The Impact of Central Nervous System Penetration Effectiveness of Highly Active Antiretroviral Therapy on Brain Integrity in HIV+ Adults

Laurie M. Baker[1], Robert H. Paul[1], Jodi M. Heaps[1], Christina Usher[1], Elizabeth T. Westerhaus[2], Jee Yoon Chang[2], Beau M. Ances[2]

University of Missouri- St. Louis[1], Washington University in St. Louis[2]

Background

- Highly active antiretroviral therapy (HAART) reduces morbidity and mortality due to human immunodeficiency virus (HIV)[1,2] however, HAART does not eradicate the virus and reservoirs remain even among individuals with undetectable plasma VL.[3,4]
- As such, HIV has evolved into a chronic medical condition characterized by varying degrees of residual symptoms that require long-term treatment.
- It remains uncertain whether HAART regimens with a high degree of central nervous system penetration effectiveness (CPE)[5-7] exert beneficial neurological outcomes in HIV-infected (HIV+) individuals on stable treatment.
- The relevance of CPE on brain integrity is unclear as some studies have revealed potential benefits of high CPE HAART regimens[7,8], while others have shown no effect[9-10], and some have demonstrated potentially adverse effects.[11-13]
- Furthermore, HIV-associated neurocognitive disorder (HAND) is still observed in HIV+ individuals in the HAART era.[14,15] Prior to HAART, the most severe form of cognitive impairment (i.e., HIV-associated-dementia; HAD) affected up to 10-15% of patients.[16] Since the introduction of HAART, the prevalence of HAD has been reduced (~3-5%)[17], but milder forms of cognitive impairment persist.[18]
- Importantly, individuals with milder versions of HAND remain at risk for continued progression of cognitive impairment.[19,20]
- These findings highlight the importance of identifying variables associated with poor clinical outcomes among individuals receiving HAART.
- The present cross sectional study examined the relationship between HAART, CPE, and brain integrity in HIV+ adults.

Methods

Participants

- HIV+ individuals on stable HAART (≥ 3 months) were recruited from the Infectious Disease Clinic at Washington University in St. Louis (WUSTL) or the AIDS Clinical Trials Group at WUSTL.
- Participants were excluded if they reported a history of head injury with loss of consciousness over 30 minutes, major psychiatric disorders, opportunistic CNS infections, or contraindications for MRI scanning.

Neuropsychological Performance

- Neuropsychological tests included measures known to be sensitive to HIV with values converted into standardized scores (z scores) based on published normative scores.
- A standardized score was aggregated for each domain and a cognitive score was determined (NPZ-4).
  - Hopkins Verbal Learning Test- Revised (HVLT-R) Immediate Memory[21,22]; Trail Making Test-A (TMT-A)[23]; Trail Making Test-B (TMT-B)[32]; Verbal Fluency (Animal fluency)[24]

Clinical Measures

- Plasma CD4 T-cell count and HIV VL were obtained within 3 months of study visit and nadir CD4 T-cell count was recorded as lowest value from either self report or review of medical records.
- Duration of infection was recorded based on time since diagnosis (per patient recall and/or review of medical records).
- All medications were recorded at study visit based on medical records

Neuroimaging

- Utilized 3T Siemens Tim Trio whole body MR scanner (Siemens AG, Erlangen Germany) using a 12-channel transmit/receive head coil.
- Structural volumetric images were acquired in the sagittal plane using a T1-weighted 3-dimensional MPRAGE sequence [time of repetition (TR) = 2400ms, echo time (TE)= 3.16ms, inversion time (TI)= 1000ms flip angle = 8 degrees, 162 slices, and voxel size = 1 x 1 x 1mm^3].
- Freesurfer software suite (v5.1)[25] was used to quantify structural brain volumes.
- Brain regions were parcellated into ROIs using a surface deformation program[26-28] and all subject images were aligned into a common atlas (MNI305).[29]
- ROIs often affected by HIV were evaluated and included: total cortical grey matter, total cortical white matter, thalamus, caudate, and putamen.[30-33]
- Each volume was normalized to total ICV using a least square residual regression model.[34]

Methods

Statistical Analysis

- Primary Analysis
  - Examined differences in neuropsychological performance and structural brain volumetrics between individuals prescribed high (≥ 7) and low (< 7) CPE regimens.[5-7]
  - Cognition (NPZ-4) between groups was measured using univariate analysis of variance (ANOVA).
  - Multivariate analysis of variance (MANOVA) was used to examine the relationships between CPE and individual test z-scores (HVLT-R, TMT-A and B, Animal fluency).
  - Differences in brain volumetrics between the groups were also assessed using MANOVA.
- Secondary Analysis
  - Examined the relationship between measures of brain integrity (neuropsychological performance and neuroimaging) and total CPE score as a continuous variable
  - The association between NPZ-4 score and CPE score was measured utilizing linear regression analysis.
  - Multiple linear regression was used to examine the relationships between CPE and individual test z-scores.
  - The relationship between brain volumetrics and CPE score was also measured using multiple linear regression.

Table 1. Subject Characteristics

Variables	Total Sample (N=64)	Low CPE (n=29)	High CPE (n= 35)
Age (years) (SD)	37.97 (12.92)	36.34 (15.18)	39.31 (10.74)
Education (years) (SD)[a]	13.17 (2.37)	13.14 (2.34)	13.20 (2.40)
Sex (% Male)	77	69	63
Ethnicity (C/AA/A)[b]	15/49/0	9/20/0	7/28/0
CD4 Nadir (cells/mm^3) (IQR)	255.6 (113.25, 360.25)	218.46 (110.75, 337.25)	273.47 (153.25, 405.25)
Recent CD4 (cells/mm^3) (IQR)	583.9 (376.75,797.00)	510.57 (288.75, 649.25)	639.03 (449.00, 868.50)
Plasma VL (copies/mL)[c] (IQR)	1.7 (1.30,1.32)	1.82 (1.30,1.56)	1.57 (1.30, 1.30)
Duration of Infection (months) (SD)	107.68 (88.01)	89.04 (86.01)	122.05 (88.03)

[a] Education based on mean number of years completed; [b] C= Caucasian, AA= African American, A= Asian;
[c] Viral load $\log_{10}$ transformed; SD= standard deviation; IQR= interquartile range

Results

- Primary Analysis
  - The ANOVA examining the impact of CPE score (high vs. low) on NPZ-4 revealed no significant differences between groups ($p > 0.05$).
  - There were also no significant differences between CPE groups on individual neuropsychological tests (p's > 0.05).
  - The MANOVA examining the impact of CPE score on brain volumes revealed no significant differences between CPE groups ($p > 0.05$).
- Secondary Analysis
  - No significant relationships were observed between CPE (continuous variable) with cognition (NPZ-4) ($p > 0.05$) and individual neuropsychological tests (p's > 0.05).
  - Multiple linear regression model examining the impact of CPE score as a continuous variable on multiple brain volumes revealed no significant associations ($p > 0.05$).

Table 2. Effect of CPE score on neuropsychological performance and select ROIs

	Low CPE (n=29) Mean (SD)	High CPE (n= 25) Mean (SD)	*p value*
Neuropsychological Z (NPZ)-scores			
NPZ-4	-.61 (.70)	-.59 (.60)	0.89
HVLT-R Immediate Recall	-1.33 (.80)	-1.23 (.80)	0.63
TMT-A	-.44 (1.40)	-.41 (1.30)	0.92
TMT-B	-.67 (1.40)	-.93 (1.50)	0.48
Animal Fluency	-.02 (.90)	.21 (.80)	0.29
Structural Brain Volumetrics			
Whole Brain Grey Matter (mm^3)	607014 (52402)	613056 (53049)	0.64
Whole Brain White Matter (mm^3)	464299 (34375)	467574 (61315)	0.79
Thalamus (mm^3)	13404 (1504)	13636 (1785)	0.57
Caudate (mm^3)	7109 (905)	7011 (865)	0.65
Putamen (mm^3)	10715 (1267)	10760 (1510)	0.82

Conclusions

- Results of the analyses revealed that higher CPE does not influence neuropsychological performance or brain volumes in regions typically impacted by HIV in individuals on stable treatment.
- It is possible that other mechanisms may be more salient predictors of brain integrity among individuals on long-term HAART than CPE.
  - A recent area of research has focused on understanding the ability of HAART to suppress HIV within circulating monocytes and brain macrophages.
  - Shikuma and colleagues have introduced a monocyte effectiveness (ME) scale based on the ability of HAART to sufficiently suppress the virus within circulating monocytes and brain macrophages.[35]
  - The authors suggested a combined CPE score and ME may better predict cognitive outcomes than each score independently,[35] highlighting an avenue for future research on cognitive impairment in individuals on HAART.
- Comprehensive longitudinal analyses in a HIV+ cohort before and after HAART initiation using CPE and ME scores are warranted to capture the relative impact of HAART upon brain integrity.

References

1. Valcour, V. G. (2012). HIV, aging, and cognition: emerging issues. *Topics in antiviral medicine*, *21*(3), 119-123.
2. Palella Jr, F. J., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., ... & Holmberg, S. D. (1998). Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *New England Journal of Medicine*, *338*(13), 853-860.
3. Chun, T. W., Justement, J. S., Murray, D., Hallahan, C. W., Maenza, J., Collier, A. C., ... & Fauci, A. S. (2010). Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication. *AIDS (London, England)*, *24*(18), 2803. an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. *Proceedings*
4. Chun, T. W., Stuyver, L., Mizell, S. B., Ehler, L. A., Mican, J. A. M., Baseler, M., & Fauci, A. S. (1997). Presence of *of the National Academy of Sciences*, *94*(24), 13193-13197.
5. Letendre, S., Marquie-Beck, J., Capparelli, E., Best, B., Clifford, D., Collier, A. C., ... & Ellis, R. J. (2008). Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Archives of neurology*, *65*(1), 65-70.
6. Letendre, S. L., Ellis, R. J., Everall, I., Ances, B., Bharti, A., & McCutchan, J. A. (2009). Neurologic complications of HIV disease and their treatment. *Topics in HIV medicine: a publication of the International AIDS Society, USA*, *17*(2), 46.
7. Letendre, S. (2011). Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. *Topics in antiviral medicine*, *19*(4), 137-142.
8. Cysique, L. A., Vaida, F., Letendre, S., Gibson, S., Cherner, M., Woods, S. P., ... & Ellis, R. J. (2009). Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology*, *73*(5), 342-348.
9. Caniglia, E. C., Cain, L. E., Justice, A., Tate, J., Logan, R., Sabin, C., ... & Hernán, M. A. (2014). Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. *Neurology*, 10-1212.
10. Ellis, R. J., Letendre, S., Vaida, F., Haubrich, R., Heaton, R. K., Sacktor, N., ... & McCutchan, J. A. (2014). Randomized Trial of Central Nervous System–Targeted Antiretrovirals for HIV-Associated Neurocognitive Disorder. *Clinical infectious diseases*, *58*(7), 1015-1022.
11. McManus, H., Li, P. C. K., Nolan, D., Bloch, M., Kiertiburanakul, S., Choi, J. Y., ... & Wright, E. (2011). Does use of antiretroviral therapy regimens with high central nervous system penetration improve survival in HIV-infected adults?. *HIV medicine*, *12*(10), 610-619.
12. Robertson, K., Jiang, H., Kumwenda, J., Supparatpinyo, K., Evans, S., Campbell, T. B., ... & Nair, A. (2012). Improved neuropsychological and neurological functioning across three antiretroviral regimens in diverse resource-limited settings: AIDS Clinical Trials Group Study A5199, the International Neurological Study. *Clinical infectious diseases*, *55*(6), 868-876.
13. Kahouadji, Y., Dumurgier, J., Sellier, P., Lapalus, P., Delcey, V., Bergmann, J. F., ... & Paquet, C. (2013). Cognitive function after several years of antiretroviral therapy with stable central nervous system penetration score. *HIV medicine*, *14*(5), 311-315.
14. Heaton, R. K., Franklin, D. R., Deutsch, R., Letendre, S. L., Ellis, R. J., Casaletto, K., ... & Mintz, L. (2014). Neurocognitive change in the era of HIV combination antiretroviral therapy: A longitudinal CHARTER Study. *Clinical Infectious Diseases*, ciu862.
15. Clifford, D. B. (2007). HIV-associated neurocognitive disease continues in the antiretroviral era. *Topics in HIV medicine: a publication of the International AIDS Society, USA*, *16*(2), 94-98.
16. McArthur, J. C., Hoover, D. R., Bacellar, H., Miller, E. N., Cohen, B. A., Becker, J. T., ... & Saah, A. (1993). Dementia in AIDS patients incidence and risk factors. *Neurology*, *43*(11), 2245-2245.
17. Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., ... & Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. *Neurology*, *75*(23), 2087-2096.
18. Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., ... & Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of neurovirology*, *17*(1), 3-16.
19. Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M. F., Visco-Comandini, U., ... & Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *45*(2), 174-182.
20. Grant, I., Franklin, D. R., Deutsch, R., Woods, S. P., Vaida, F., Ellis, R. J., ... & Heaton, R. K. (2014). Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology*, 10-1212.
21. Benedict, R. H., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test–Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*, *12*(1), 43-55.
22. Brandt, J., & Benedict, R. H. (2001). *Hopkins verbal learning test, revised: professional manual*. Psychological Assessment Resources.
23. Reitan RM, Davison LA (1974) Clinical neuropsychology: current status and applications. Hemisphere, New York.
24. Goodglass, H., & Kaplan, E. (1972). *The assessment of aphasia and related disorders* (pp. 1-80). Philadelphia: Lea & Febiger.
25. Martinos Center, Harvard University, Boston, MA; http://surfer.nmr.mgh.harvard.edu).
26. Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis: II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*, *9*(2), 195-207.
27. Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, *31*(3), 968-980.
28. Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage*, *9*(2), 179-194.
29. Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., ... & Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral cortex*, *14*(1), 11-22.
30. Aylward, E. H., Henderer, J. D., McArthur, J. C., Brettschneider, P. D., Harris, G. J., Barta, P. E., & Pearlson, G. D. (1993). Reduced basal ganglia volume in HIV-1-associated dementia Results from quantitative neuroimaging. *Neurology*, *43*(10), 2099-2099.
31. Cohen, R. A., Harezlak, J., Schifitto, G., Hana, G., Clark, U., Gongvatana, A., ... & Navia, B. (2010). Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. *Journal of neurovirology*, *16*(1), 25-32.
32. Jernigan, T. L., Archibald, S., Hesselink, J. R., Atkinson, J. H., Velin, R. A., McCutchan, J. A., ... & Grant, I. (1993). Magnetic resonance imaging morphometric analysis of cerebral volume loss in human immunodeficiency virus infection. *Archives of neurology*, *50*(3), 250-255.
33. Stout, J. C., Ellis, R. J., Jernigan, T. L., Archibald, S. L., Abramson, I., Wolfson, T., ... & Grant, I. (1998). Progressive cerebral volume loss in human immunodeficiency virus infection: a longitudinal volumetric magnetic resonance imaging study. *Archives of neurology*, *55*(2), 161-168.
34. Zatz, L. M., & Jernigan, T. L. (1983). The ventricular-brain ratio on computed tomography scans: validity and proper use. *Psychiatry research*, *8*(3), 207-214.
35. Shikuma, C. M., Nakamoto, B., Shiramizu, B., Liang, C. Y., DeGruttola, V., Bennett, K., ... & Valcour, V. G. (2012). Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV. *Antiviral therapy*, *17*(7), 1233.

Acknowledgements

Supported by the National Institute of Nursing Research (R01NR012907, R01NR012657, and R01NR014449 to B.M.A.); Grossman Chancellor's Fellowship (M.O.); National Science Foundation IGERT (0548890 to M.O.), Paula C. and Rodger O. Riney Fund (B.M.A.) and the National Institute of Aging (R01 NS052420) (R.H.P.). Research was conducted and supported by the Washington University Institute of Clinical and Translational Sciences (UL1 TR000448 from the National Center for Advancing Translational Sciences (NCATS).