

# Emerging Considerations in neuroAIDS Internationally: Events in Acute and Early Infection

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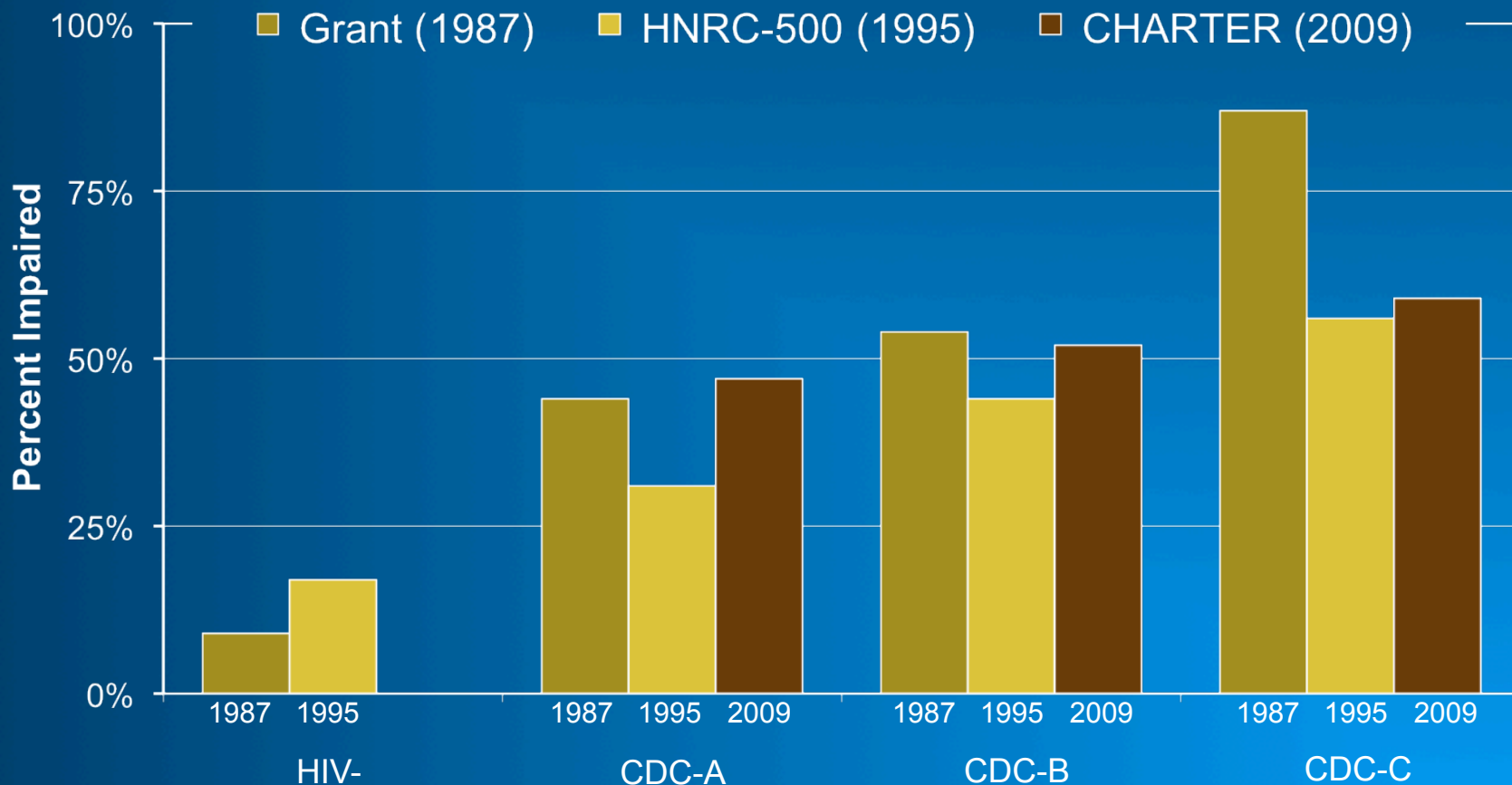
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# Although combination ARVs improve health and prolong survival, neuroAIDS remains prevalent



# Public Health Importance of studies on Acute/ Early infection

- » There are estimated to be 5,000,000 new cases of HIV worldwide annually (40,000 in USA)
- » World wide prevalence is 40,000,000
- » As people survive longer, and if we estimate 35% develop HAND, there may be 14,000,000 cases with neurocognitive impairment
- » In USA, with about 1,000,000 HIV cases, there may be 350,000 with HAND. This makes HIV the 2<sup>nd</sup> most important source on cognitive impairment (after traumatic brain injury) among adults in their most productive years
- » If HAND can be prevented initially, significant source of morbidity is eliminated, and quality of life improved



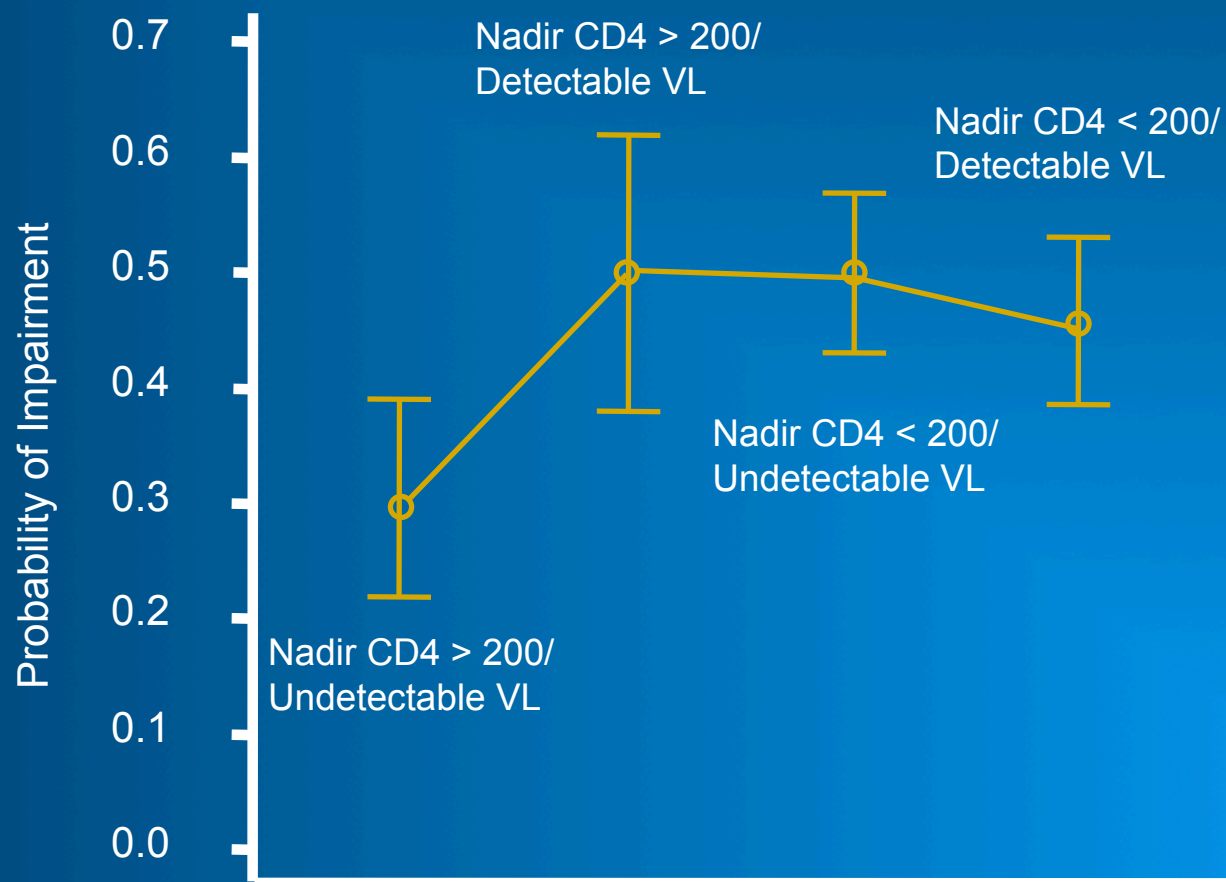
# Neurocognitive Impairment in CHARTER Cases

## Associated with:

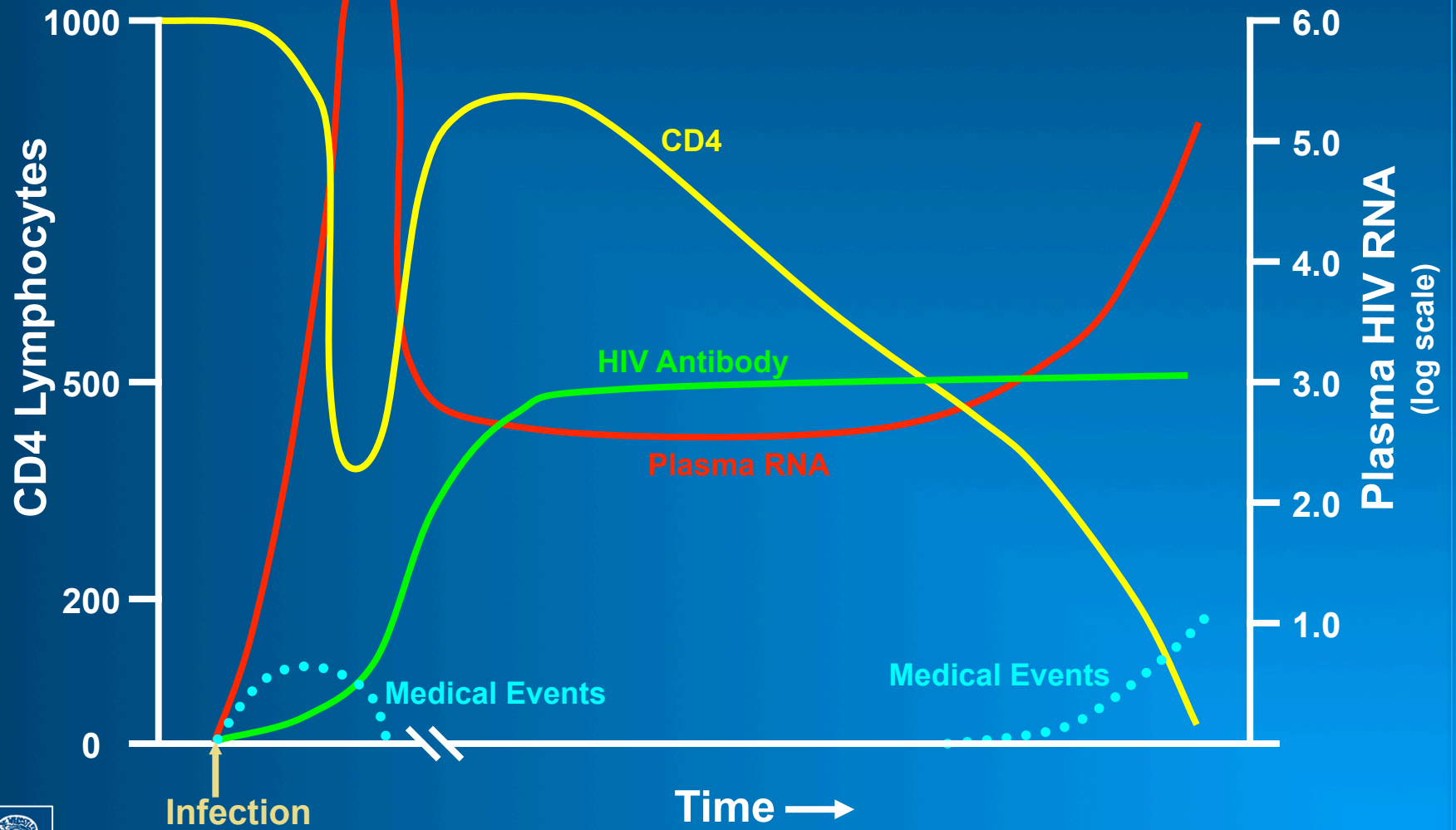
- » Nadir CD4 < 200 ( $p = .01$ )
- » ARV ( $p = .005$ ): current ARV treated worse than those never on ARV (but nadir CD4 < 200 in 74% of currently treated v. 27% never treated)
- » Plasma VL x Nadir CD4 < 200 ( $p = .006$ ): undetectable VL and nadir CD4 > 200 were less impaired
- » No univariate associations to current CD4 , plasma or CSF viral load



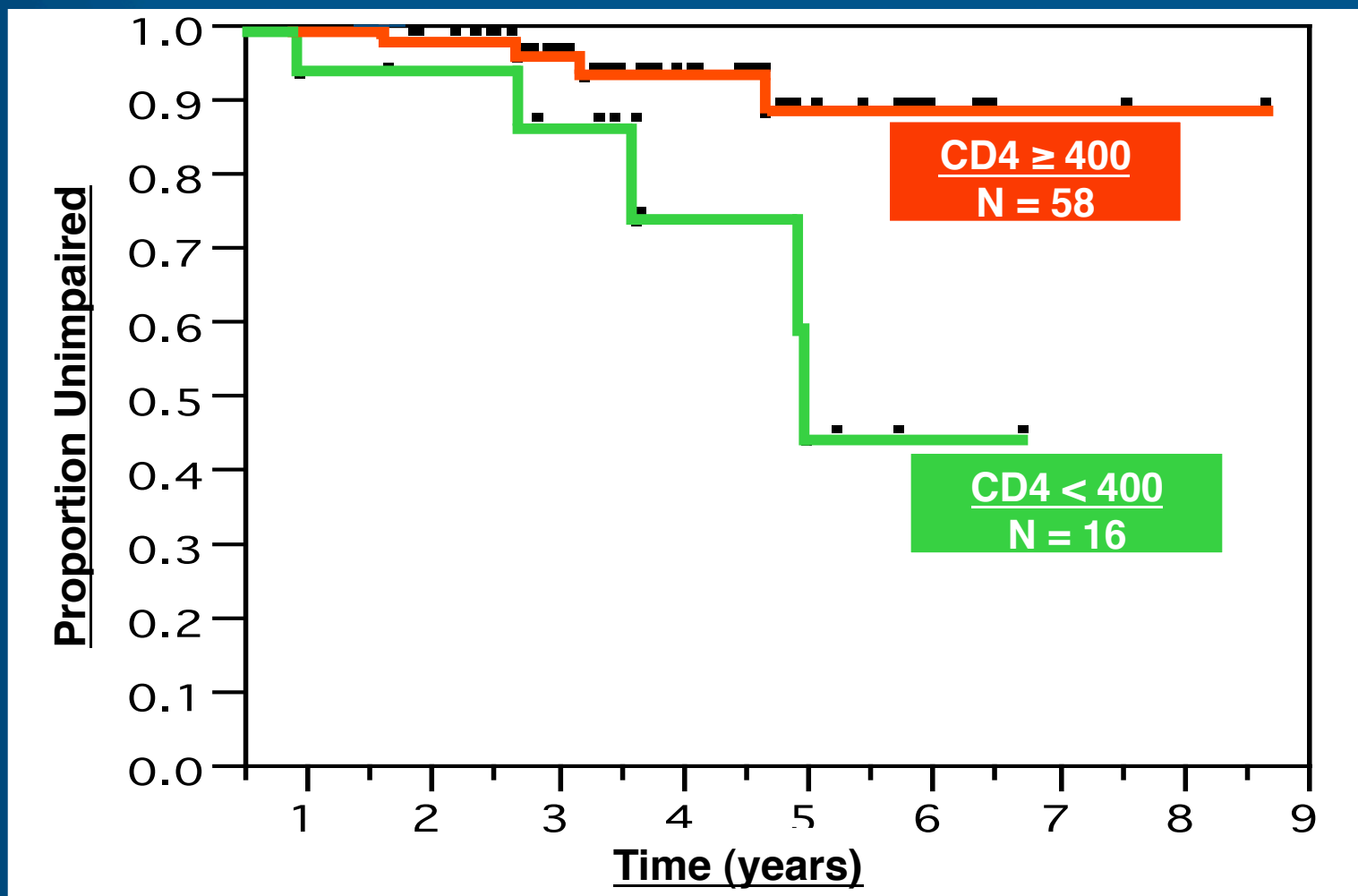
# Reduced Risk of NCI in Those with Absent History of Severe Immunosuppression and Good Virologic Control



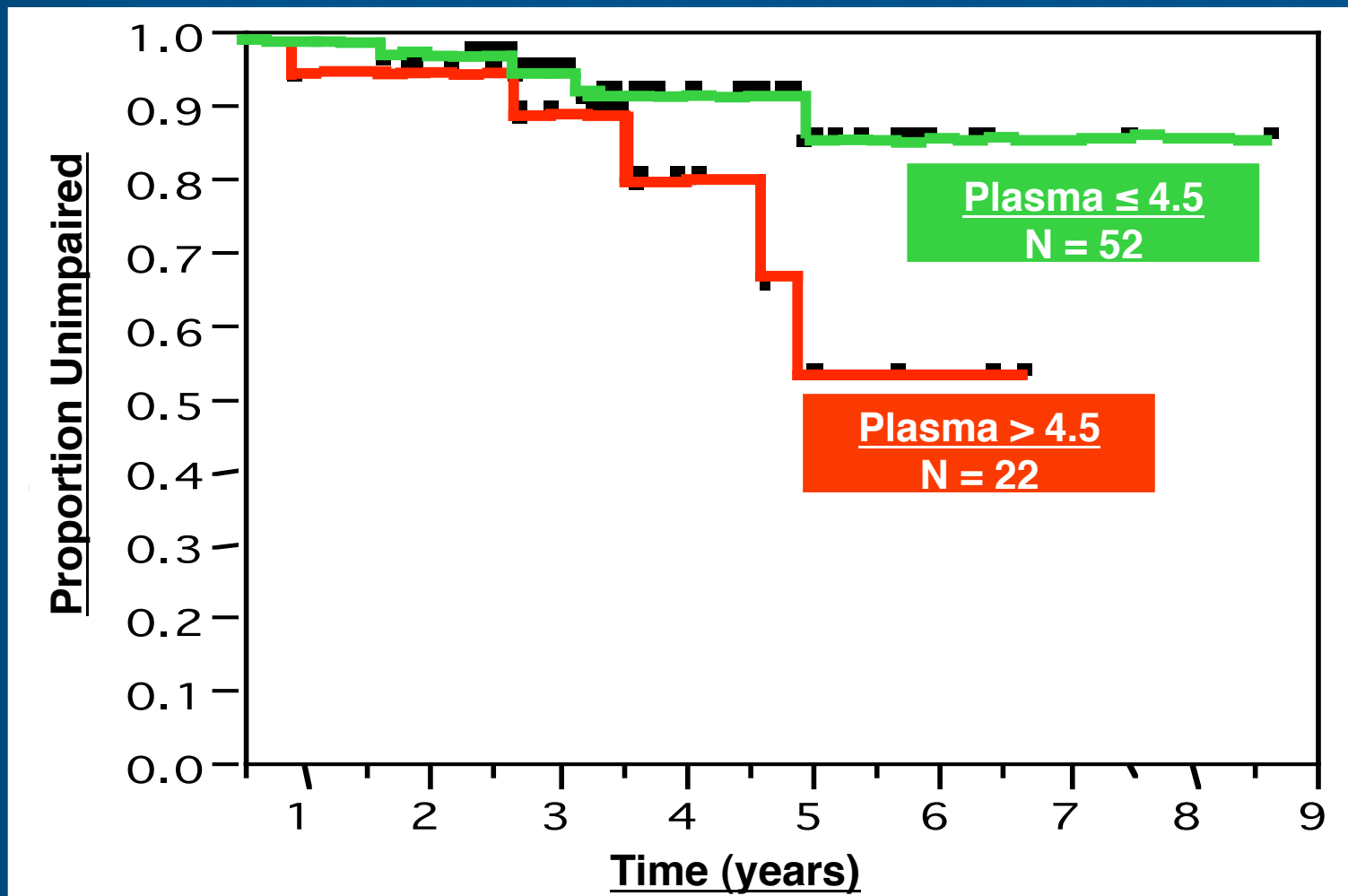
# Markers of HIV Infection Progression Over Time



# Time to NP Impairment Split by CD4 Group

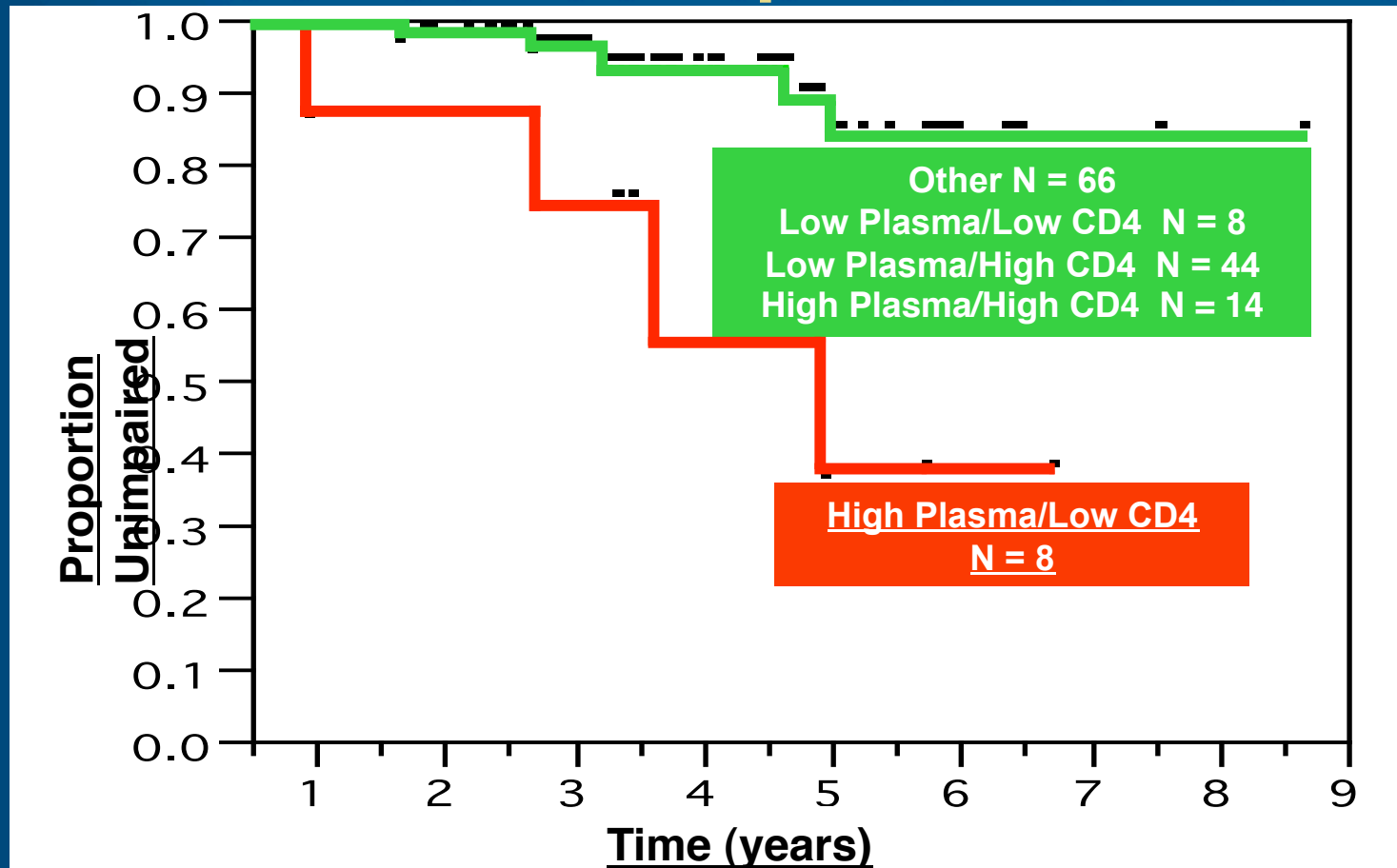


# Time to NP Impairment Split by Plasma HIV-RNA Group





# Time to NP Impairment Split by Highest Risk (Hi Plasma HIV-RNA/Low CD4) vs. All Other Risk Group Combinations



Plasma  $\leq 4.5$  logs vs.  $> 4.5$  logs

CD4  $\geq 400$  vs.  $< 400$

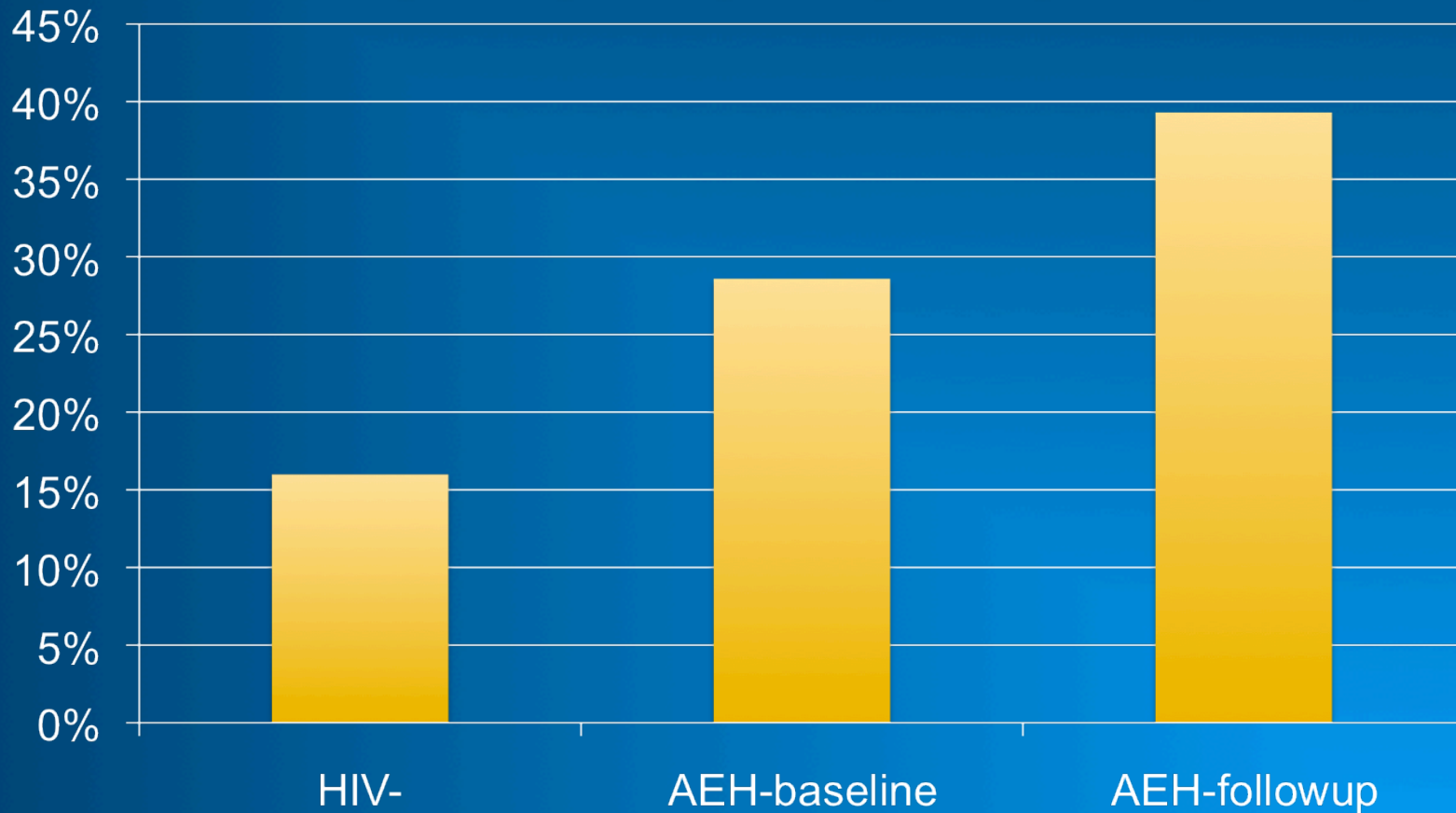


# CHARTER Study Acute and Early Infection Cohort Characteristics (n=70)

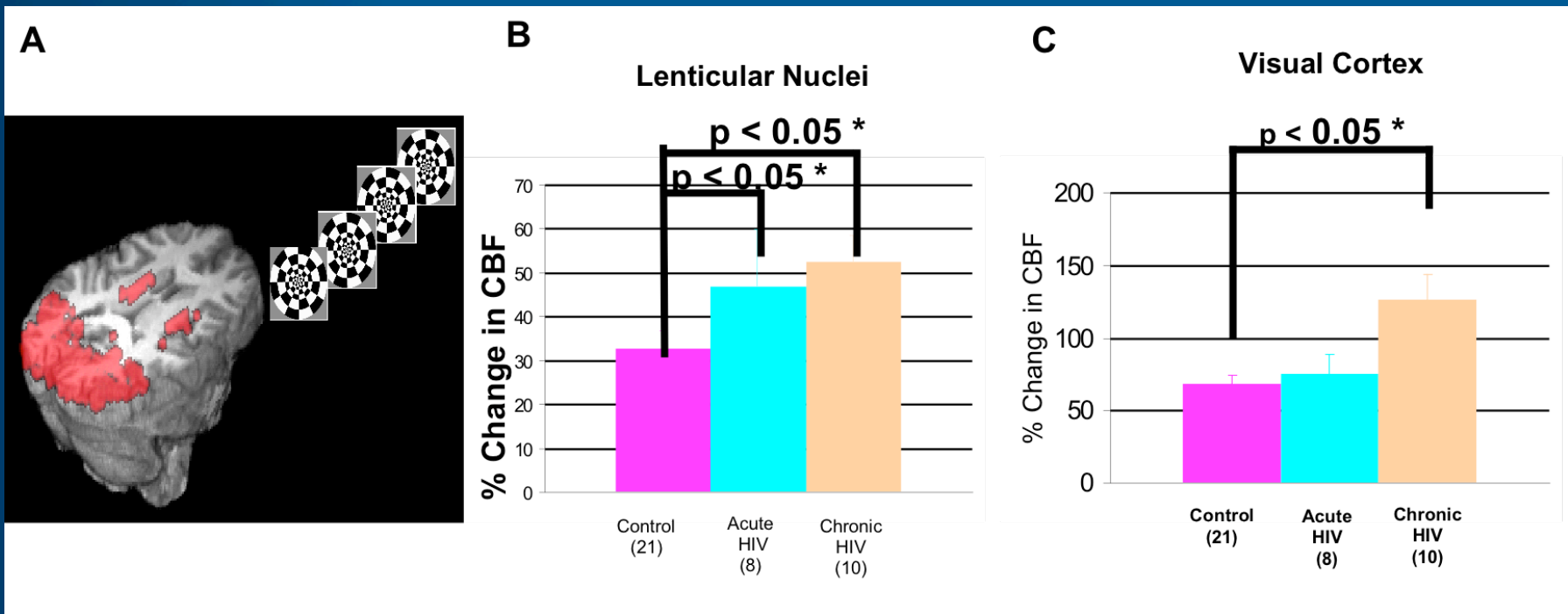
|   | Mean (n)   | SD   |
|---|------------|------|
| <b>Age</b>                                      | 34.4       | 10.3 |
| <b>Education</b>                                | 13.2       | 2.3  |
| <b>Gender (%M)</b>                              | 78.6% (55) |      |
| <b>Ethnicity</b>                                |            |      |
| White   | 62.9% (44) |      |
| Black   | 22.9% (16) |      |
| Hispanic  | 14.2% (10) |      |
| <b>% Acute</b>                                  | 24.3% (17) |      |
| <b>Estimated duration of infection (months)</b> | 6.2        | 3.6  |
| <b>% Impaired</b>                               | 28.6% (20) |      |



# NP Impairment in AEH Cohort at Baseline and 6-month follow-up



# Cerebral Blood Flow Changes in Controls, AEH and Chronic HIV cases

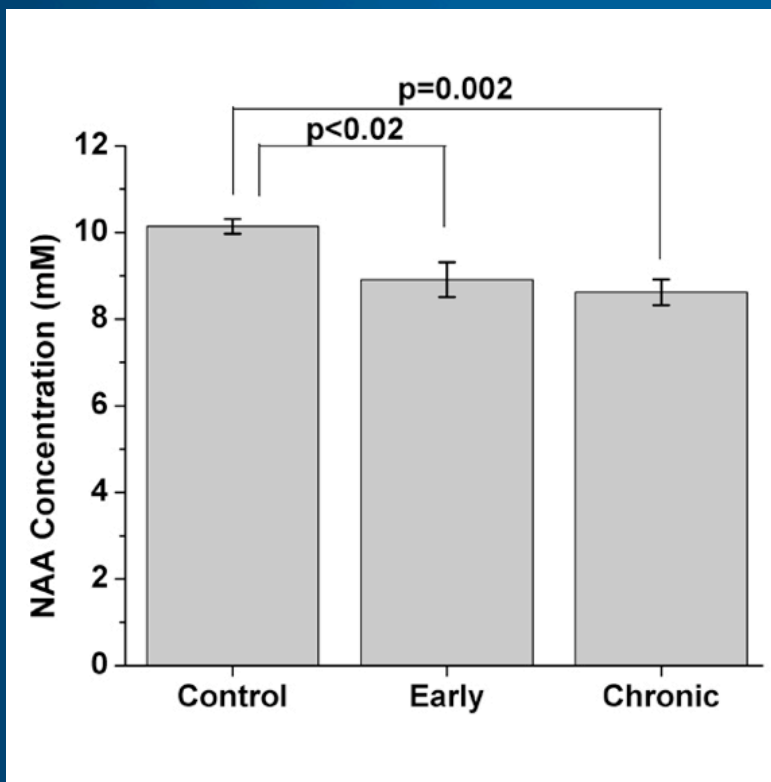


[Ances BM et al. J Neurovirol. 2008 Oct;14\(5\):418-24](#)

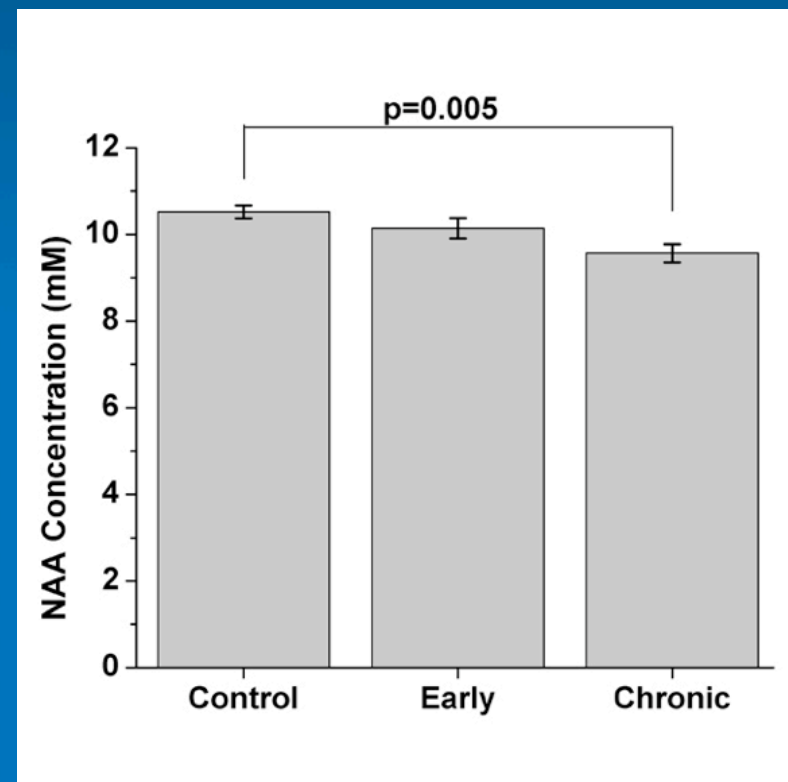


# Altered NAA in AEH and Chronic HIV

Frontal Cortical Gray Matter



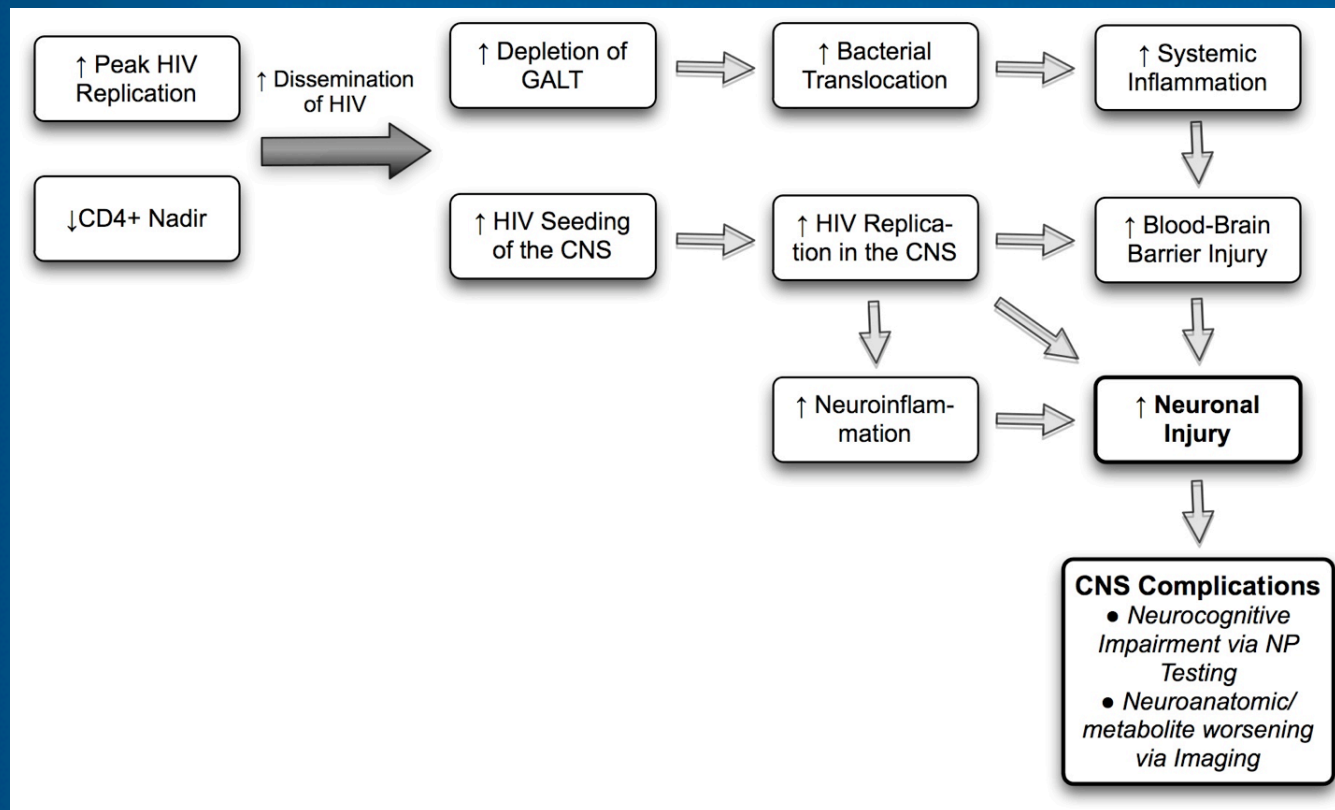
Centrum Semiovale White Matter



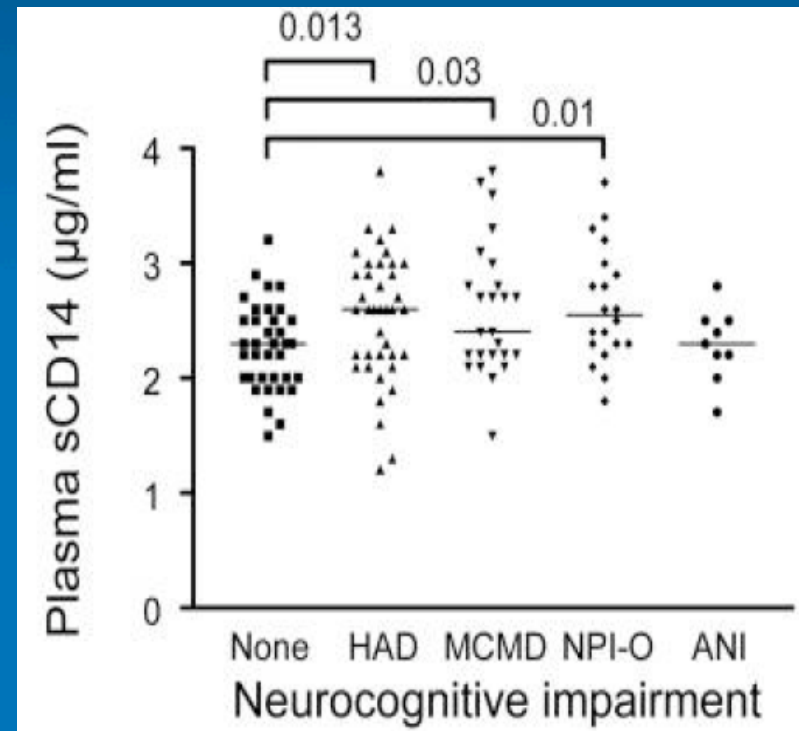
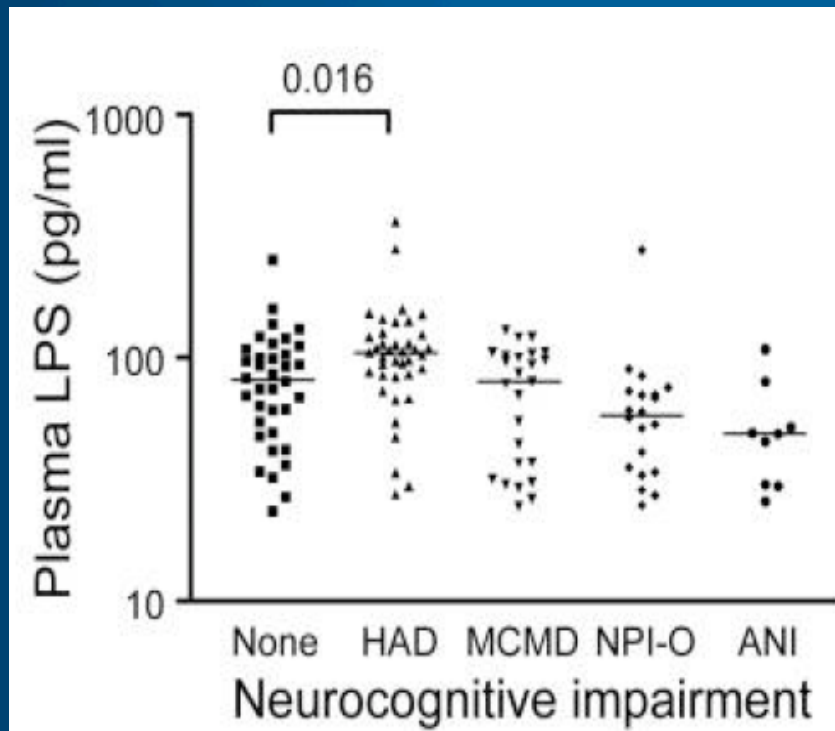
*Lentz et al., 2009*



# Model for CNS Complications in Acute and Early HIV Infection



# Plasma lipopolysaccharide (LPS) and sCD14 monocyte activation marker related to HAND in AIDS patients with CD4 < 300



[Ancuna et al., PLoS ONE. 2008; 3\(6\): e2516](#)



# Summary of HAND and AEH

- » Neurocognitive impairment is present within 6 mos of infection
- » 10% decline over 6 mos
- » Associated with plasma biomarkers of neuronal injury [eg tau) and inflammation/cell migration (uPAR)
- » Evidence of neuronal injury also on MRS ( lower NAA)
- » Increased CBF in basal ganglia (perhaps indicates inflammatory change)
- » High VL and low CD4 increase hazard of HAND in future





## HAND and AEH: examples of questions

- » Do early gut associated lymphocyte (GALT) depletion, and bacterial translocation, trigger systemic inflammation favoring migration of HIV and immune cells into the CNS?
- » Is GALT injury associated with spikes in VL that increase trafficking of HIV into CNS?
- » Do drugs of abuse that modify immune responses, eg., methamphetamine; opioids amplify the above?
- » Do coinfections, eg., TB, malaria, HCV also amplify these?
- » Does acute treatment with CNS penetrating ARV abort these early CNS events?
- » Utility of “neuroprotective” and “anti-inflammatory” adjuncts



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## Thank you!

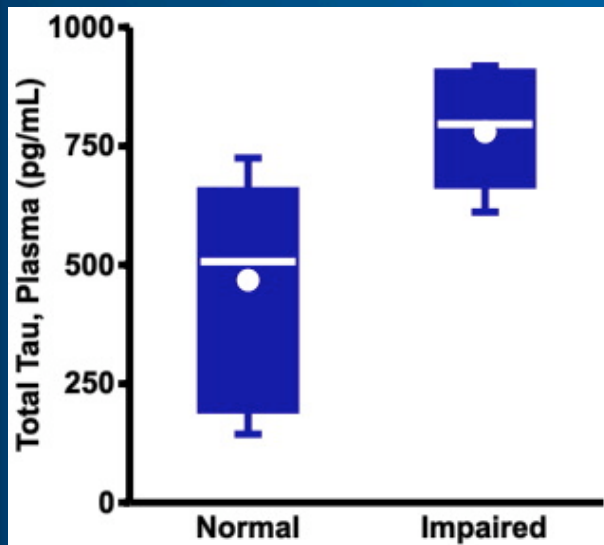
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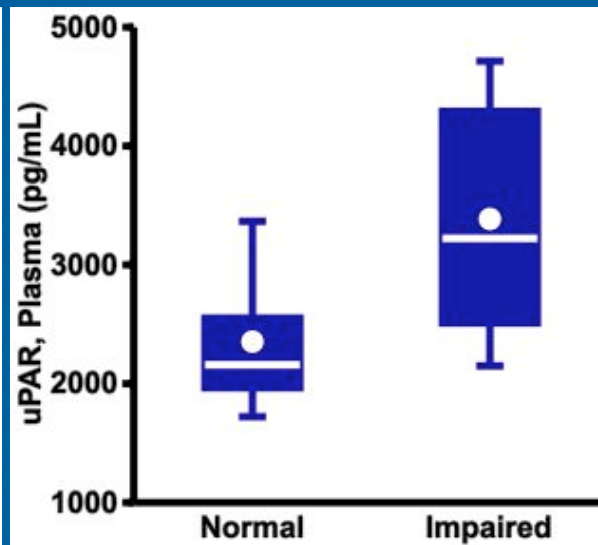


# Elevated Blood (but not CSF) Biomarkers associated with NP Impairment in AEH Cases

Tau (plasma)



uPAR (plasma)



MCP-1 (CSF)

