

# CNS Complications of ART

Linda L. Chao, Ph.D.  
Magnet Resonance Unit, San Francisco VAMC  
Departments of Radiology and Psychiatry,  
UCSF

## Background

- Prior to introduction of antiretroviral therapy (ART), HIV injury to the CNS was common.
- ART has suppressed viral load, increased CD4, reduced the incidence of AIDS dementia.
- However, ART has poor ability to penetrate the blood-brain barrier.

# Goals

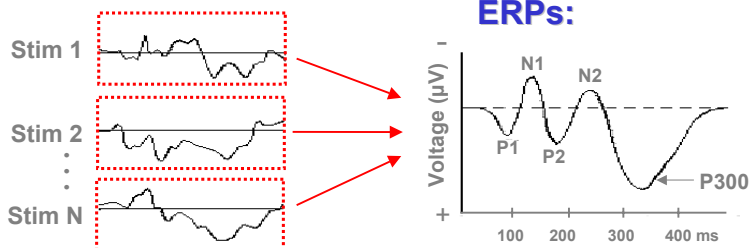
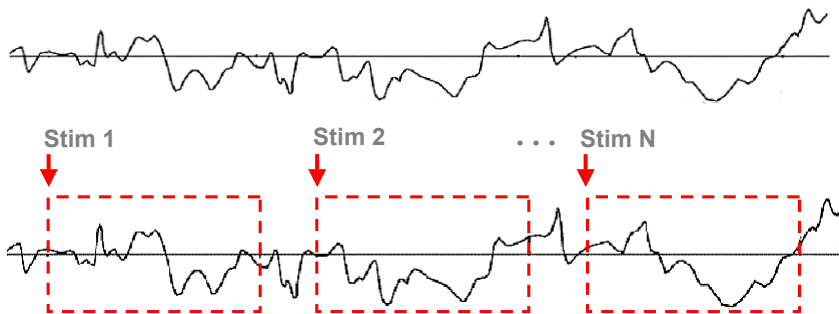
Overall goal:

- Determine if there is evidence of ongoing CNS injury in HIV+ subjects on ART .

Methods:

- event-related potentials (ERPs) and structural MRI

**Raw EEG:**



## ERP Components

Components	Cognitive Process	Brain Region
<b>CNV</b>	Anticipation Motor & cognitive preparation	Prefrontal cortex Basal ganglia
<b>P3a</b>	Novelty detection Orienting response	Prefrontal cortex Limbic structures
<b>P3b</b>	Attention Short-term memory retrieval	Posterior association cortex

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## Abnormal contingent negative variation in HIV patients receiving antiretroviral therapy

Linda L. Chao,<sup>1,2,3,CA</sup> Valerie A. Cardenas,<sup>1,2</sup> Dieter J. Meyerhoff,<sup>1,2</sup> Johannes C. Rothlind,<sup>3</sup> Derek L. Flenniken,<sup>1</sup> Joselyn A. Lindgren<sup>1</sup> and Michael W. Weiner<sup>1,2,3,4,5</sup>

<sup>1</sup>Magnetic Resonance Unit, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, 116R, San Francisco, CA 94121; <sup>2</sup>Departments of Radiology

<sup>3</sup>Psychiatry <sup>4</sup>Medicine and <sup>5</sup>Neurology, University of California, San Francisco, CA, USA

<sup>CA</sup>Corresponding Author and Address: llchao@itsa.ucsf.edu

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The contingent negative variation, an event-related potential related to neural activity in the frontal lobe and basal ganglia, neuropsychological tests and structural MRI were used to examine CNS function and structure in HIV-positive patients receiving antiretroviral therapy. Relative to controls, HIV patients had smaller thalamic volume and reduced late contingent negative variation amplitude that correlated with caudal atrophy. Behaviorally, viremic patients were more impaired than virally suppressed

patients and controls on neuropsychological measures of psychomotor speed, selective attention and mental flexibility. These results suggest that antiretroviral therapy may not be effective in protecting cortical and subcortical structures against HIV-related neuropathology regardless of immune function. However, the benefits of antiretroviral therapy on immune function appear to facilitate neurocognitive performance. *NeuroReport* 14:2111–2115 © 2003 Lippincott Williams & Wilkins.

**Key words:** Antiretroviral therapy; Contingent negative variation; Event-related potential; HIV; MRI

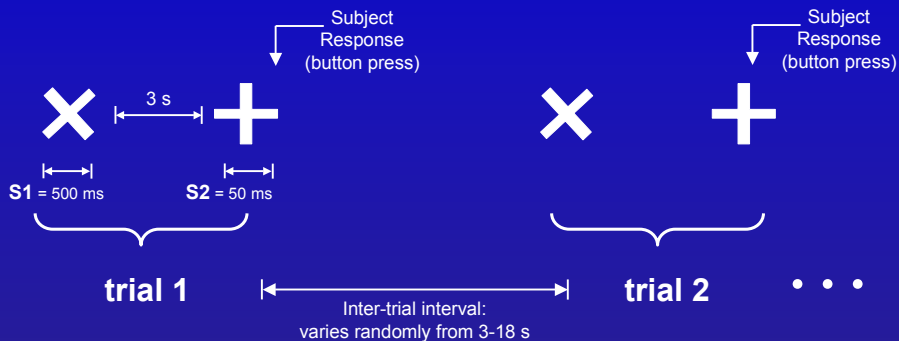
# Subjects

	N	Age (yrs)	Education (yrs)	CD4 (cells/mm <sup>3</sup> )	Log Plasma viral load (copies/ml)
HIV+	39	45.9 ± 7.3	15.4 ± 1.9	403 ± 217	2.8 ± 1.2
HIV-	39	43.5 ± 7.6	16.0 ± 2.1	798 ± 290	--

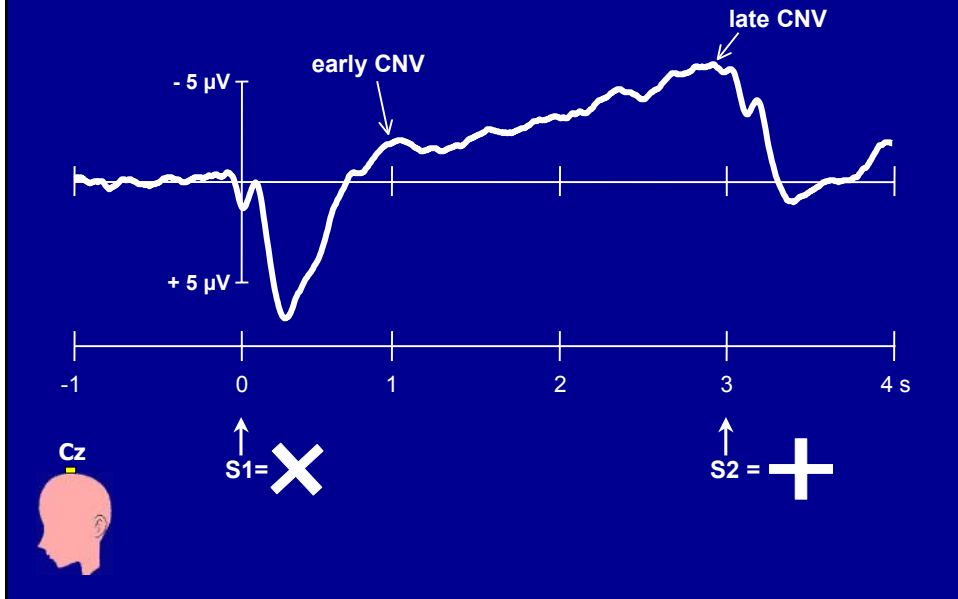
All HIV+ patients were on antiretroviral therapy:

- either mono- or dual-drug therapy with nucleoside reverse transcriptase inhibitors (e.g., zidovudine, stavudine, or lamivudine)
- or combination therapy with at least one protease inhibitor (i.e., highly active antiretroviral therapy, HAART).

# Schematic of CNV Paradigm

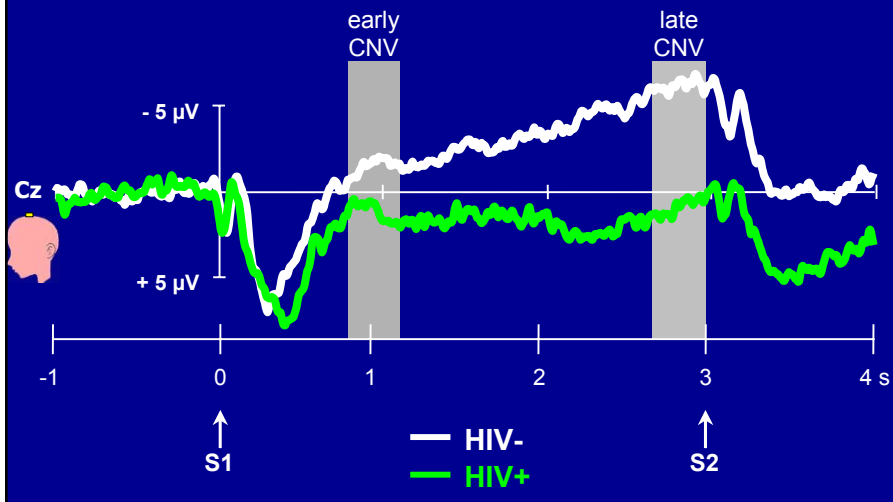


# Anatomy of the CNV



# ERP Results

- HIV marginally ( $p=0.07$ ) reduced the early CNV.
- HIV significantly reduced ( $p<0.0001$ ) the late CNV.

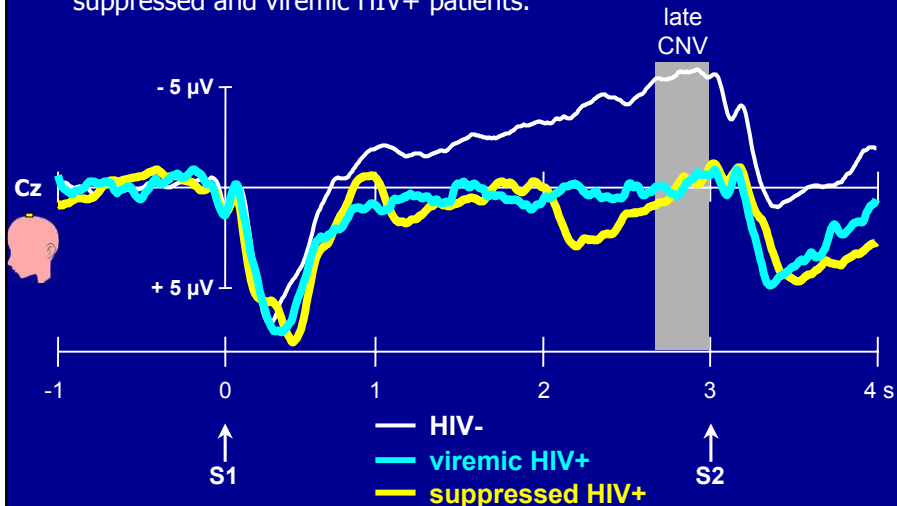


# Subjects

	N	Age (yrs)	Education (yrs)	CD4 (cells/mm <sup>3</sup> )	Log Plasma viral load (copies/ml)
suppressed HIV+	16	45.7 ± 6.9	15.1 ± 1.6	427 ± 211	< 1.7
viremic HIV+	23	46.1 ± 6.9	15.6 ± 1.1	385 ± 224	3.5 ± 1.1
HIV-	39	43.5 ± 7.6	16.0 ± 2.1	798 ± 290	--

# ERP Results

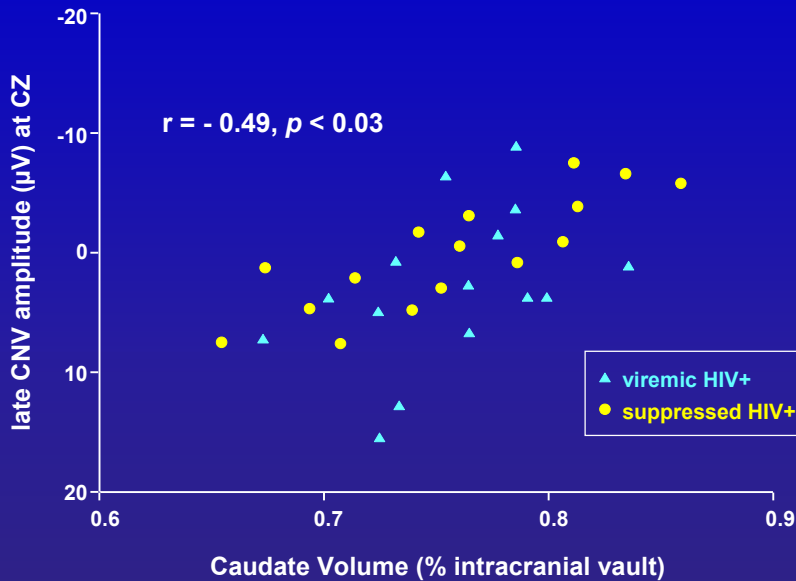
- Suppressed and viremic HIV+ patients had smaller late CNV than HIV-.
- There was no significant early CNV amplitude differences between suppressed and viremic HIV+ patients.



# ERP Components

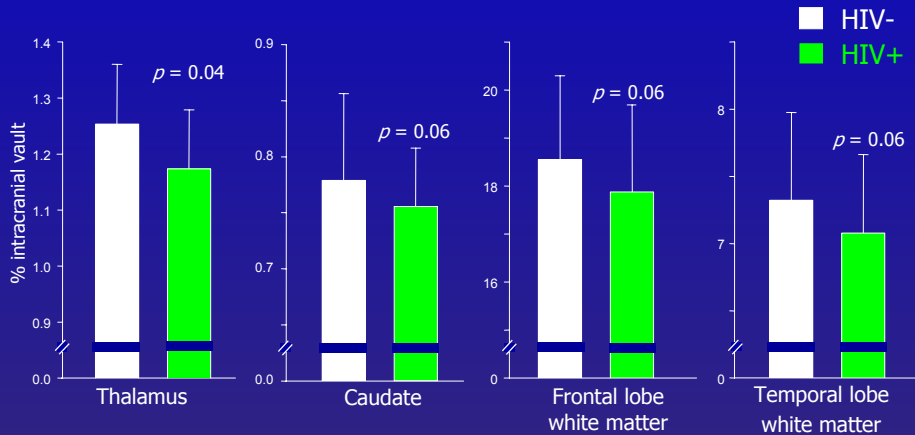
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<b>P3b</b>	Attention Short-term memory retrieval	Posterior association cortex

## Results



## Volumetric MRI Results

- HIV significantly reduced the volume of the thalamus.
- HIV moderately reduced caudate, frontal lobe white matter, and temporal lobe white matter volumes.



## Conclusion

- ART may not be completely effective in protecting cortical and subcortical structures against HIV-related injury, despite its beneficial effects on immune function.



## ERP evidence of impaired central nervous system function in virally suppressed HIV patients on antiretroviral therapy

Linda L. Chao<sup>a,b,c,\*</sup>, Joselyn A. Lindgren<sup>a</sup>, Derek L. Flenniken<sup>a</sup>, Michael W. Weiner<sup>a,b,c,d,e</sup>

<sup>a</sup>Magnetic Resonance Unit, Department of Radiology, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, 116R, San Francisco, CA 94121, USA

<sup>b</sup>Department of Radiology, University of California, San Francisco, CA, USA

<sup>c</sup>Department of Psychiatry, University of California, San Francisco, CA, USA

<sup>d</sup>Department of Medicine, University of California, San Francisco, CA, USA

<sup>e</sup>Department of Neurology, University of California, San Francisco, CA, USA

Accepted 21 February 2004

## Subjects

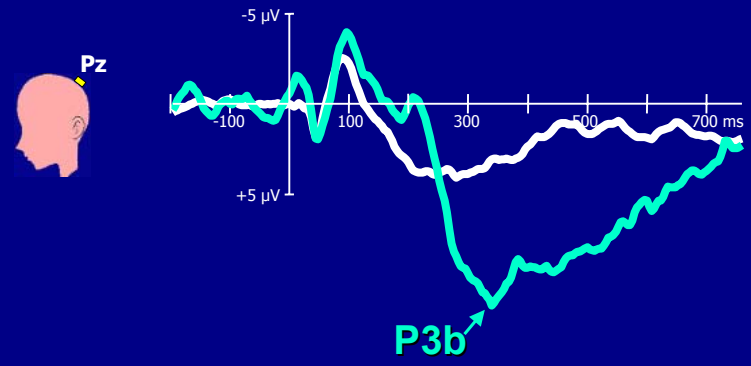
	N	Age (yrs)	Education (yrs)	CD4 (cells/mm <sup>3</sup> )	Plasma viral load (copies/ml)
HIV+	15	44.5 ± 7.6	15.1 ± 1.7	441 ± 203	< 50
HIV-	15	44.1 ± 8.0	15.6 ± 1.8	834 ± 206	--

All HIV+ patients were on antiretroviral therapy:

- either mono- or dual-drug therapy with nucleoside reverse transcriptase inhibitors (e.g., zidovudine, stavudine, or lamivudine)
- or combination therapy with at least one protease inhibitor (i.e., highly active antiretroviral therapy, HAART).

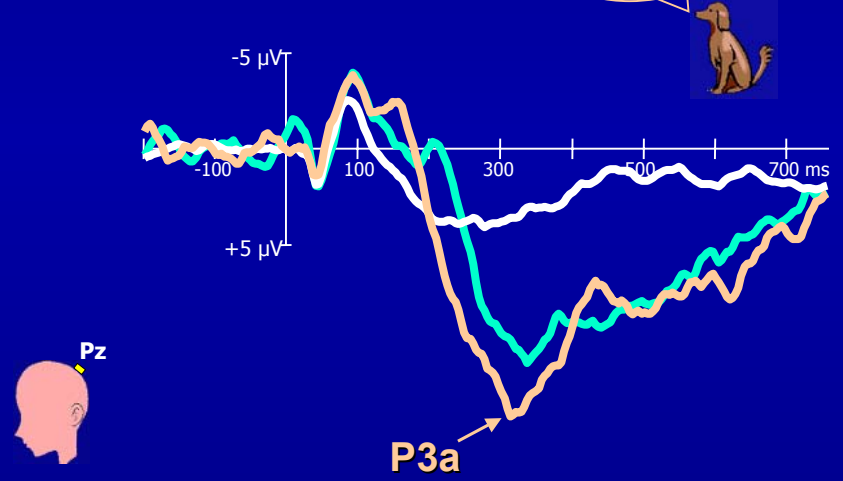
# Schematic of Auditory Oddball Paradigm

300 Hz 900 Hz 300 Hz 300 Hz 300 Hz ...



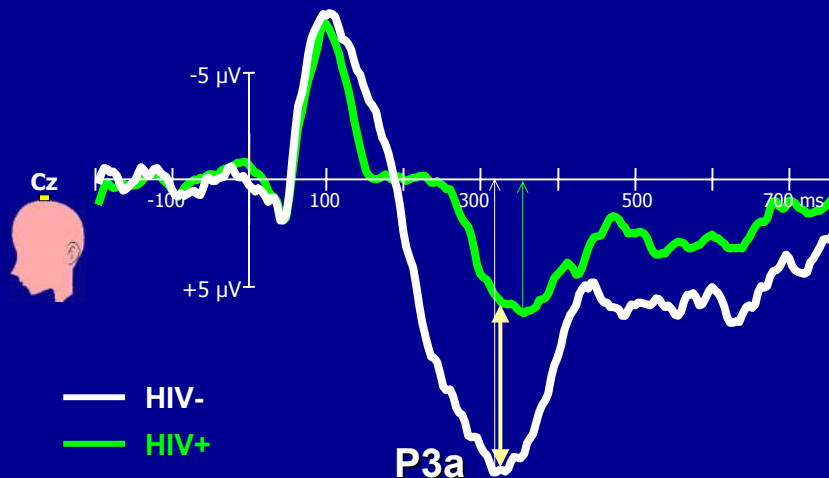
# Schematic of Auditory Oddball Paradigm

300 Hz 900 Hz 300 Hz 300 Hz "arf-arf" 300 Hz ...



## ERP Results

- HIV reduced the amplitude and prolonged the latency of the P3a component elicited by the novel stimuli.

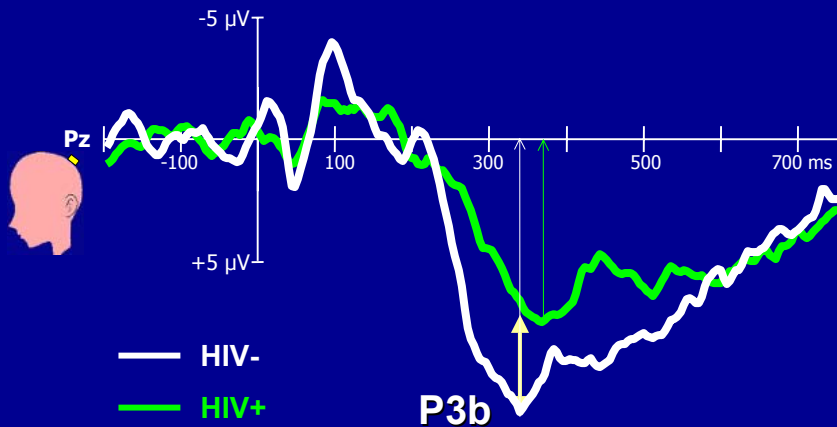


## ERP Components

Components	Cognitive Process	Brain Region
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P3b	Attention Short-term memory retrieval	Posterior association cortex

## ERP Results

- HIV reduced the amplitude and delayed the latency of the P3b component associated with target stimuli.

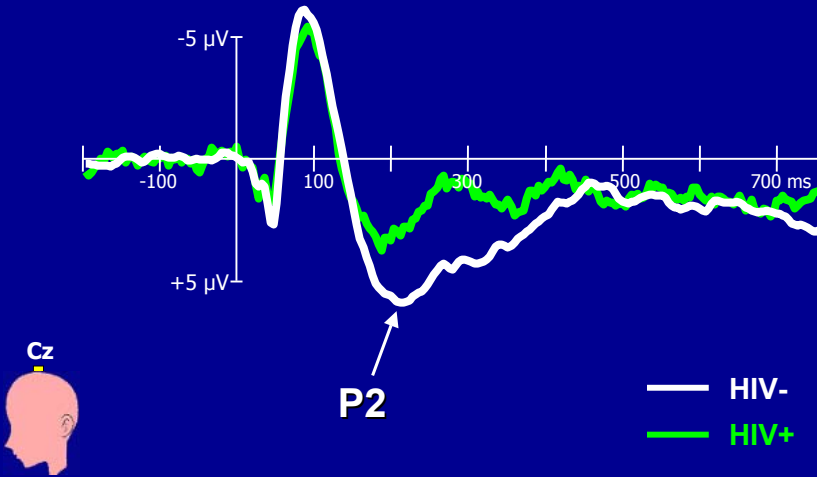


## ERP Components

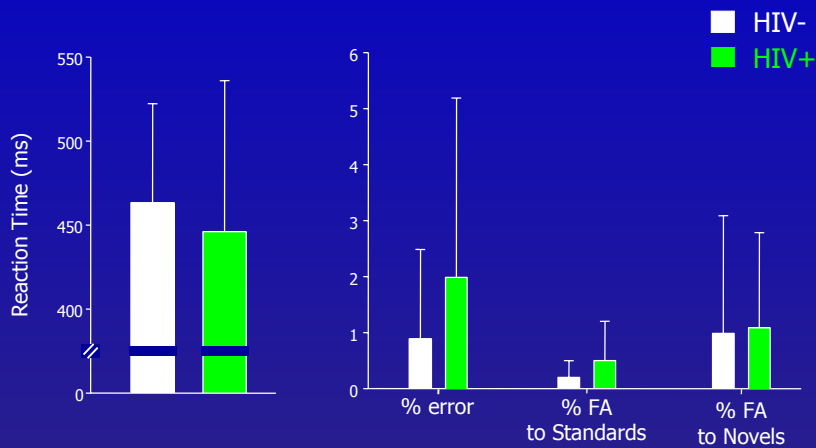
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## ERP Results

- HIV reduced the amplitude of the P2 component.



## Oddball Behavioral Results



## Summary

These *cross sectional* data show:

- HIV+ subjects on ART have evidence of CNS injury.
- Virally suppressed HIV+ subjects also show evidence of CNS injury.

## Interpretation

- CNS injury could reflect an *ongoing* process.
- Cross sectional evidence of CNS injury could be due to *previous* effects of:
  - HIV
  - immunodeficiency
  - treatment

# Longitudinal Structural MRI study

## GOAL:

Determine if there is *ongoing* CNS injury in HIV+ subjects on ART

- Virally suppressed HIV+ (< 400 copies/ml)
- Viremic HIV+ subjects ( $\geq$  400 copies/ml)

## Subjects

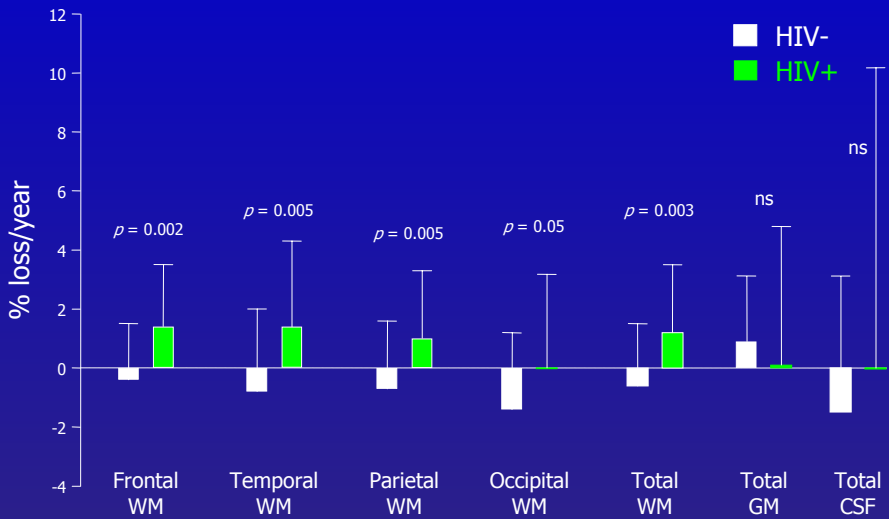
	N	Age (yrs)	Interscan interval (yrs)	CD4 (cells/mm <sup>3</sup> )	Log Plasma viral load (copies/ml)
HIV+	23	44 $\pm$ 6	2.2 $\pm$ 0.2	383 $\pm$ 214	2.6 $\pm$ 1.5
HIV-	38	41 $\pm$ 9	2.0 $\pm$ 0.2	790 $\pm$ 270	--

- All HIV+ subjects were on ART.

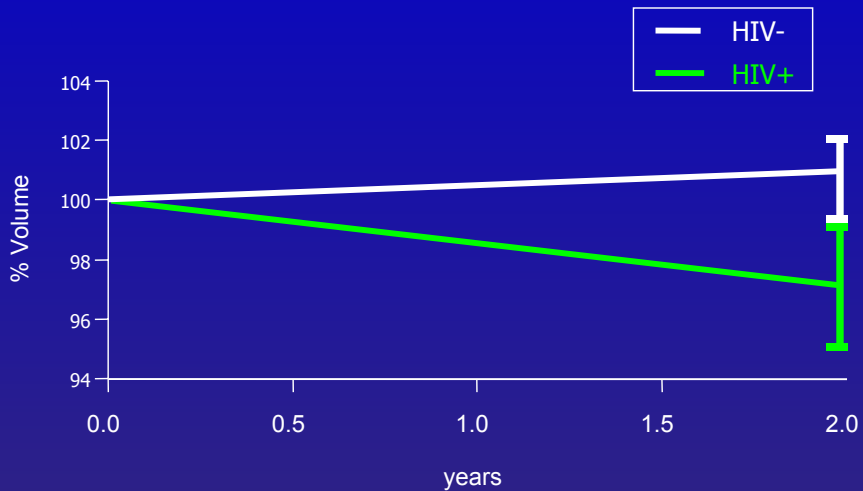
\* Note:

60% HIV- subjects were male  
100% HIV+ patients were male.

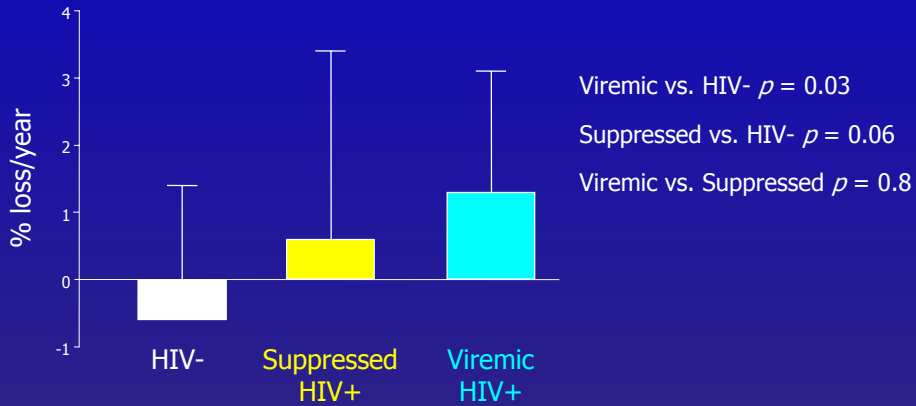
## Brain Atrophy Rates: HIV+ vs. HIV- subjects



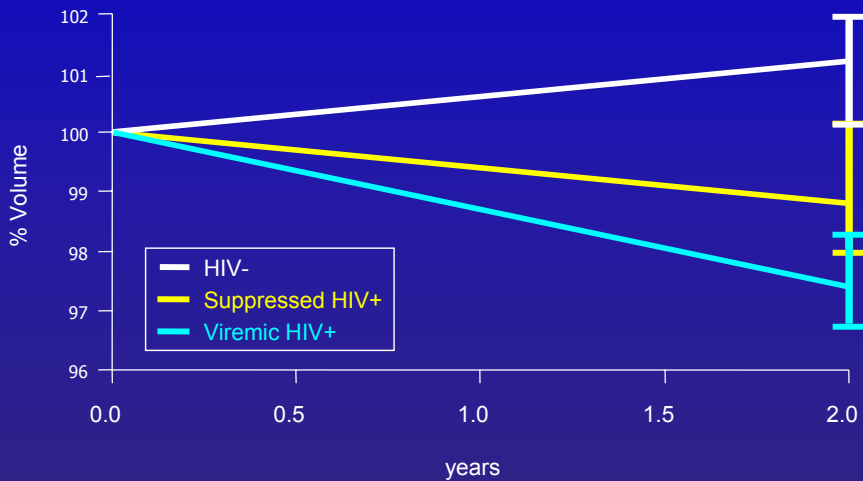
## Total White Matter Atrophy Rates: HIV+ vs. HIV- Subjects



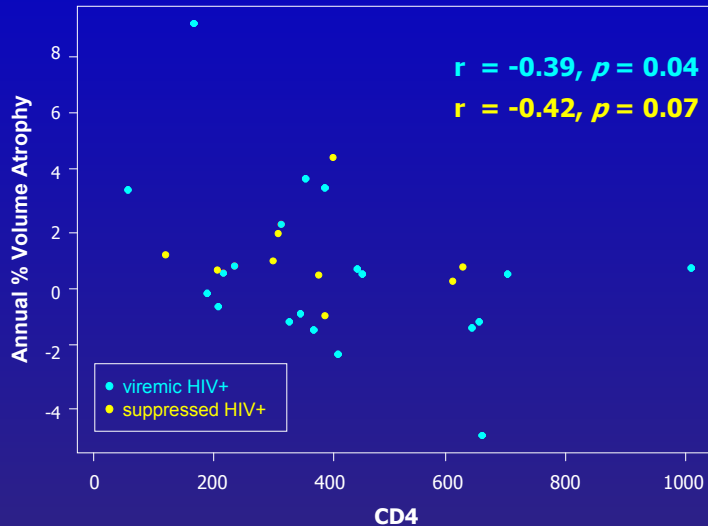
## Rates of Total White Matter Atrophy: Viremic vs. Suppressed HIV+ Subjects



## Rates of Total White Matter Atrophy: Viremic vs. Suppressed HIV+ Subjects



## Relationship between CD4 and White Matter Atrophy Rate in HIV+ Subjects on ART



## Summary

- Longitudinal MRI study indicates increased rates of white matter atrophy in HIV+ subjects on ART.
  - More severe change in viremic subjects.
- Mechanism and significance of this finding remain to be determined.

## Possible Mechanisms of Ongoing White Matter Atrophy

- Direct or indirect effects of HIV
  - Macrophage activation
- Toxic effects of anti-retroviral treatment
- Other factors

## Possible Implications

- Ongoing white matter atrophy could:
  - lead to cognitive impairments (e.g., dementia)
  - increase vulnerability to other CNS disorders (e.g., Alzheimer's disease)
- The CNS may be a major target of injury associated with HIV.
  - Therefore, it should be monitored in future treatment trials, including neuroprotective agents.

## Future Directions

- Extend and expand longitudinal study
- Examine role of:
  - Viral mutations/replication rate
  - Macrophage activation
  - Treatment effects
- Correlate with cognitive function

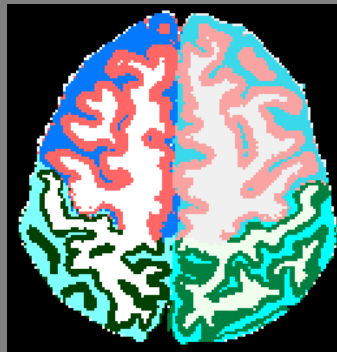
## Acknowledgements

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R. Grant, M.D.  
J.A. Lindgren, M.S.

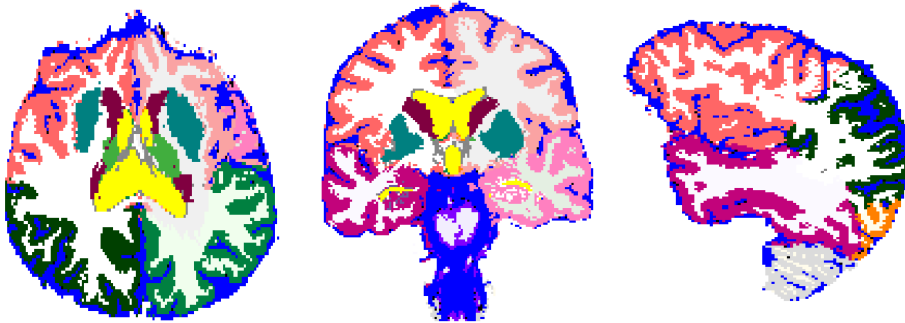
NIAAA PROGRAM PROJECT GRANT  
PO1 11493

"Chronic Alcohol Abuse: Effects on HIV CNS Morbidity"

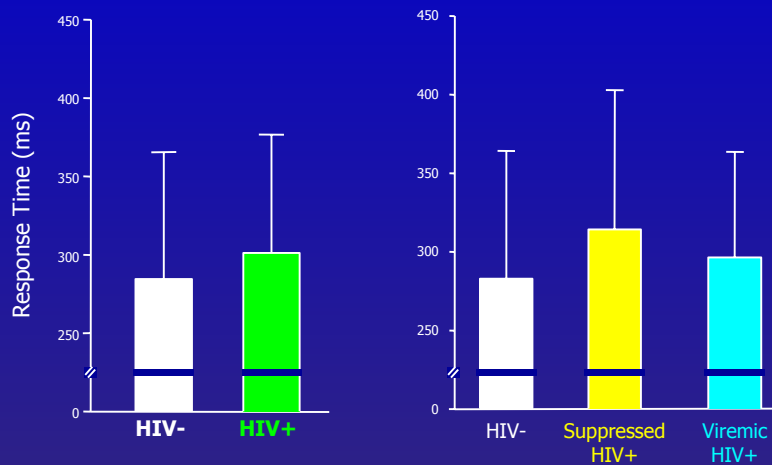
## Lobar and Subcortical Structure Identification



## Hi-Resolution Segmentation

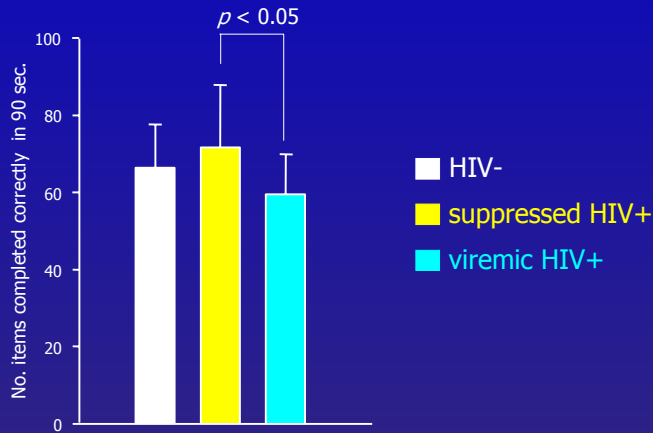


## CNV Behavioral Results



## Neuropsychological Results

- Viremic HIV+ patients were more impaired than virally suppressed HIV+ patients on oral symbol-digit modalities test.



## Neuropsychological Results

- HIV+ patients were more impaired than HIV- subjects on the word reading and the color/word conditions of the Stroop test.
- Viremic HIV+ patients were more impaired than virally suppressed HIV+ patients on the color naming and color/word conditions.

