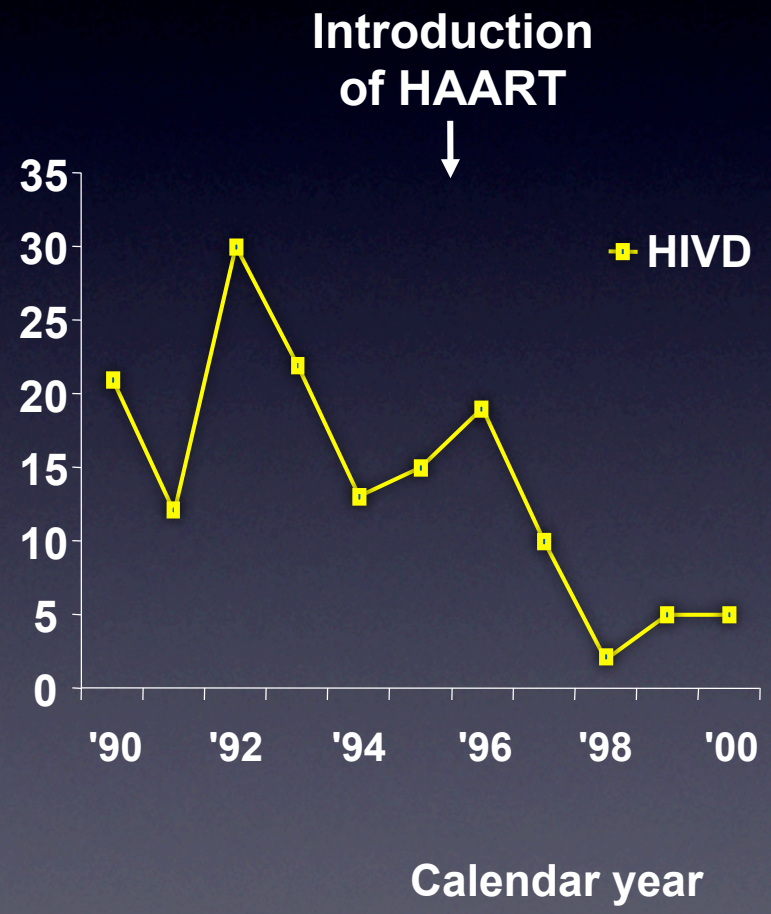
HIV-1 SuperLow Viral Load as a Monitoring Tool for Antiretroviral Drug Penetration

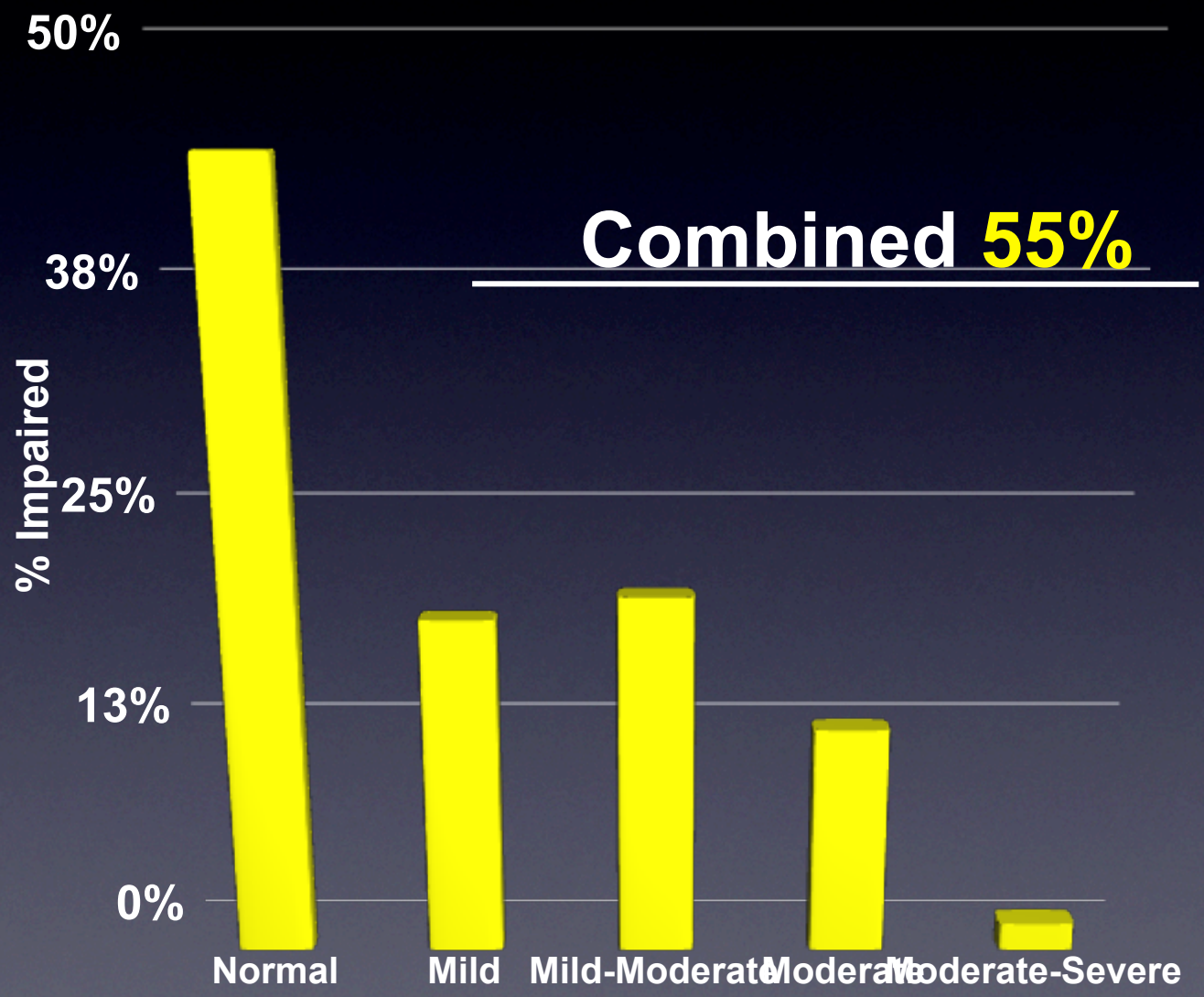
Daniel R McClernon
McClernon, LLC

Changing Epidemiology
Declining Incidence of Neurologic Complications



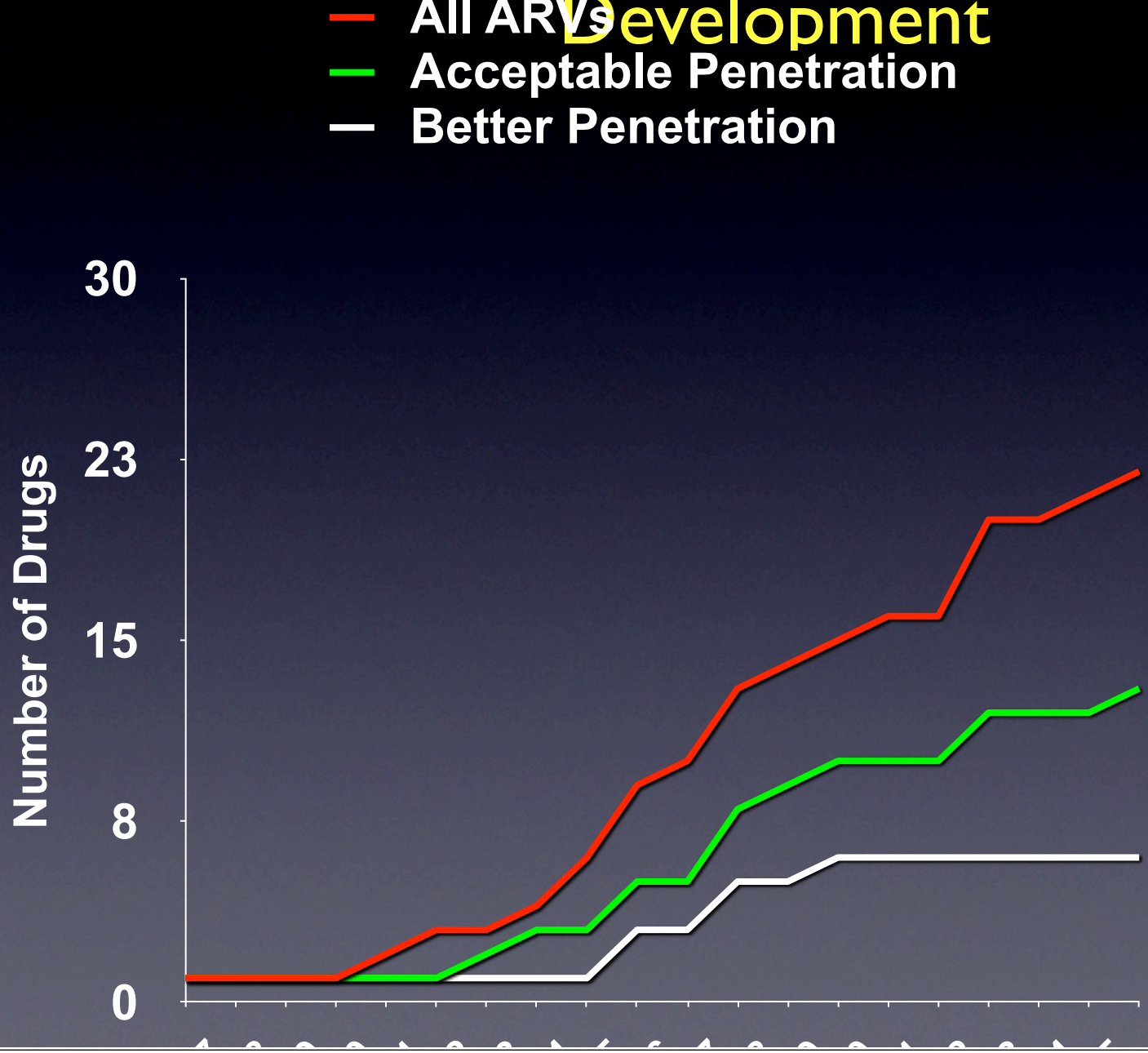
Sacktor N. JNV. 2002; 8(S2):115-121

Changing Epidemiology
Prevalence of Impaired Performance in 2005



CNS HIV AntiRetroviral Therapy Effects Research Project

Antiretroviral Treatment
Slower Pace of Neuroeffective ARV Development



Antiretroviral Treatment
Factors Influencing Distribution into CNS

- Protein Binding
- Molecular Weight
- Lipophilicity
- Ionization
- Molecular pumps

Antiretroviral Treatment
CNS Penetration-Effectiveness Score

	1	0.5	0
NRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine	Efavirenz	
PIs	Indinavir Indinavir-r Lopinavir-r	Amprenavir-r Atazanavir Atazanavir-r Darunavir-r	Amprenavir Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion Inhibitors			Enfuvirtide

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NNRTIs	Delavirdine **Nevirapine**	Efavirenz	**2.5**
PIs	Indinavir Indinavir-r Lopinavir-r	Amprenavir-r Atazanavir Atazanavir-r Darunavir-r	Amprenavir Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion Inhibitors			Enfuvirtide

Background
Charter Study Rationale

- Antiretroviral therapy (ART) can reduce HIV-1 RNA below the lower limit of quantitation of commercial assays (<50c/ml) but replication could persist at low levels.

- Viral adaptation to immunologic and pharmacologic pressures.

- Ongoing brain injury.

- Protected compartments, such as the CNS, may be at particular risk for persistent HIV replication because antiretrovirals may not reach therapeutic levels within these sites.

Methods

- Participants
  - 317 HIV-infected individuals from the CHARTER cohort who completed standardized assessments, had successful lumbar punctures, and had HIV RNA levels measured in both plasma and CSF.
- Laboratory Procedures
  - McClernon, LLC utilized a SuperLow HIV-1 EasyQ assay (modified protocol) and experimental algorithm that allows detection of HIV-1 RNA down to 2 copies/ml RNA (basic kit commercially available from bioMerieux).

SuperLow EasyQ HIV-1

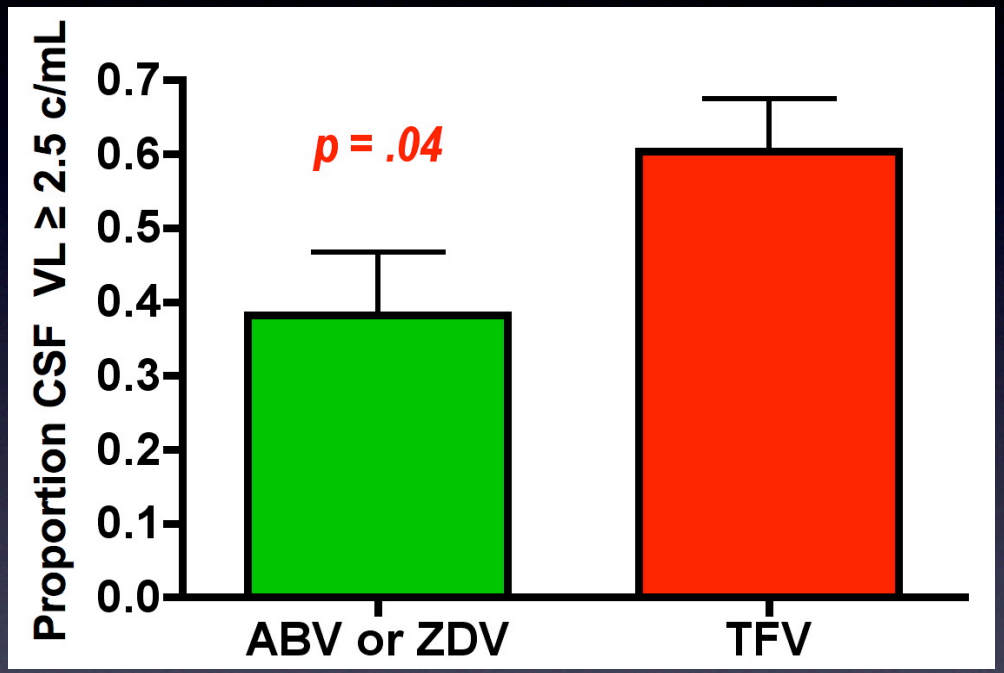
- Magnetic silica based extraction technology.
- HIV-1 gag-based primer set, internally controlled.
- Real Time NASBA reaction. NASBA= Nucleic Acid Sequenced Based Amplification. Isothermal amplification.
- Molecular beacon detection.
- Quantitation is based on the relative amounts of HIV-1 RNA and the calibrator RNA present at the start of the NASBA reaction.

Objectives

- Determine the proportion of CSF specimens that had HIV RNA > 2 c/mL among those that were below 50 c/mL.
- Determine the correlates of HIV RNA levels > 2 c/mL, including the effect of antiretroviral penetration.

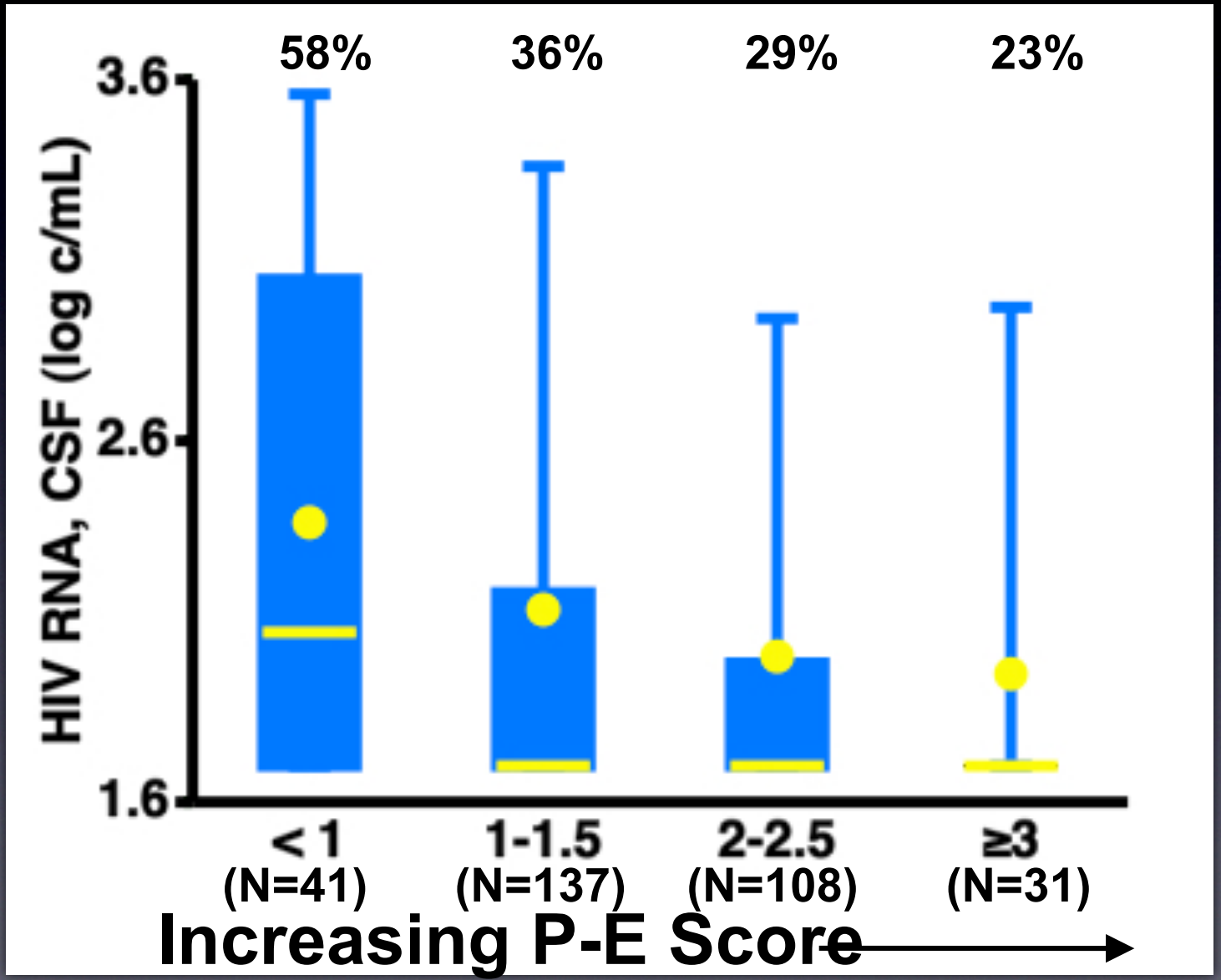
Antiretroviral Treatment
Factors Influencing Distribution into CNS

- Lower CPE Scores trended towards being associated with detectable HIV in CSF (p=.09)
- TFV users had more than twice the odds of having detectable HIV in CSF as users of either ABV or ZDV (OR 2.46, p=.04)

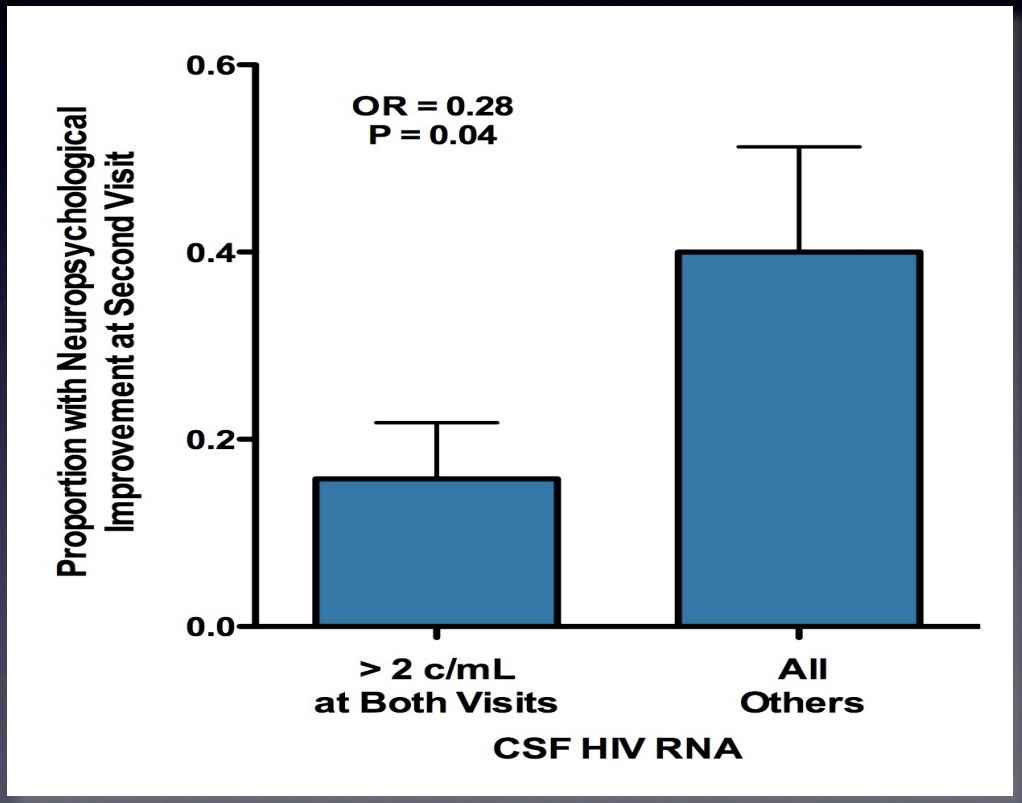


Letendre et al, 16th CROI, Abstract 369

Results
P-E Scores and HIV RNA in CSF



Lower Neurocognitive improvement in Subjects with Detectable HIV in CSF



Summary and Conclusions

- Worse antiretroviral penetration was associated with detectable HIV in CSF.
- An enhanced SuperLow HIV-1 real time assay detected HIV RNA in 49% of CSF specimens that were undetectable by the standard Roche Cobas assay. We conclude a more sensitive HIV viral load assay may be needed to monitor CSF in treated individuals.
- Demonstrated possible clinical utility of SuperLow HIV-1 VL assay in HIV CNS disease. Must be confirmed with prospective trials.

Acknowledgements

- bioMerieux
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THANK YOU