* values.

tissue segmentation is performed on the original (nonregistered) MP-RAGE images and volumes are then scaled by the scaling factor to derive the normalized measurements.

A separate algorithm, Freesurfer,[11] was used to derive measurements of individual regions and landmarks of the brain (table e-1 on the *Neurology*® Web site at www.neurology.org), depicted in figure e-1. To eliminate operator variability in manual editing, a fully automated approach was used. Case-by-case visual inspection indicated consistent image quality across all scans; skull stripping and segmentation results met quality assurance standards for both cortical and subcortical segmentation. Measurements for individual regions (table e-1) were divided by the intracranial cavity volume derived in Freesurfer to adjust for individual differences in head size.

Cognitive assessment. A neuropsychological test battery that has been used in HIV neurologic outcome studies[14] was used to evaluate cognitive function.

Statistical analysis. The brain volumetric measurements, which were the primary variables for analysis, were continuous variables. Distributional assumptions were evaluated using the Shapiro-Wilk test. Group comparisons were accomplished with independent *t* tests or Wilcoxon signed rank test; χ^2 or Fisher exact test was used for categorical variables. Comparison of brain volumetric measurements in HIV and control groups was considered a priori analysis and a significance level of 0.05 was used. Secondary analyses involving multiple subgroups (e.g., HIV naive, HIV receiving ARV treatment, and controls) were accomplished with analysis of variance or Kruskal-Wallis test, followed by Tukey adjusted pairwise comparison. False discovery rate was used to control the error rate for group comparisons of individual neuropsychological tests. Pearson or Spearman correlation coefficients were used to examine relationships between clinical measures and brain volumetric measurements that distinguished HIV and control groups. The quantitative early infection assay was used to estimate length of infection. Multivariable regression was used to examine the influence of subject characteristics on brain volumetric differences between the groups. Covariates of interest, including age, education, race, gender, past month alcohol use, past month cocaine use, and past month amphetamine use, were initially evaluated in univariate analyses for relationship with each brain volumetric measurement that differed in HIV and control groups. Covariates with $p < 0.25$ in the univariate analysis were then included in a multivariable regression model using backward elimination at a significance level of 0.05. A similar approach was used separately in the HIV group to evaluate clinical variables available only for this group (viral load [log transformed], CD4+ cell count, CD8, duration of infection, and ARV status [naive or initiated]) in addition to subject characteristics, for association with brain volumetric measurements. All analyses were executed with SAS 9.2 software (SAS Institute, Cary, NC).

RESULTS

Brain volumetric measurements. Reductions were identified in SIENAX measures for total gray matter ($p = 0.0547$) and cortical gray matter ($p = 0.0109$) in the HIV group (table 2). Total brain, total white matter, and ventricular volumes did not differ. Freesurfer measurements for individual brain regions were then compared (table e-1). The third ventricle was enlarged ($p = 0.036$) in the HIV group. Freesurfer measurements for cerebral cortex were reduced ($p = 0.040$), with lower values for both hemispheres compared with controls (mean ± SD: left 0.1581 ± 0.01 vs 0.1652 ± 0.01, $p = 0.021$; right 0.1604 ± 0.01 vs 0.1675 ± 0.01, $p = 0.039$).

Volumetric measurements that differed in the groups were also examined in the most recently infected HIV subgroup (infected <6 months). This analysis indicated a consistent pattern, with reductions identified in SIENAX measures for total ($t^{34} = 2.95$; $p = 0.006$; mean ± SD: 863,347 ± 72,793.5 vs 925,978 ± 54,840.7) and cortical gray matter ($t^{34} = 2.99$; $p = 0.005$; mean ± SD: 660,068 ± 68,553.8 vs 712,101 ± 34,820.4) compared with controls. Similarly, in the most recently infected HIV subgroup, Freesurfer measurements for third ventricle were enlarged ($t^{33} = -2.24$; $p = 0.032$; mean ± SD: 0.000668 ± 0.0001 vs 0.000572 ± 0.000134) and were nearly significantly reduced for cerebral cortex ($t^{33} = 1.91$; $p = 0.065$; mean ± SD: 0.1583 ± 0.0155 vs 0.1663 ± 0.009) compared with controls.

Cognitive status. As shown in table 3, the HIV group (n = 43) had weaker performance on Digit Symbol ($p = 0.001$), Rey Complex Figure Recall ($p = 0.003$), Verbal Fluency ($p = 0.007$), Rey Auditory Verbal Learning ($p = 0.024$), Letter-Number Sequencing ($p = 0.021$), Grooved Pegboard (dominant: $p = 0.033$ and nondominant: $p = 0.033$), and Odd Man Out ($p = 0.032$) (all *p* values adjusted for false discovery rate). Correlations of individual neuropsychological tests with brain volumetric measures are shown in table e-2.

Table 3 Neuropsychological measures

	HIV mean (SD)	Control mean (SD)	FDR p Value
Digit Symbol	57.21 (9.63)	68.05 (8.11)	0.001[a]
Verbal Fluency	34.6 (7.50)	42.09 (10.18)	0.007[a]
Rey Complex Figure Recall	21.90 (7.08)	27.84 (4.48)	0.003[a]
Letter-Number Sequencing	11.24 (2.75)	13.52 (3.33)	0.02[a]
Rey Auditory Verbal Learning	9.42 (2.75)	11.45 (2.65)	0.02[a]
Grooved Pegboard (dominant)	65.40 (8.46)	59.60 (9.59)	0.03[a]
Grooved Pegboard (nondominant)	71.15 (9.32)	65.05 (9.79)	0.03[a]
Odd Man Out	9.74 (0.44)	9.95 (0.21)	0.03[a]
Rey Complex Figure Copy	31.93 (4.61)	34.05 (3.47)	0.13
Timed Gait	10.28 (2.24)	9.66 (1.30)	0.23
Trails A	29.30 (8.86)	26.32 (8.73)	0.25
Trails B	66.51 (26.54)	60.73 (17.24)	0.34
CALCAP Choice	426.8 (54.72)	424.3 (54.10)	0.87
CALCAP Sequential	536.2 (110.7)	540.5 (96.40)	0.88

Abbreviations: CALCAP = California Computerized Assessment Package; FDR = false discovery rate.
[a] Significant *p* values.

Multivariable analyses. To examine the influence of subject characteristics on the brain volumetric differences, age, education, race, gender, alcohol use (≥5 drinks in past month), and past month amphetamine or cocaine use were examined separately for each outcome (total gray matter, cortical gray matter, cerebral cortex, and third ventricle). Covariates with $p < 0.25$ in univariate analysis were then included in separate multivariable regression models for each brain volumetric outcome using backward elimination at a significance level of 0.05. Age was the only covariate identified for total gray matter, cortical gray matter, and cerebral cortex; there were no covariates for third-ventricular group difference. After adjusting for age, however, group differences between HIV and controls remained for cortical gray matter ($p = 0.039$) and cerebral cortex ($p = 0.051$) and were nearly significant for total gray matter ($p = 0.096$).

Table 4 Correlations: Volumetric measurements and HIV clinical measures[a]

	Entire HIV sample (n = 43)		ARV naive (n = 23)		ARV treatment (n = 20)		
	Plasma HIV RNA	CD4+	Plasma HIV RNA	CD4+	Plasma HIV RNA	CD4+	CPE
Total gray matter	0.15	−0.16	−0.03	−0.20	0.43	−0.21	0.48[b]
Cortical gray matter	0.11	−0.17	−0.02	−0.29	0.46[c]	−0.18	0.46[c]
Cerebral cortex	0.12	−0.17	−0.15	−0.43[c]	0.44[c]	−0.15	0.30
Third ventricle	−0.29[c]	0.22	−0.12	0.34	−0.03	0.03	−0.46[c]

Abbreviations: ARV = antiretroviral; CPE = CNS penetration-effectiveness rank.
[a] Spearman partial correlations adjusted for length of infection based on the early infection assay estimate.
[b] $p < 0.05$.
[c] $p < 0.10$.

HIV disease status. Table 4 presents Spearman partial correlations between the volumetric measurements that differed in the groups (total gray matter, cortical gray matter, cerebral cortex, and third ventricle) and disease progression measures (plasma HIV RNA and CD4+ cell count) for the entire HIV sample and separately for ARV-naive and ARV subgroups. Correlations with CNS penetration index are also shown. Because plasma HIV RNA and CD4+ cell count are known to be highly nonlinear in the early clinical course, correlations were adjusted for length of infection using the quantitative early infection assay. No associations with plasma HIV RNA and CD4+ cell count were identified in this cross-sectional study. Lower CNS penetration was associated with reduced total gray matter ($\rho = 0.48$; $p < 0.05$); nearly significant associations with reduced cortical gray matter ($p < 0.10$) and with third-ventricular enlargement ($p < 0.10$) were also identified in the ARV subgroup.

Further analyses considered clinical variables (CD4+ cell count, viral load [log transformed], CD8, length of infection, ARV status [naive or initiated]) and subject characteristics (age, education, race, gender, alcohol [≥5 drinks in past month], and past month drug use) for associations with brain volumetric outcomes (total gray matter, cortical gray matter, cerebral cortex, and third ventricle) separately in the HIV group. Covariates with $p < 0.25$ in univariate analysis were included in a separate multivariable regression model for each brain volumetric outcome using backward elimination at a significance level of 0.05. The only factor associated with outcome in the HIV group was age: total gray matter ($p < 0.0001$), cortical gray matter ($p < 0.0001$), cerebral cortex ($p < 0.0001$), and third ventricle ($p = 0.0196$).

DISCUSSION Findings from the Chicago Early HIV Infection Study indicate reductions in both total and cortical gray matter in a cohort infected, on average, <1 year. Analysis of individual brain regions using a separate algorithm revealed bilateral reductions in cerebral cortex with expansion of third ventricle. It is widely assumed that the brain does not incur injury in early infection. Limited autopsy information is available for this period, however, and in earliest stages, structural brain alterations may not be apparent on postmortem examination. With advances in imaging technology, it is possible to quantify structural brain alterations in vivo that may not be detected otherwise. Other quantitative imaging studies have detected alterations in neuronal markers in frontal gray matter,[15] in resting cerebral blood flow in subcortical gray matter,[16] and in brain functional connectivity.[17] The

assumption that the brain is spared in early infection may have a basis in the onset of cognitive difficulties, which usually do not present in this period. Diagnostic criteria for HIV-associated neurocognitive disorder, however, emphasize an indolent course involving mild, asymptomatic changes in initial stages. In the Chicago Early HIV Infection Study, weaker performance was indicated on several neuropsychological tests, particularly psychomotor speed (table 3). It is unlikely that these findings can be accounted for by premorbid differences in the HIV group. The groups did not differ on demographic variables or on a measure widely used to assess premorbid intellectual function in studies of cognitive deterioration.[12] Findings suggesting early onset of cognitive decline have also been observed in the CHARTER cohort.[18]

In this investigation, structural brain alterations were quantified even in the subgroup infected <6 months. Early viral pathogenesis is characterized by an intense, albeit transient, period of high-grade viremia involving exponential viral expansion to peak plasma levels of 10 million copies/mL, induction of a cytokine storm, and massive CD4+ T-cell destruction.[19] Early viral invasion of the brain has been shown at autopsy and by CSF analysis.[2–4,20–22] In a well-documented death from accidental inoculation, infected microglia/macrophages were detected in cerebral cortex and other regions at autopsy on day 15.[4] Animal NeuroAIDS models indicate that changes occur in the brain within days of infection.[23] Gray matter abnormalities and third-ventricular enlargement have been seen in acute HIV meningoencephalitis.[24] Infected macrophages, neurotoxins, or other pathogens in the meninges,[25] subarachnoid space, and parenchyma induce or express cytokines, chemokines, and various cellular death pathways and/or impair neuroprotective functions.[26] Expansion in the third ventricle, the narrow midline cavity inferior to corpus callosum, bordered by thalamus and hypothalamus, likely reflects ex vacuo dilation from tissue loss in subcortical regions and/or altered CSF outflow and increased intracranial pressure. The brain is encased in nonexpansile bone and highly vulnerable to intense or prolonged neuroinflammation and reduced perfusion.[27]

In analyses of potential factors associated with brain structural alterations in the entire cohort and separately in the HIV group, age was the only variable associated with increased risk. Differences between the groups in the brain volumetric measurements remained, however, after adjusting for age. Other studies have shown accelerated brain aging in older HIV subjects.[28,29] Findings from the Chicago cohort indicate that older age may confer increased risk from the outset of infection. Concurrent CD4+ T-cell count or plasma viral load were not associated with the brain volumetric measures (table 4). Analyses of risk relationships in this cross-sectional study must be interpreted with caution. The early natural history is highly dynamic, involving dramatic peaking of viral load, CD4 depletion, and upregulation of numerous immune mediators, all of which may normalize to varying degrees with the mounting of host defense and with treatment. Further longitudinal studies are necessary to identify factors associated with HIV neurologic outcome. Nadir CD4 levels have been found to predict neurocognitive decline when studied over the longer-term course.[30]

Volumetric measurements for the gray matter, cortical, and third-ventricular findings did not differ in ARV-initiated and ARV-naive subgroups in this observational study (data not shown). However, as shown in table 4, lower CNS penetration in the ARV subgroup was associated with reduced total gray matter; nearly significant associations with reduced cortical gray matter and third-ventricular enlargement were also observed. Whether the brain can be protected or recover from early injury is unknown. Experimental evidence indicates that HIV-induced inflammation and neuronal damage may be reversible.[31,32] Early brain structural alterations may partly explain the failure of neuroprotection strategies initiated later in infection.[33] Early ARV initiation may inhibit viral spread, restrain the establishment or expansion of viral reservoirs, reduce CD4 depletion, and preserve immune function.[34] Clinical benefit is supported by evidence that patients initiated on ARV treatment in acute HIV infection remained aviremic after suspension of therapy.[35,36] However, ARV drugs vary in CNS penetrance and suboptimal treatment confers risk.[37] Increasing prevalence of HIV-associated neurocognitive disorder[38] and evidence of cognitive improvement with treatment suspension[39] have raised concerns that ARV drugs may be neurotoxic.

Brain volumetric findings from the Chicago Early HIV Infection Study do not support the view that the brain is spared in this stage of the natural history. Moreover, if ongoing injury involves heterogeneous processes that increase (e.g., edema) and decrease (e.g., cell loss) net volume, volumetric analysis likely underestimates the overall extent of injury in this period. Changes unfolding in the brain in early infection merit closer attention. The initial virus-host interaction is considered pivotal in determining longer-term course and outcome.[40] The viral setpoint established in this period, for example, has prognostic significance for progression to AIDS and death.[40] Further longitudinal studies are necessary to determine the prognostic significance of immunologic and virologic factors for risk or resistance to neurologic injury and to determine whether early ARV treatment is beneficial to the brain. Revisiting the question of the brain's vulnerability to processes unfolding in the initial virus-host interaction may yield new insights into neurologic injury in HIV infection and inform neuroprotection strategies.

AUTHOR CONTRIBUTIONS

Ann B. Ragin, PhD, is principal investigator of the Chicago Early HIV Infection Study and contributed to the study design, including imaging procedures and analysis, interpretation of findings, and manuscript preparation. Hongyan Du, MB, MS, performed the statistical analysis for this study. Renee Ochs, BA, performed imaging procedures and analysis, and data management. Ying Wu, MD, performed imaging procedures and analysis. Christina Sammet, PhD, performed manuscript preparation, and imaging procedures and analysis. Alfred Shoukry, MD, performed imaging procedures and analysis. Leon G. Epstein, MD, performed interpretation of findings and manuscript preparation.

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REFERENCES

1. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med 1998;339:33–39.
2. Chiodi F, Fenyo EM. Neurotropism of human immunodeficiency virus. Brain Pathol 1991;1:185–191.
3. Chiodi F, Sonnerborg A, Albert J, et al. Human immunodeficiency virus infection of the brain. I. Virus isolation and detection of HIV specific antibodies in the cerebrospinal fluid of patients with varying clinical conditions. J Neurol Sci 1988;85:245–257.
4. Davis LE, Hjelle BL, Miller VE, et al. Early viral brain invasion in iatrogenic human immunodeficiency virus infection. Neurology 1992;42:1736–1739.
5. Dal Pan GJ, McArthur JH, Aylward E, et al. Patterns of cerebral atrophy in HIV-1-infected individuals: results of a quantitative MRI analysis. Neurology 1992;42:2125–2130.
6. Gelman BB, Guinto FC Jr. Morphometry, histopathology, and tomography of cerebral atrophy in the acquired immunodeficiency syndrome. Ann Neurol 1992;32:31–40.
7. Jernigan T, Archibald S, Fennema-Notestine C, et al. Clinical factors related to brain structure in HIV: the CHARTER study. J Neurovirol 2011;17:248–257.
8. Ellis RJ, Deutsch R, Heaton RK, et al. Neurocognitive impairment is an independent risk factor for death in HIV infection. San Diego HIV Neurobehavioral Research Center Group. Arch Neurol 1997;54:416–424.
9. Sevigny JJ, Albert SM, McDermott MP, et al. An evaluation of neurocognitive status and markers of immune activation as predictors of time to death in advanced HIV infection. Arch Neurol 2007;64:97–102.
10. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479–489.
11. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–355.
12. Blair JR, Spreen O. Predicting premorbid IQ: a revision of the national adult reading test. Clin Neuropsychol 1989;3:129–136.
13. Letendre S, Fitzsimmons C, Ellis R, et al; the CHARTER Group. Correlates of CSF viral loads in 1221 Volunteers of the CHARTER cohort. Presented at the 17th Annual Conference on Retroviruses and Opportunistic Infections 172; 2010; San Francisco, CA.
14. Sevigny JJ, Albert SM, McDermott MP, et al. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. Neurology 2004;63:2084–2090.
15. Lentz MR, Kim WK, Lee V, et al. Changes in MRS neuronal markers and T cell phenotypes observed during early HIV infection. Neurology 2009;72:1465–1472.
16. Ances BM, Sisti D, Vaida F, et al. Resting cerebral blood flow: a potential biomarker of the effects of HIV in the brain. Neurology 2009;73:702–708.
17. Wang X, Foryt P, Ochs R, et al. Abnormalities in resting-state functional connectivity in early human immunodeficiency virus infection. Brain Connect 2011;1:207–217.
18. Moore DJ, Letendre SL, Morris S, et al. Neurocognitive functioning in acute or early HIV infection. J Neurovirol 2011;17:50–57.
19. Goldman L, Ausiello D. Cecil Medicine, 23rd ed. Philadelphia: Elsevier Saunders; 2008.
20. Hassine D, Gray F, Chekroun R, et al. Early cerebral lesions in HIV infection. Postmortem radio-pathologic correlations in non-AIDS asymptomatic seropositive patients [in French]. J Neuroradiol 1995;22:148–160.
21. Everall I, Gray F, Barnes H, Durigon M, Luthert P, Lantos P. Neuronal loss in symptom-free HIV infection. Lancet 1992;340:1413.
22. Everall IP, Luthert PJ, Lantos PL. Neuronal loss in the frontal cortex in HIV infection. Lancet 1991;337:1119–1121.
23. Lackner AA, Veazey RS. Current concepts in AIDS pathogenesis: insights from the SIV/macaque model. Annu Rev Med 2007;58:461–476.
24. Yoshizawa T, Motonishi S, Saitoh M. Case of acute primary HIV infection with meningoencephalitis demonstrating high signal intensity of the bilateral globus pallidus in T2-weighted MRI [in Japanese]. Rinsho Shinkeigaku 2007;47:597–600.
25. Lamers SL, Gray RR, Salemi M, Huysentruyt LC, McGrath MS. HIV-1 phylogenetic analysis shows HIV-1 transits through the meninges to brain and peripheral tissues. Infect Genet Evol 2011;11:31–37.
26. Lindl KA, Marks DR, Kolson DL, Jordan-Sciutto KL. HIV-associated neurocognitive disorder: pathogenesis and therapeutic opportunities. J Neuroimmune Pharmacol 2010;5:294–309.
27. Nath A, Clements JE. Eradication of HIV from the brain: reasons for pause. AIDS 2011;25:577–580.
28. Valcour V, Shikuma C, Shiramizu B, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. Neurology 2004;63:822–827.
29. Becker JT, Maruca V, Kingsley LA, et al. Factors affecting brain structure in men with HIV disease in the post-HAART era. Neuroradiology 2012;54:113–121.
30. Marcotte TD, Deutsch R, McCutchan JA, et al. Prediction of incident neurocognitive impairment by plasma

HIV RNA and CD4 levels early after HIV seroconversion. Arch Neurol 2003;60:1406–1412.
31. Trillo-Pazos G, Kandanearatchi A, Eyeson J, King D, Vyakarnam A, Everall IP. Infection of stationary human brain aggregates with HIV-1 SF162 and IIIB results in transient neuronal damage and neurotoxicity. Neuropathol Appl Neurobiol 2004;30:136–147.
32. Greco JB, Westmoreland SV, Ratai EM, et al. In vivo 1H MRS of brain injury and repair during acute SIV infection in the macaque model of neuroAIDS. Magn Reson Med 2004;51:1108–1114.
33. Brew BJ. Lost in translation: again, another failed neuroprotection trial. Neurology 2007;69:1308–1309.
34. Schmid A, Gianella S, von Wyl V, et al. Profound depletion of HIV-1 transcription in patients initiating antiretroviral therapy during acute infection. PLoS One 2010;5:e13310.
35. Trono D, Van Lint C, Rouzioux C, et al. HIV persistence and the prospect of long-term drug-free remissions for HIV-infected individuals. Science 2010;329:174–180.
36. Hocqueloux L, Prazuck T, Avettand-Fenoel V, et al. Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. AIDS 2010;24:1598–1601.
37. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol 2008;65:65–70.
38. 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.
39. Robertson KR, Su Z, Margolis DM, et al. Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort. Neurology 2010;74:1260–1266.
40. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma [erratum in Science 1997;275:14]. Science 1996;272:1167–1170.