

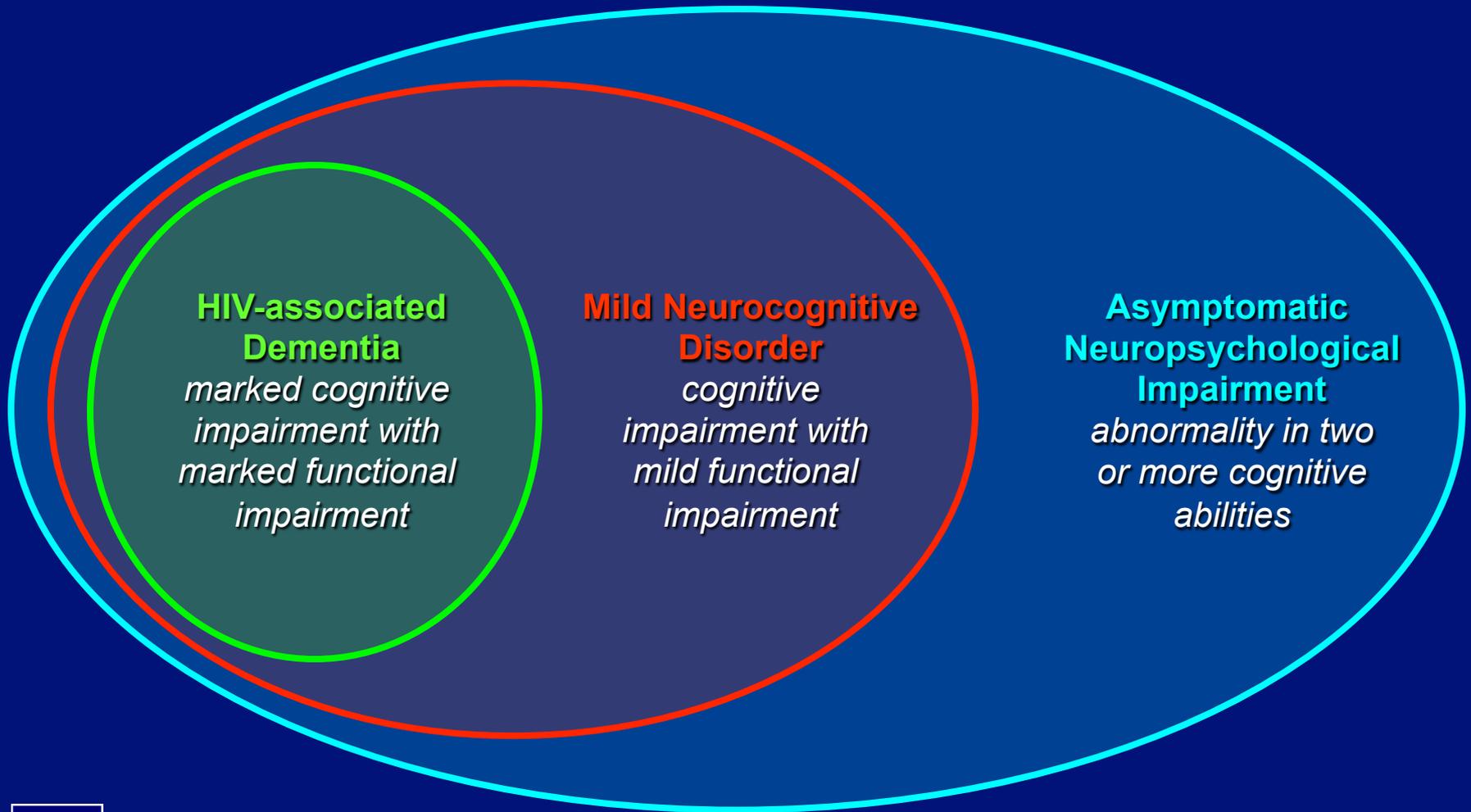
# HIV, HCV, Drug Abuse and the Brain

Igor Grant M.D.

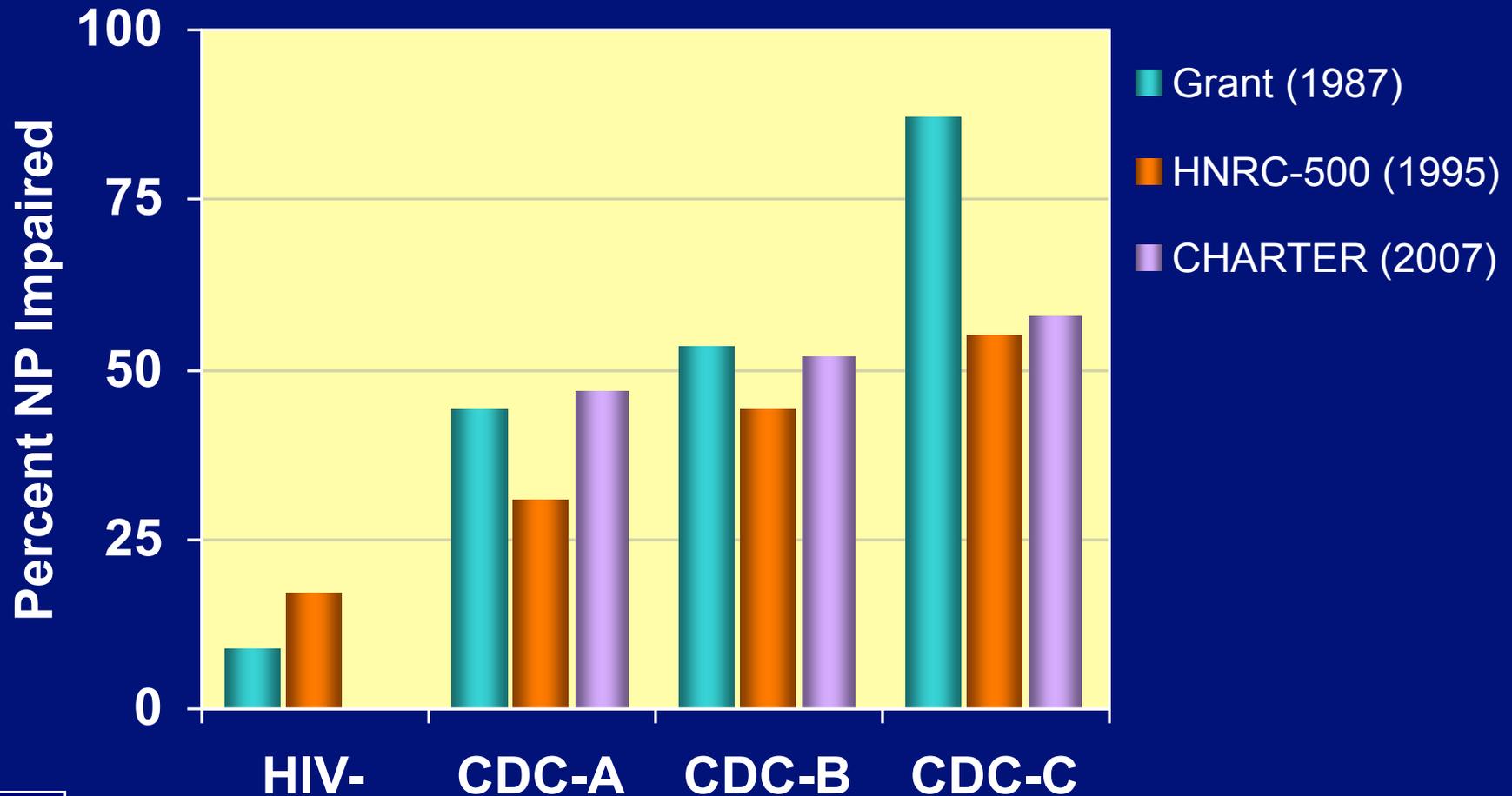
HIV Neurobehavioral Research Center,  
University of California, San Diego



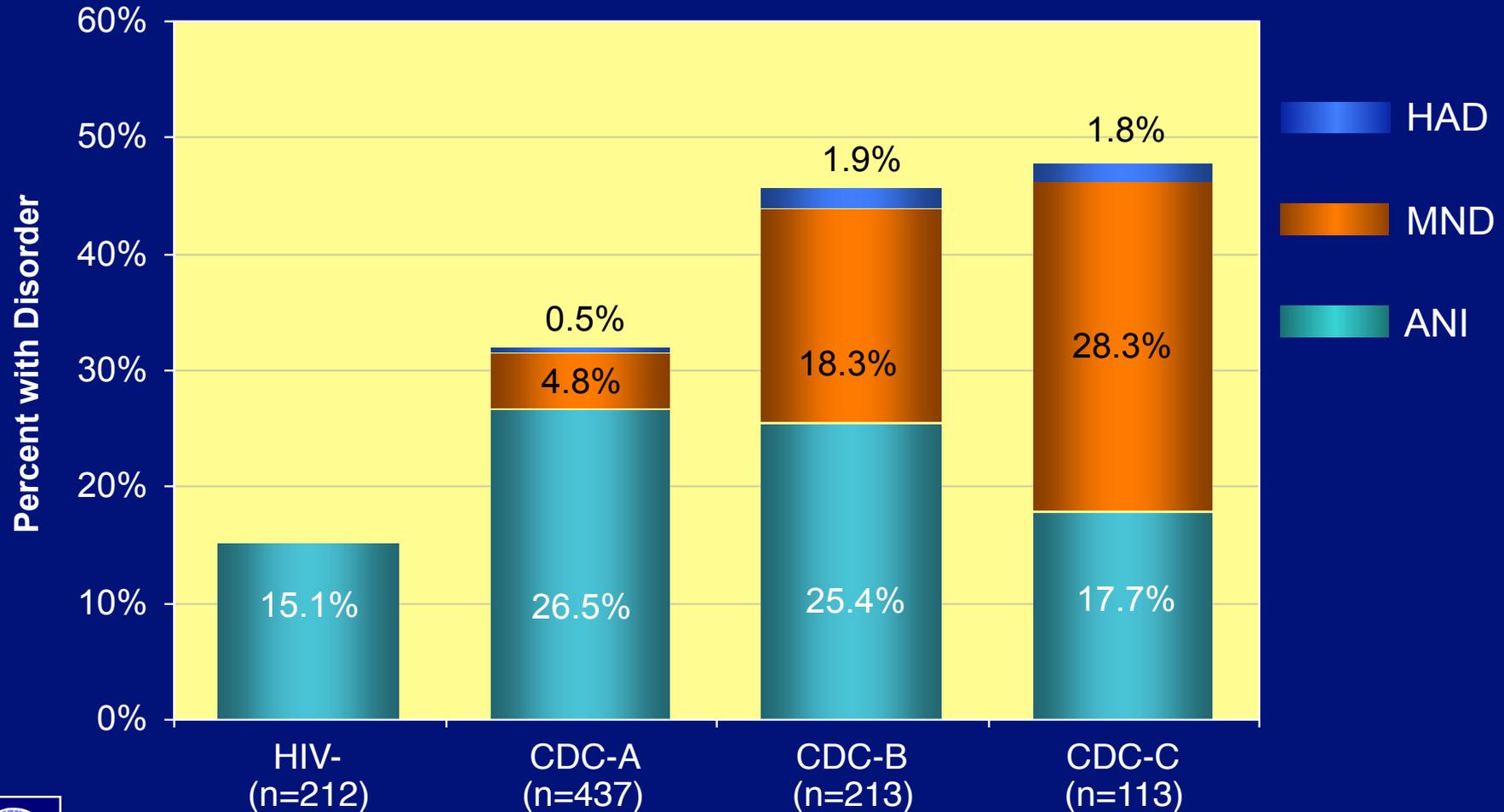
# Range of HIV Associated Neurocognitive Disorders (HAND)



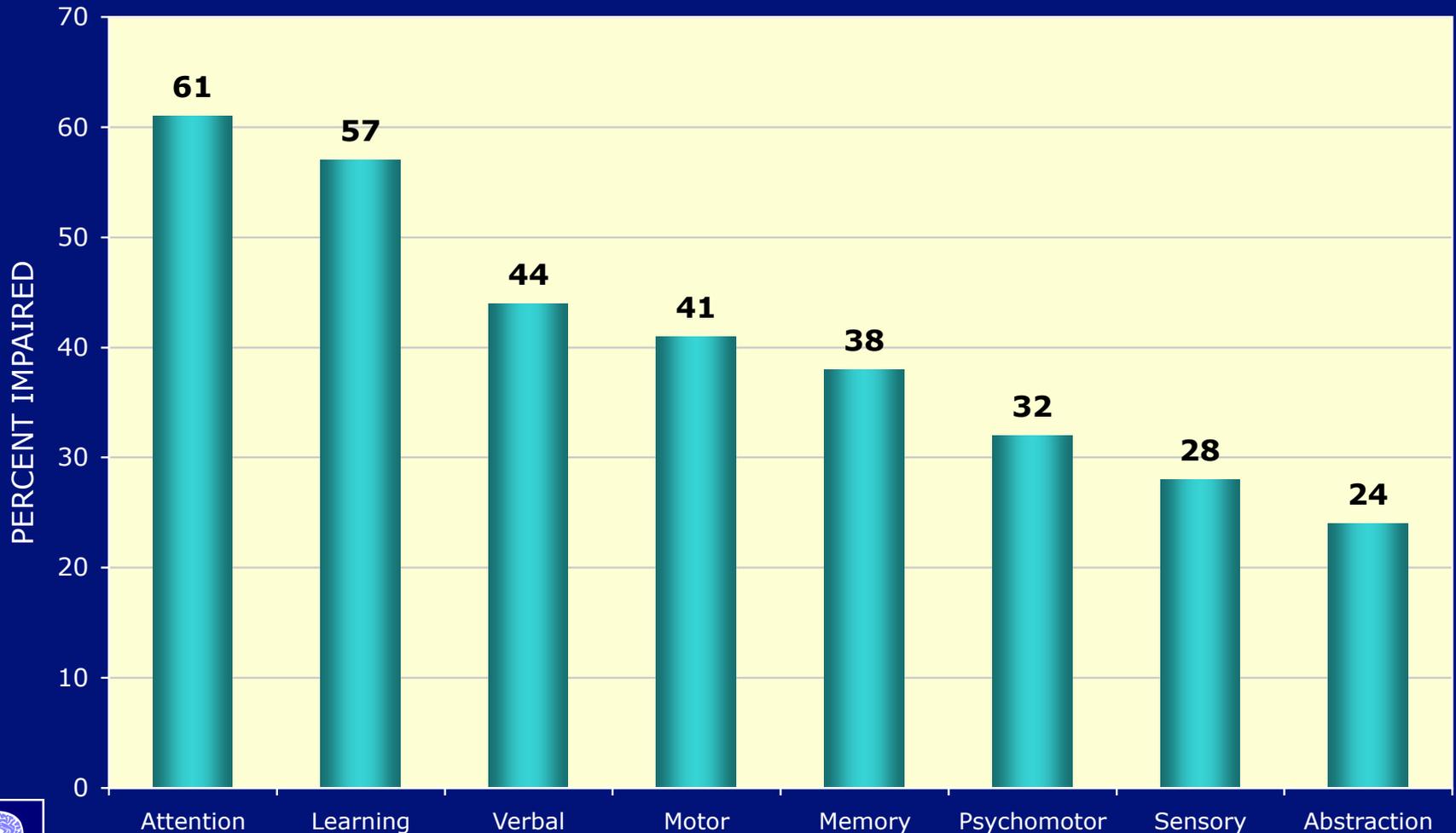
# Although Combination Antivirals Improve Health and Prolong Survival, NeuroAIDS Remains Prevalent



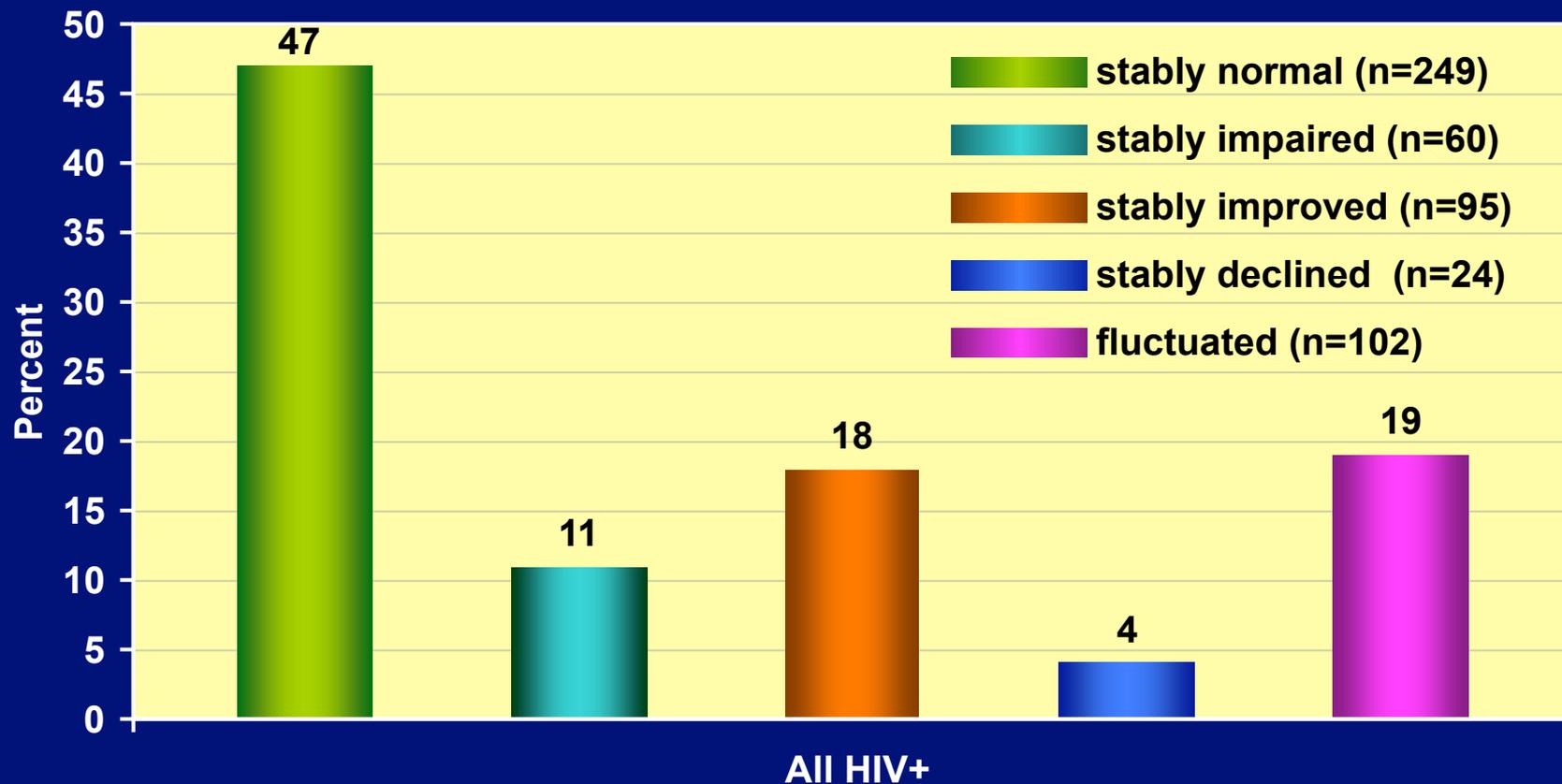
# Prevalence of HAND by Stage of HIV Disease



# Proportions of Persons Judged to have Global NP Impairment that have Specific Ability Deficit



# NP Course for HIV Neurocognitive States (from HNRC, N=534)

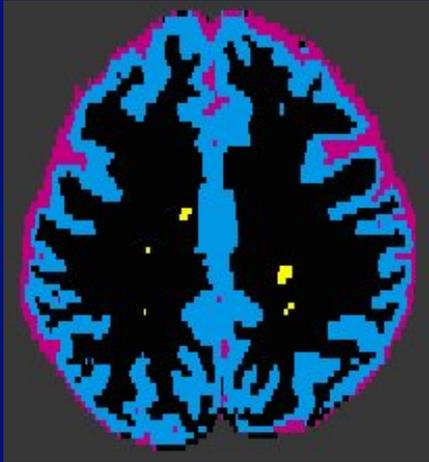


Antinori A., et al., 2007, *Neurology*, 69, 1789-1799.

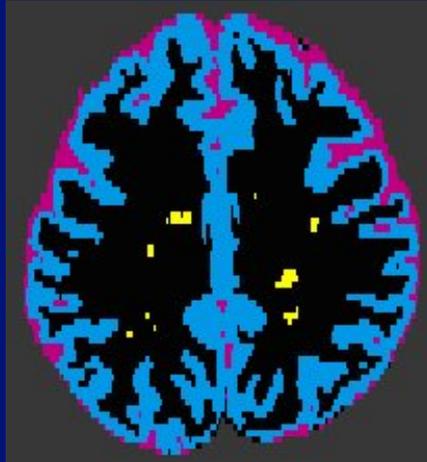
# Dynamic Nature of White Matter Change

## *Increasing WM Abnormalities*

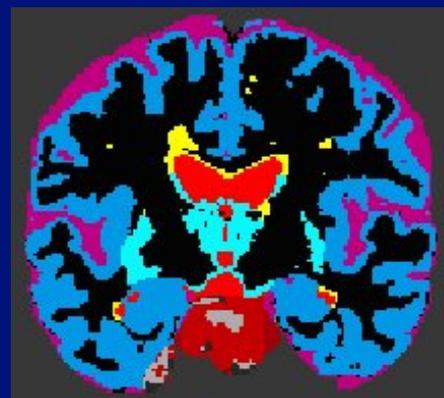
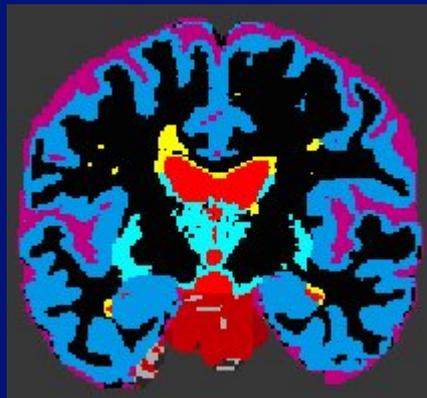
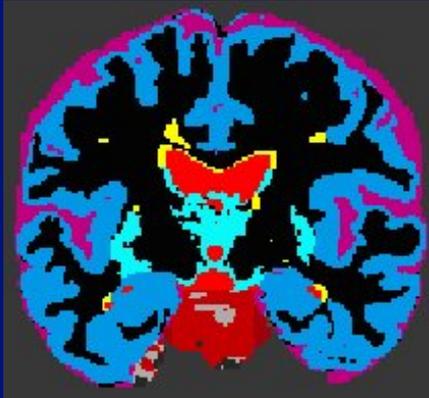
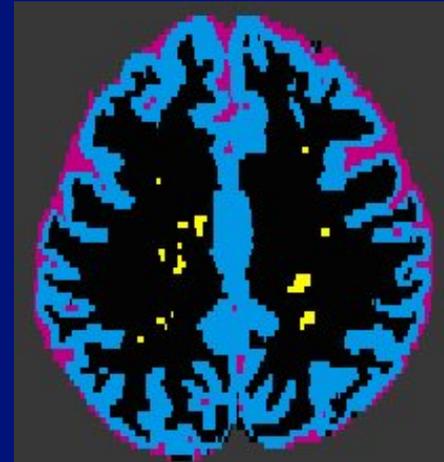
Baseline



One year



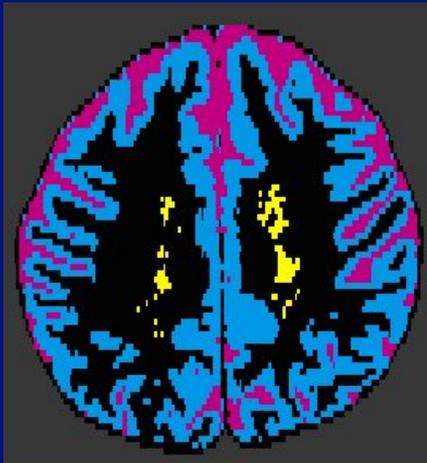
Two years



# Dynamic Nature of White Matter Change

## *Decreasing WM Abnormalities*

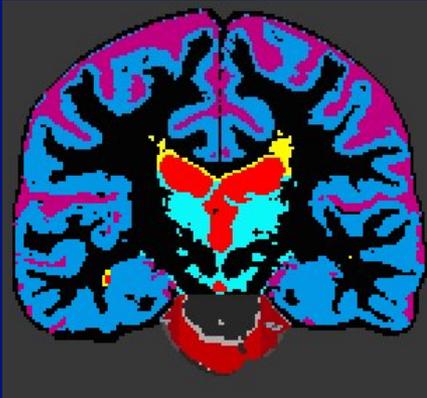
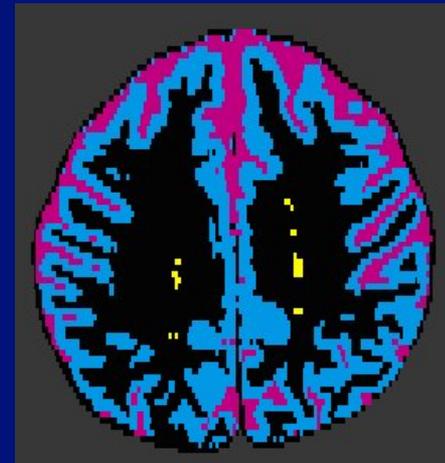
Baseline



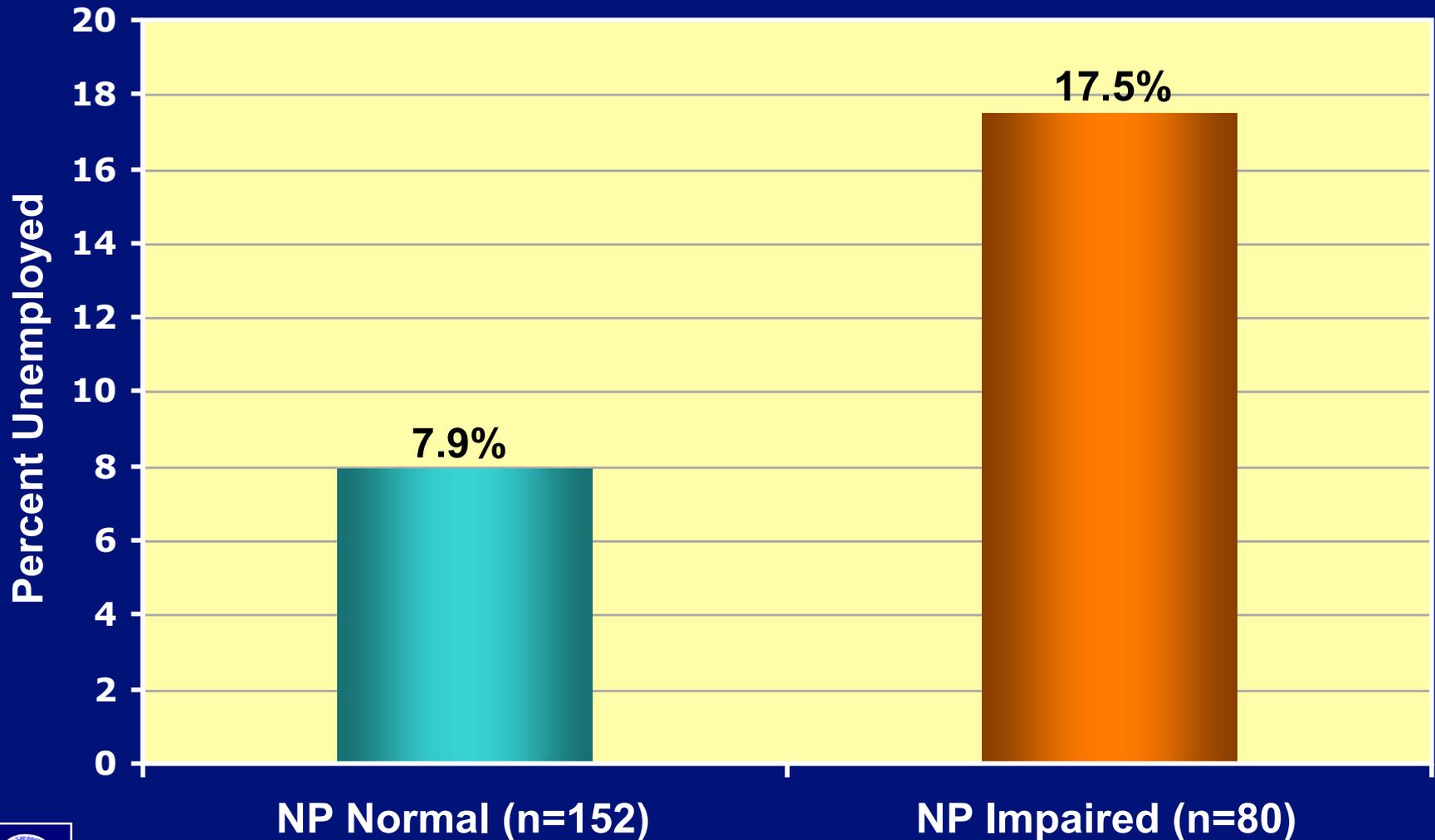
One year



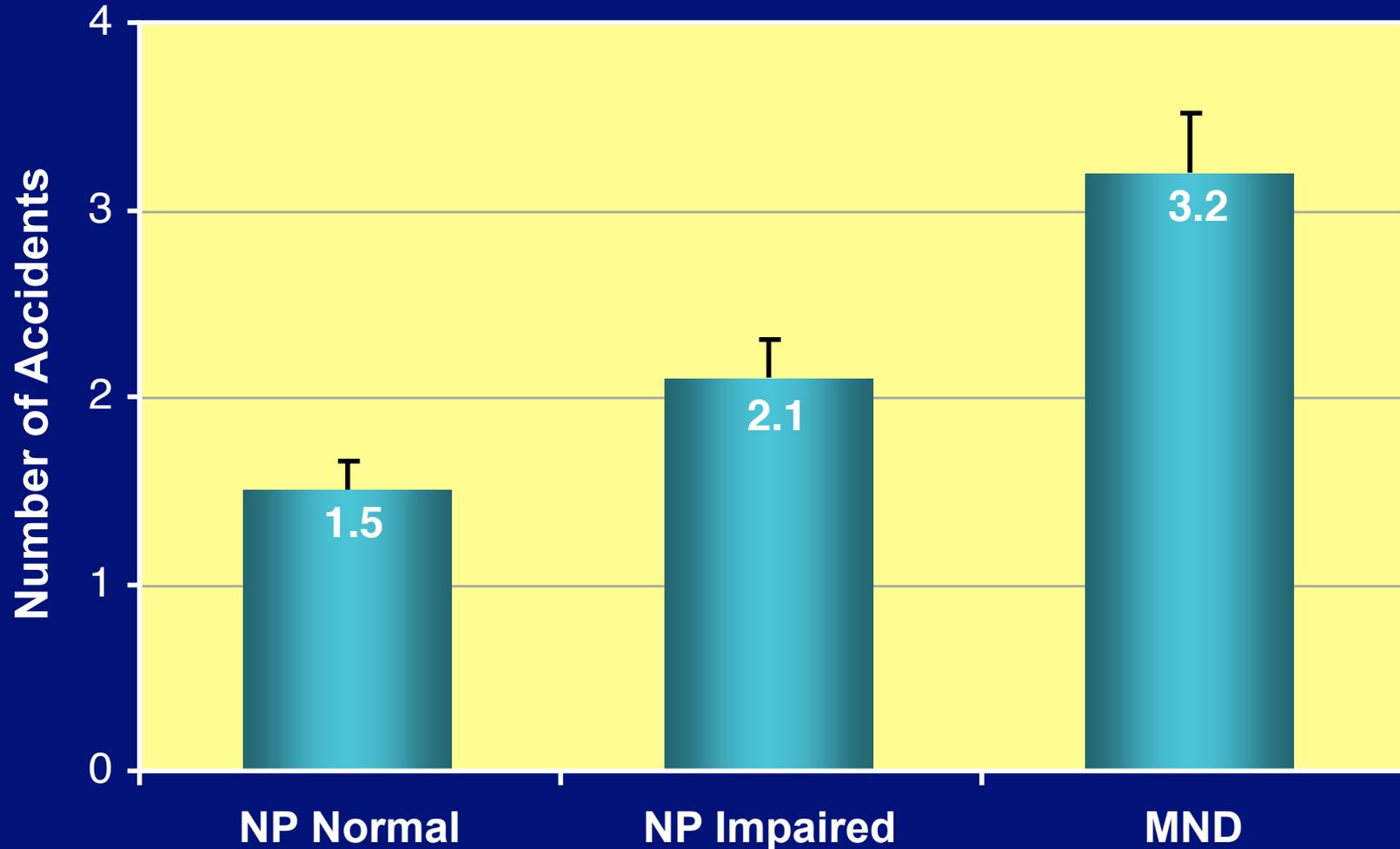
Two years



# Meaning of NP Impairment: Employment

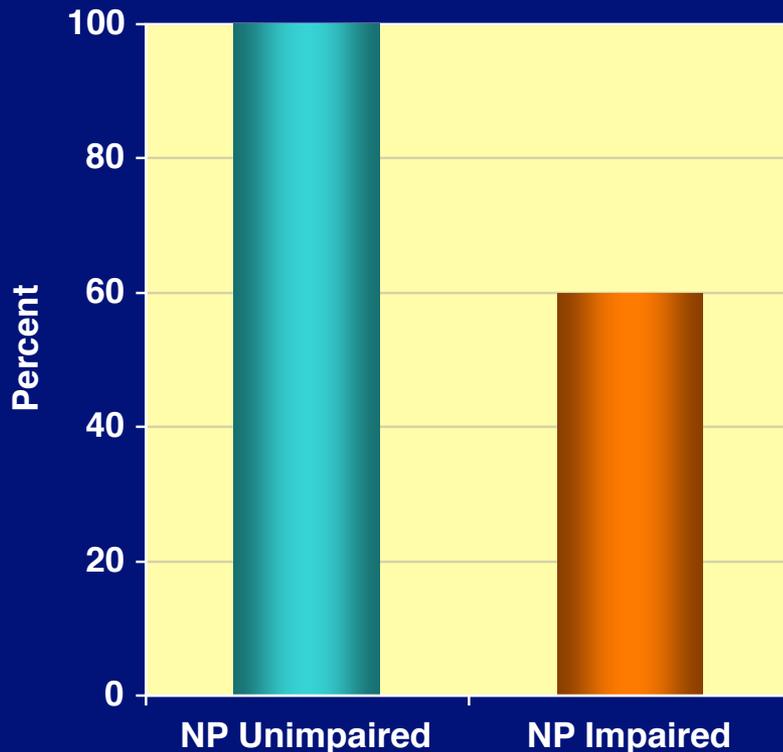


# Mean Number of Accidents on City Driving Simulation

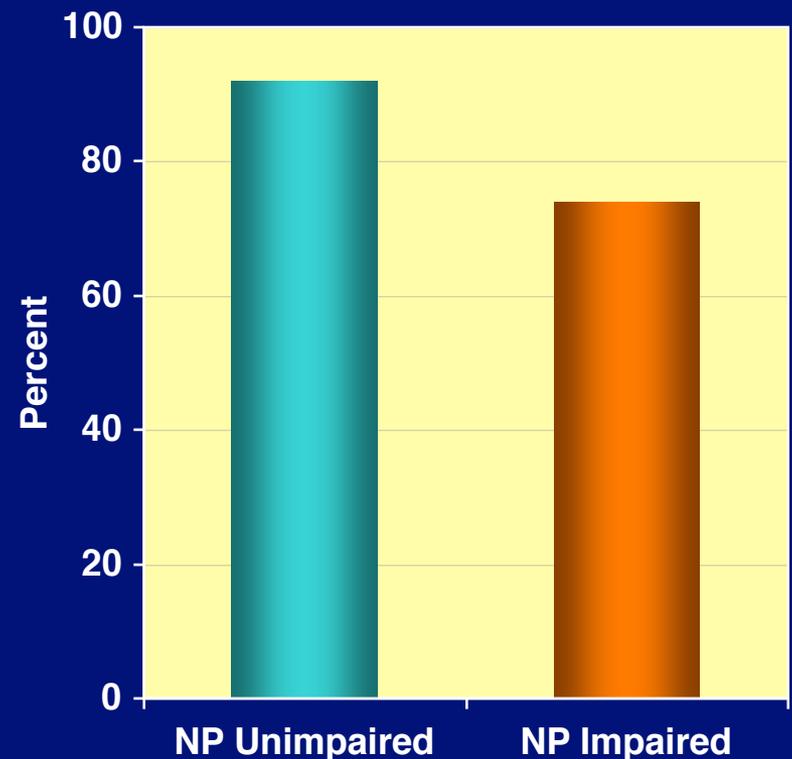


# Adherence to Antiretrovirals Related to Neurocognitive Impairment

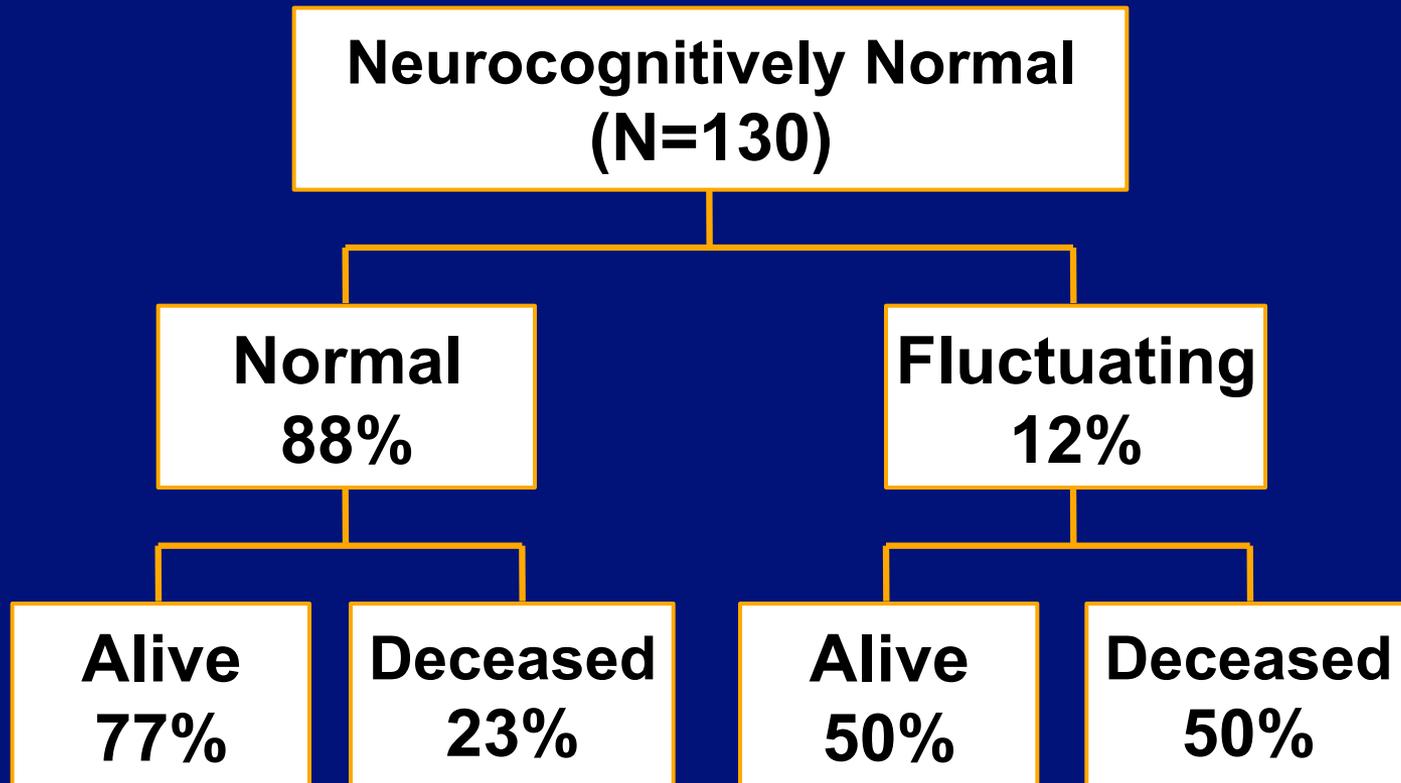
Percent That Followed Schedule  
“Most of the Time”



Percent That Followed Specific Instructions  
Regarding Medications “Most of the Time”

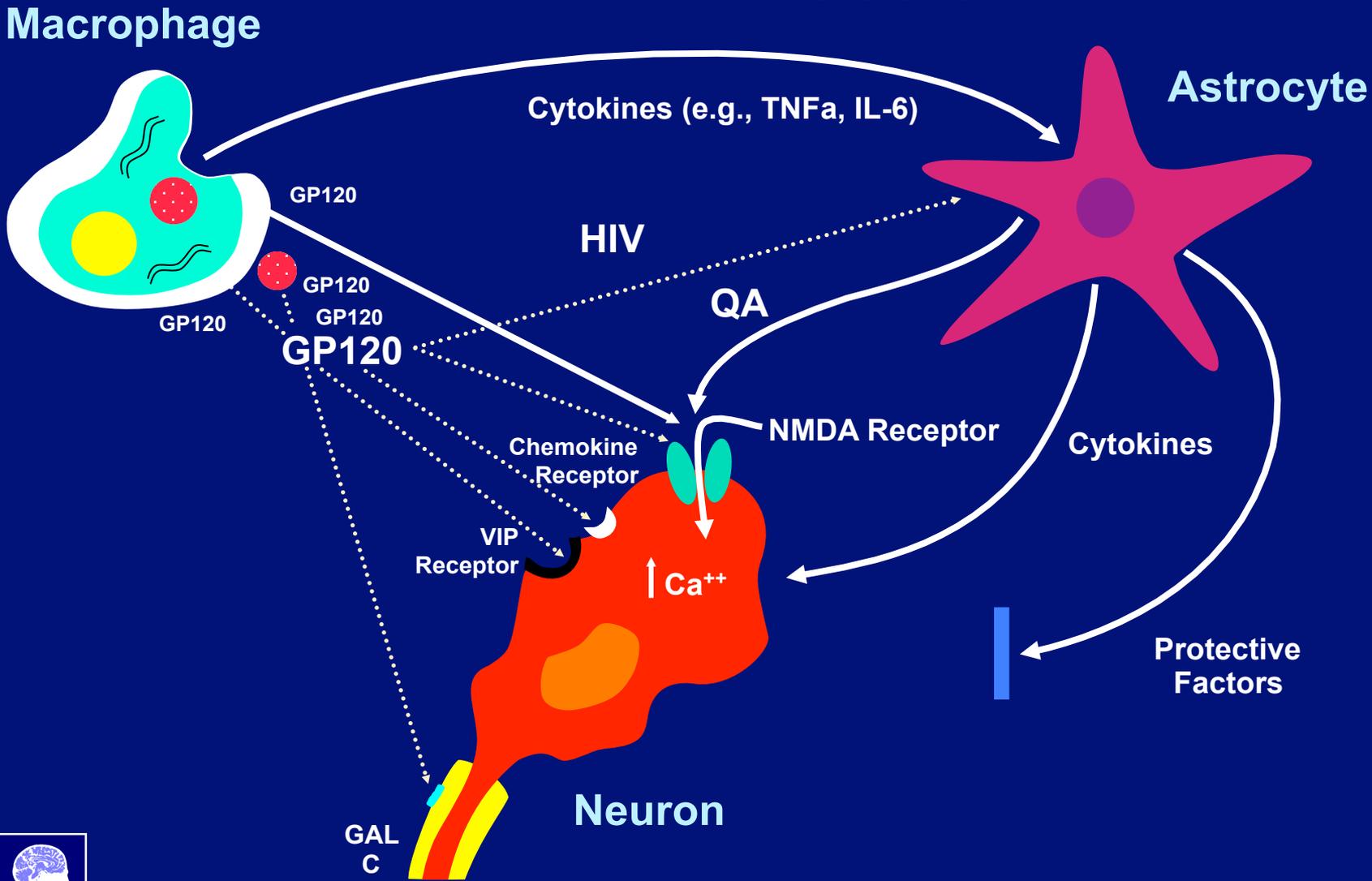


# Longitudinal Course of Participants who were Neurocognitively Normal at Baseline

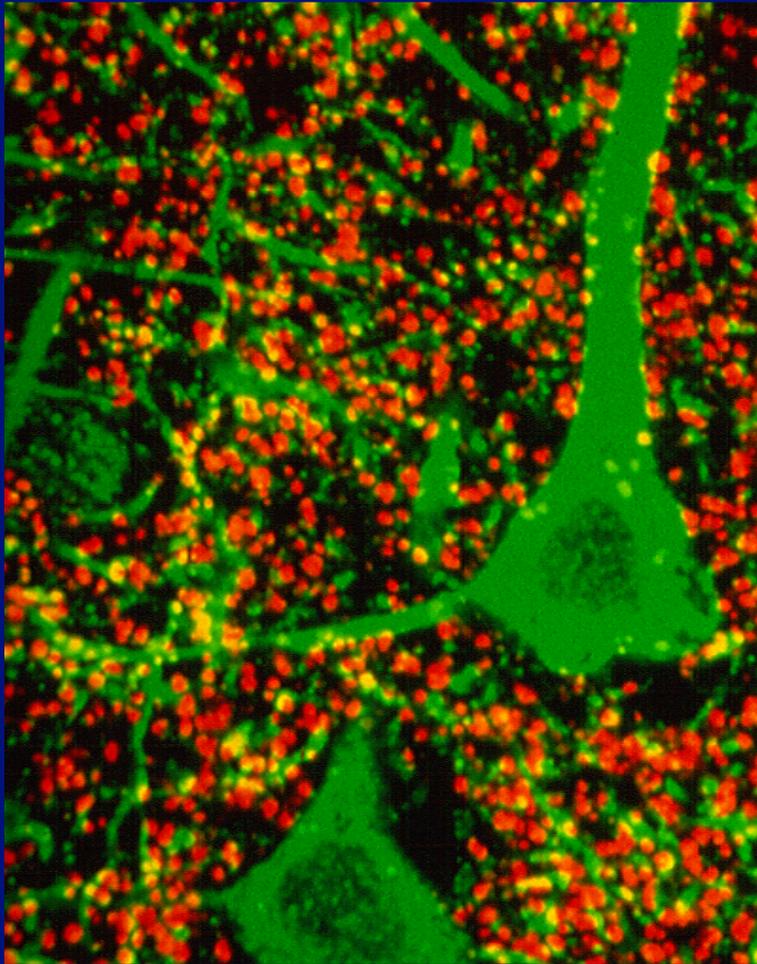


Participants with annual and/or semiannual assessments over a minimum of 2 and up to 8 years

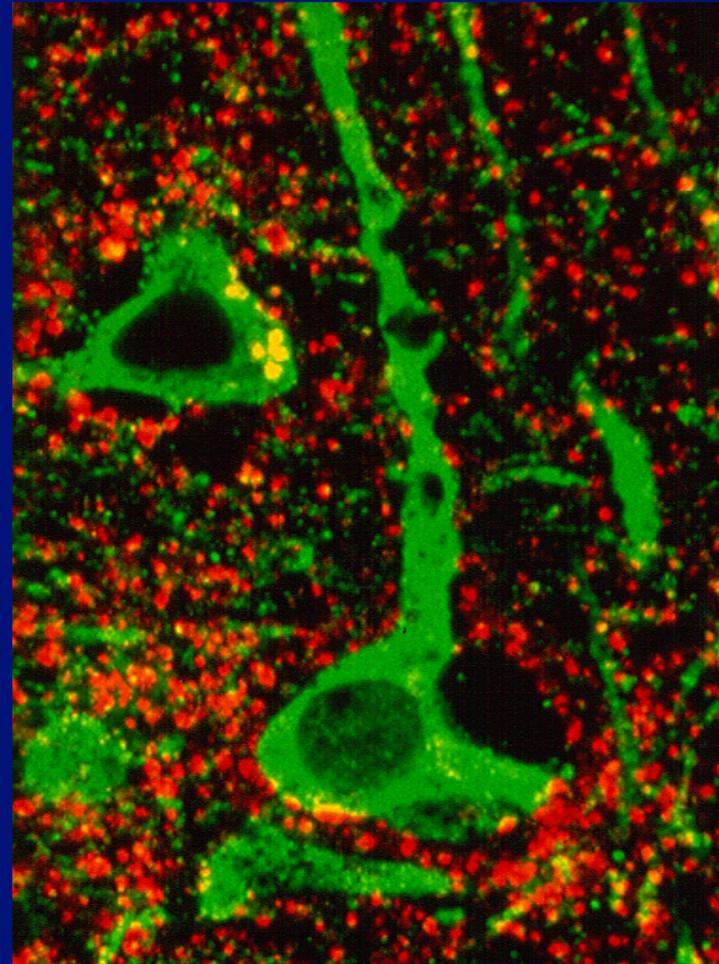
# Possible Mechanisms of Neurotoxicity in HIV-1 Infection



# Synaptophysin and MAP-2 Immunostaining



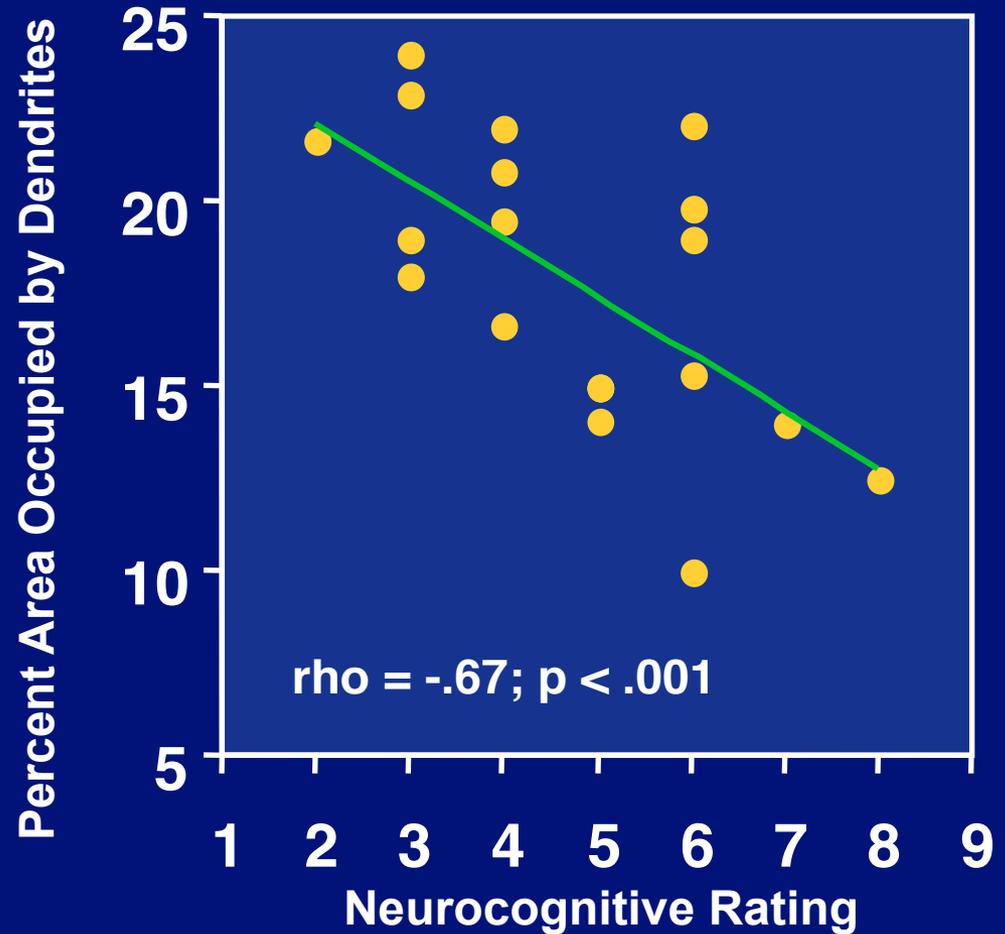
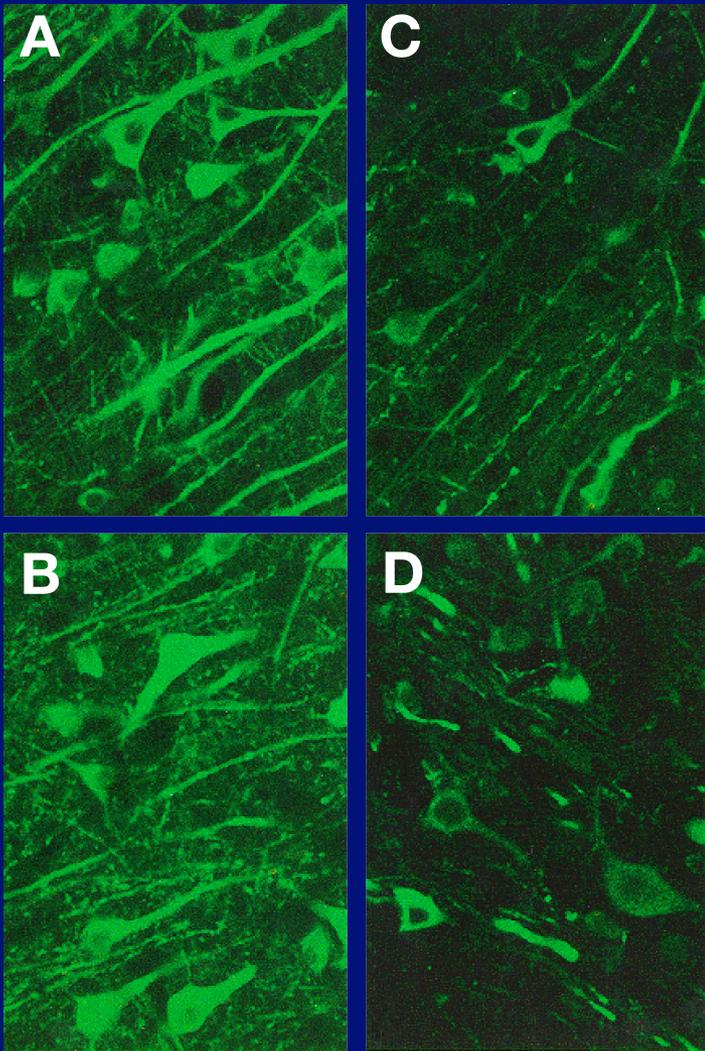
HIV-



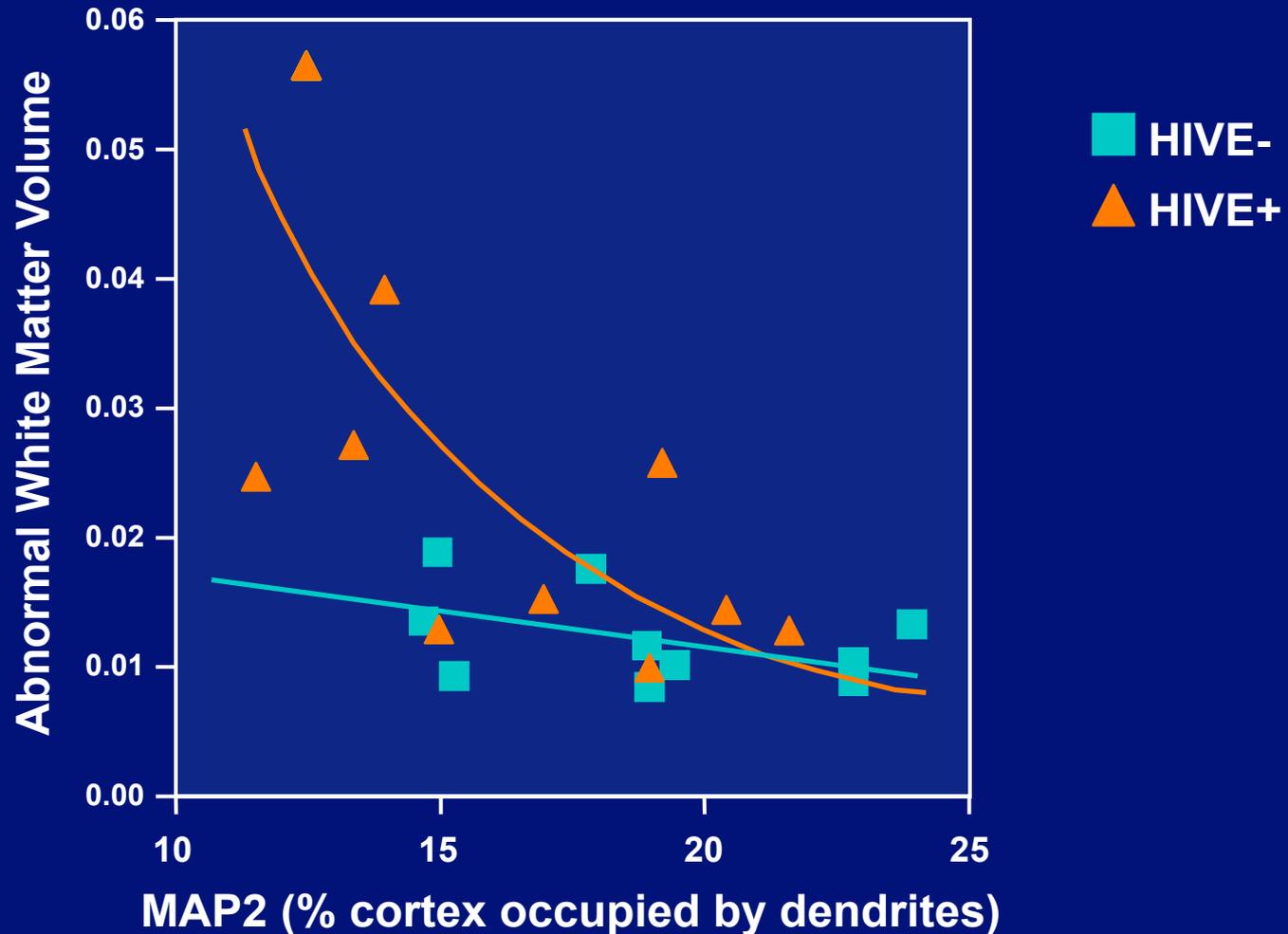
HIV+



# Dendritic Complexity Relates to the Severity of HAND



# Increased Abnormal White Matter Is Related to Dendritic Loss at Autopsy

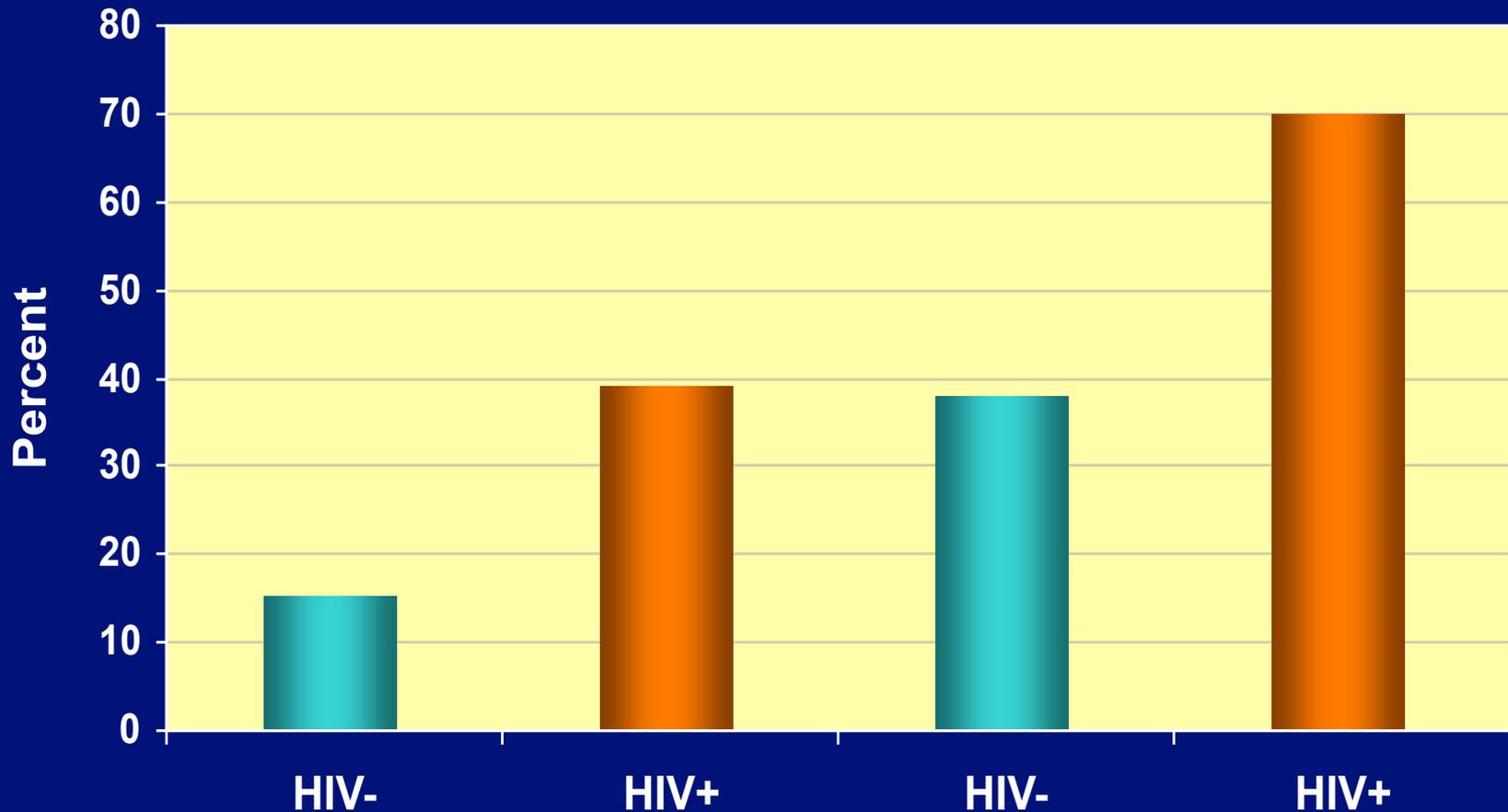


# Cofactors in HIV Associated Neurocognitive Complications

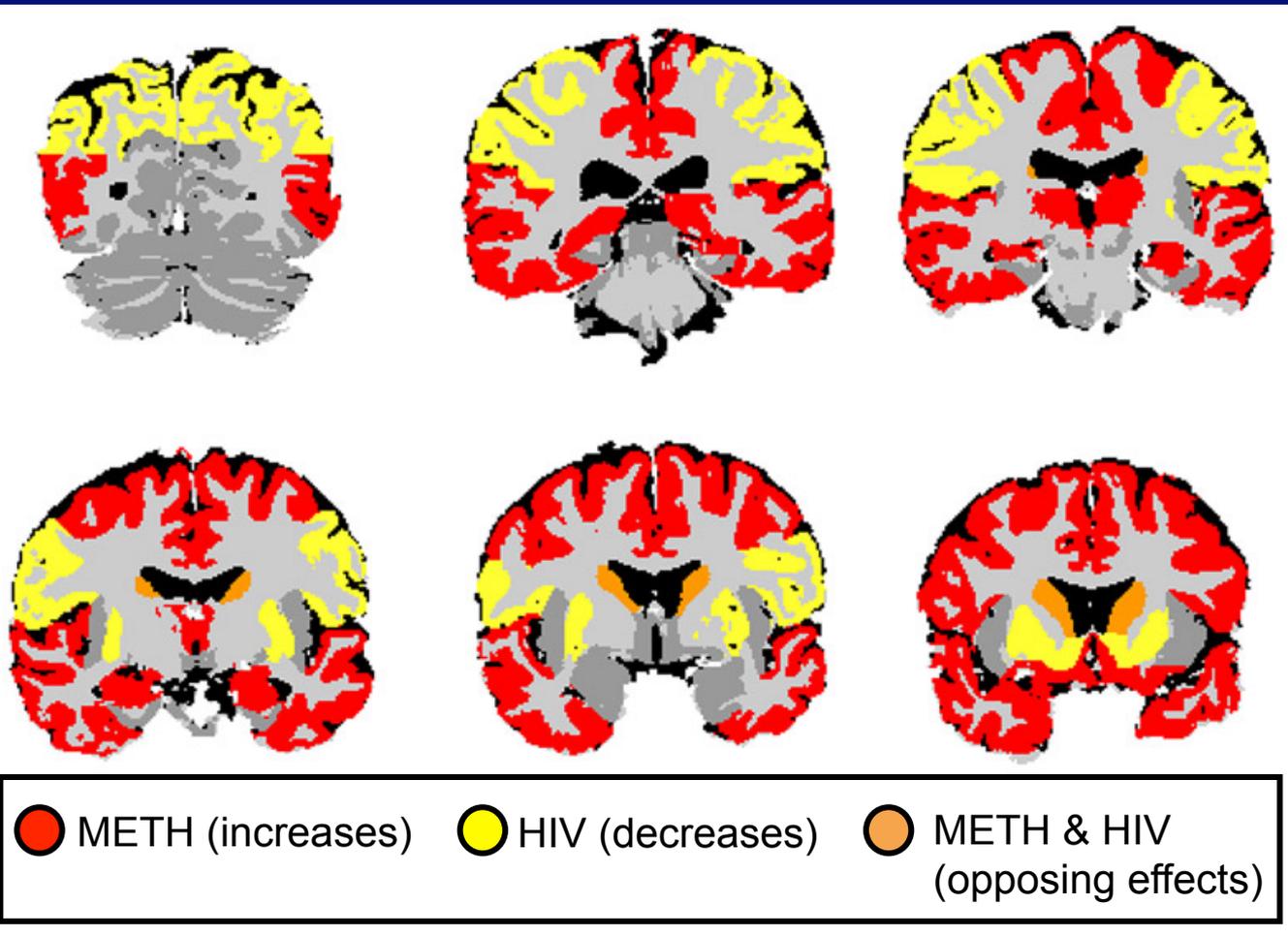
- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments



# Percent Having Global NP Impairment by Methamphetamine Abuse and HIV Status

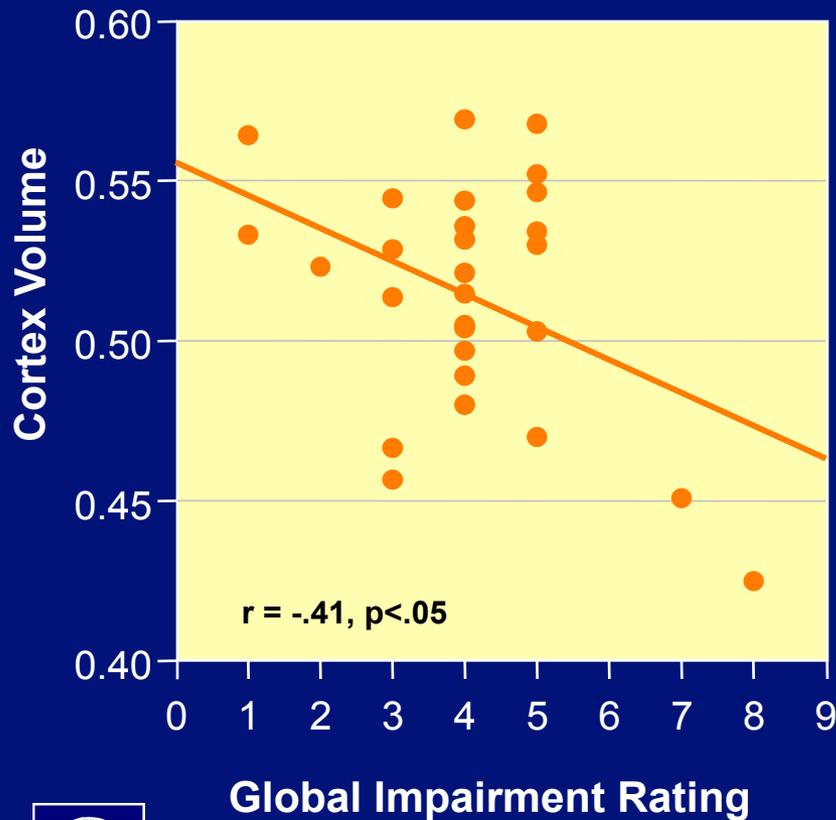


# Significant Regional Volume Alterations Related to METH and/or HIV

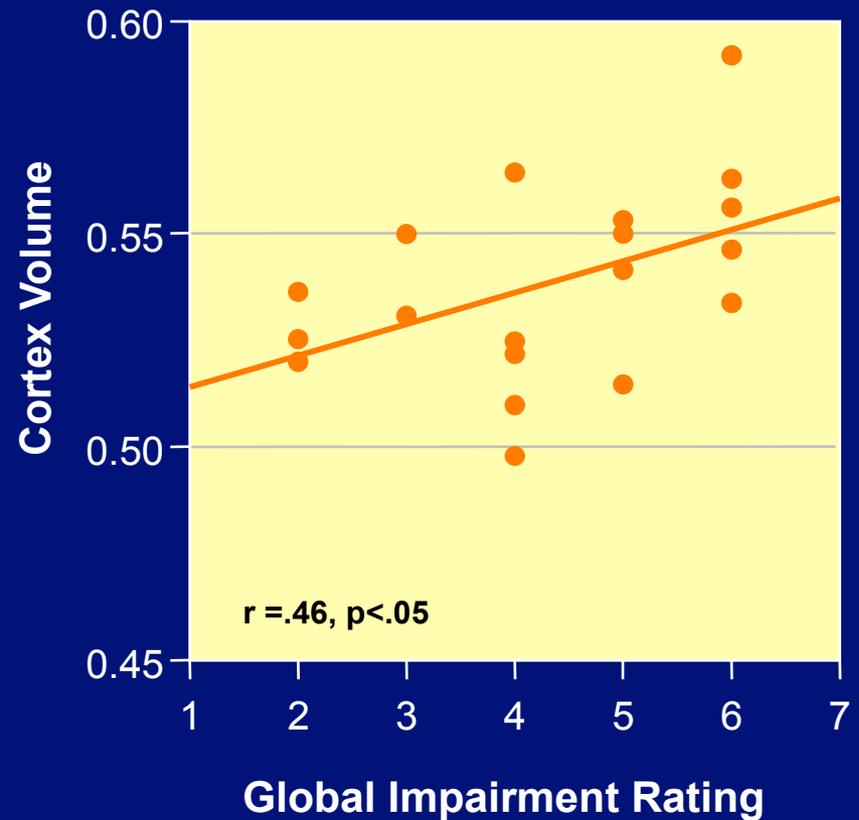


# Association of Cortical Volumes with Impairment

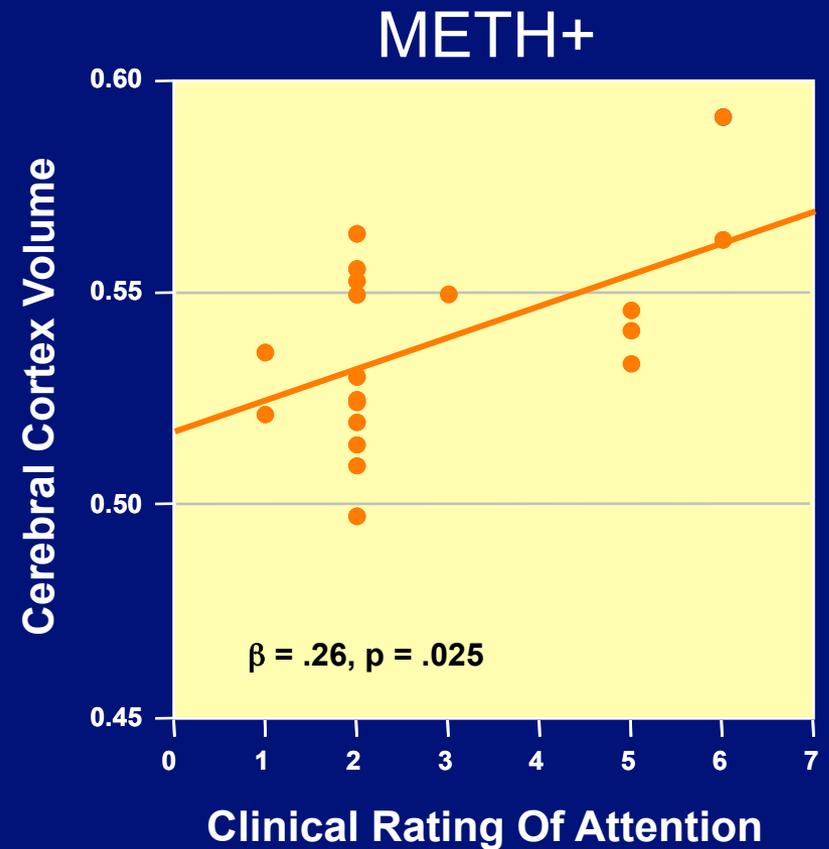
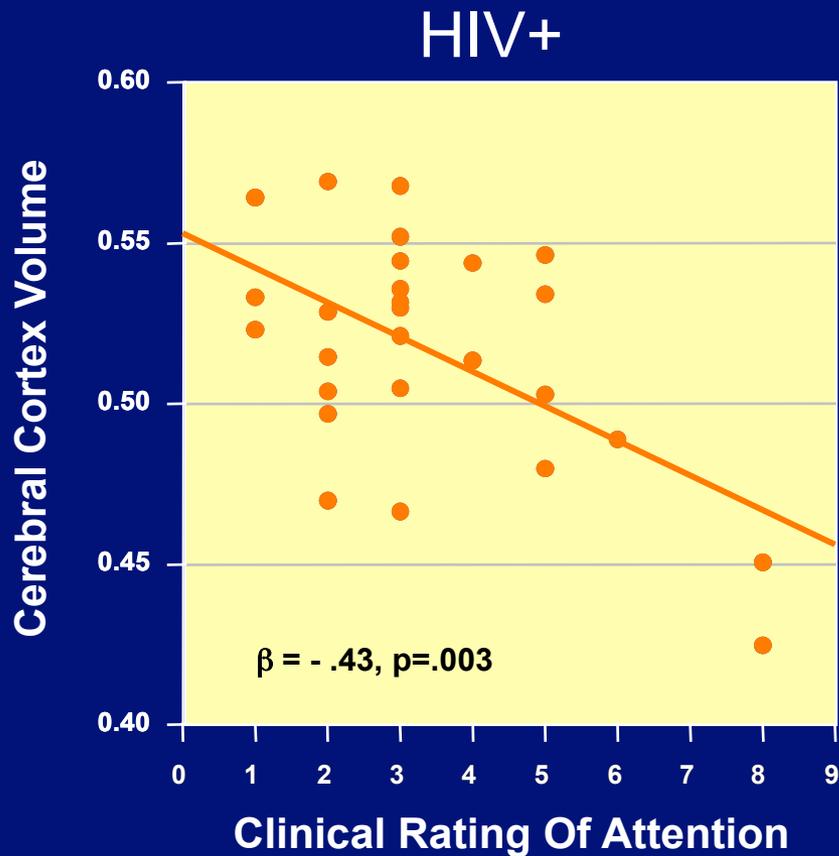
HIV+



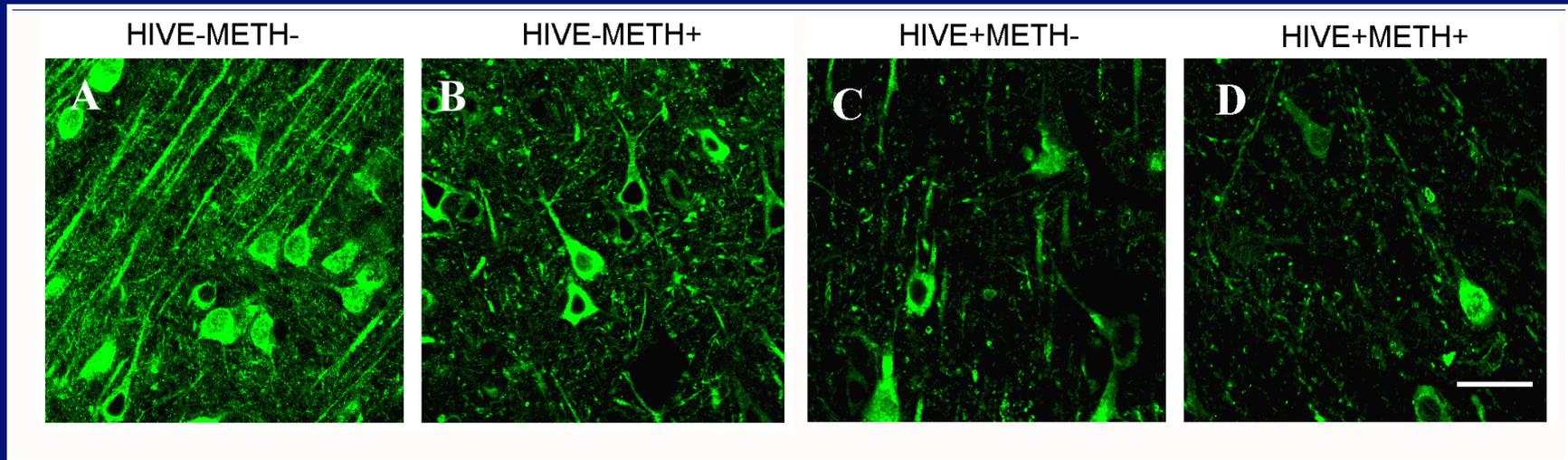
METH+



# Association of Cortical Volumes with Attention Deficits



# MAP-2 in Midfrontal Cortex of HIV+ Cases With or Without HIVE and With or Without METH



- A) Preserved neuronal and dendritic structure in HIV patient HIVE (-) METH (-).
  - B) Moderate neuronal and dendritic damage in a HIVE (-) METH (+) patient.
  - C) Moderate to severe neuronal damage in an HIVE (+) METH (-) patient.
  - D) Severe neuronal and dendritic damage in an HIVE (+) METH (+) patient.
- Bar = 25 microns



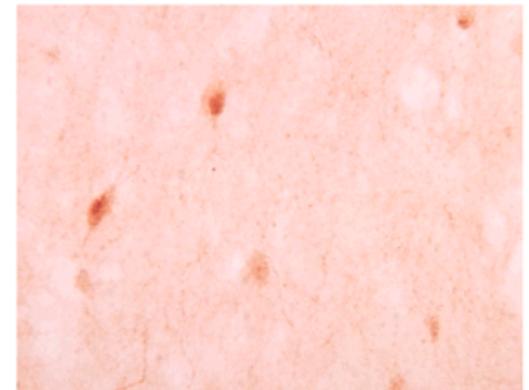
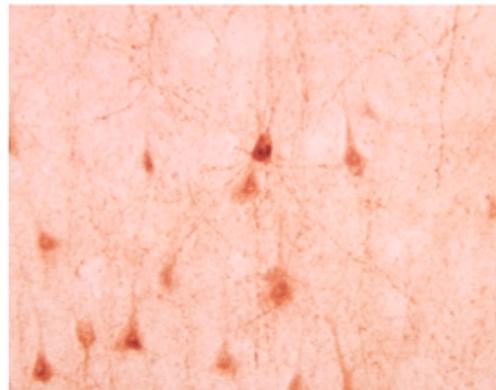
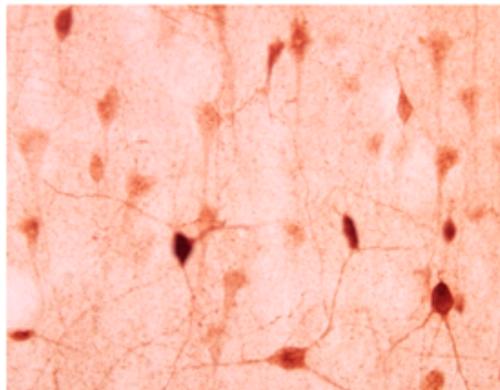
# Degeneration of Interneurons in HIV+ METH+ Users

HIV- METH-

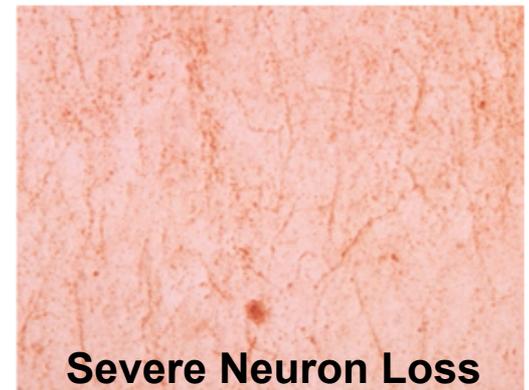
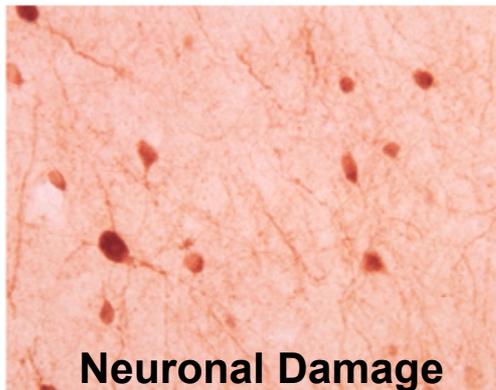
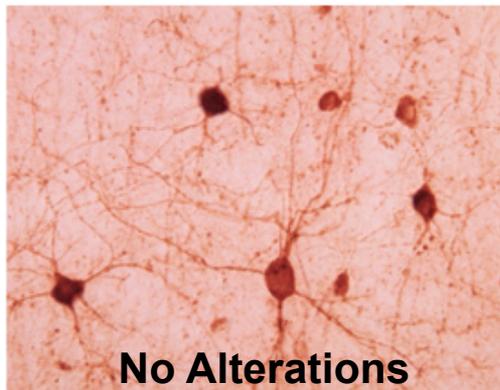
HIV+ METH-

HIV+ METH+

Calbindin



Parvalbumin



No Alterations

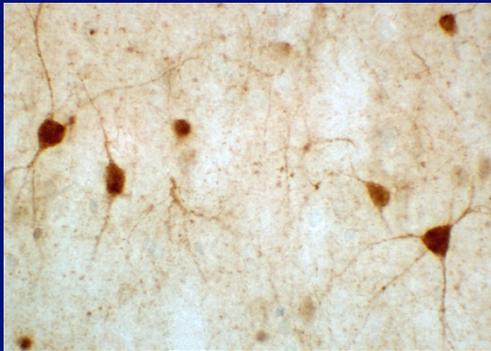
Neuronal Damage

Severe Neuron Loss

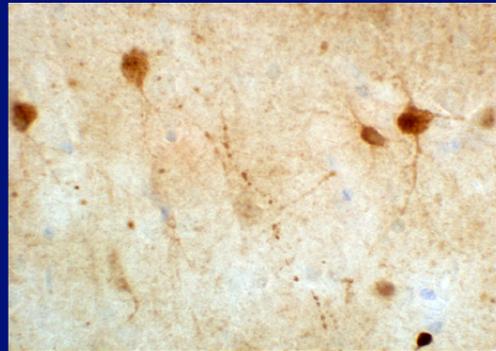


# Loss of Calbindin Interneurons Is Associated With Cognitive Impairment and Memory Loss in METH Users With HIV

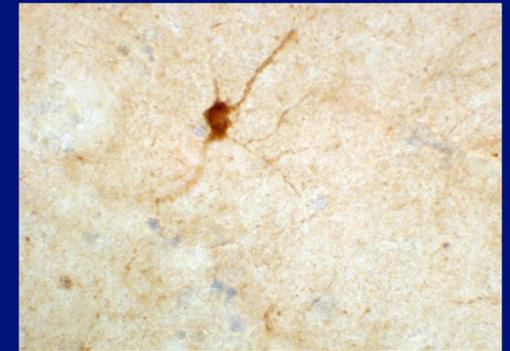
HIV+ (Control)



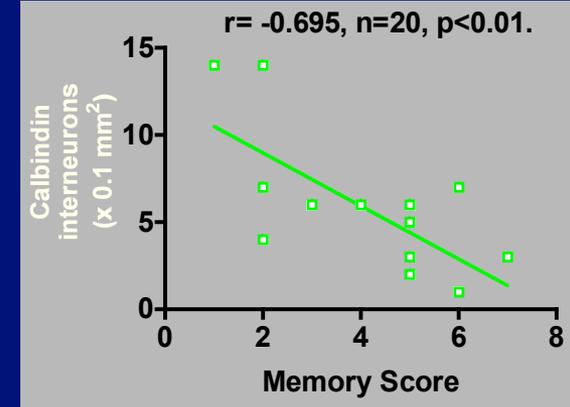
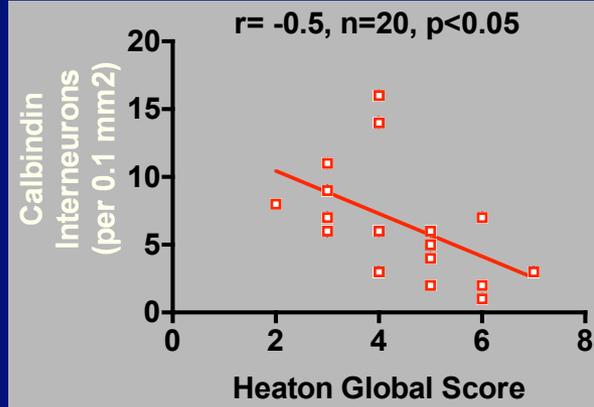
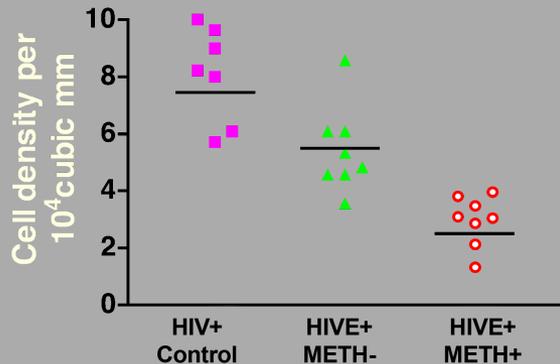
HIVE+ METH-



HIVE+ METH+



Calbindin Immunoreactive Interneurons

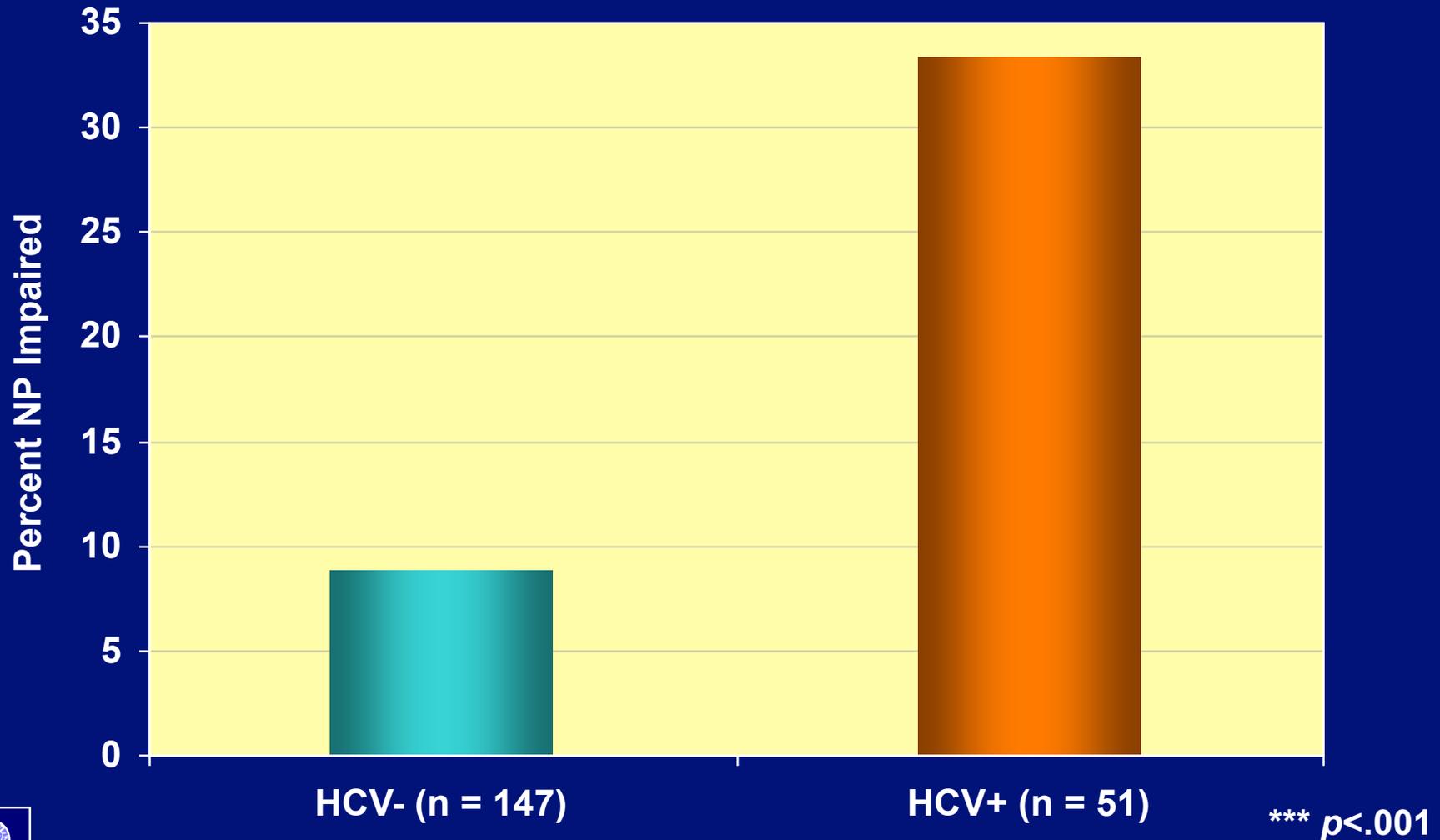


# Cofactors in HIV Associated Neurocognitive Complications

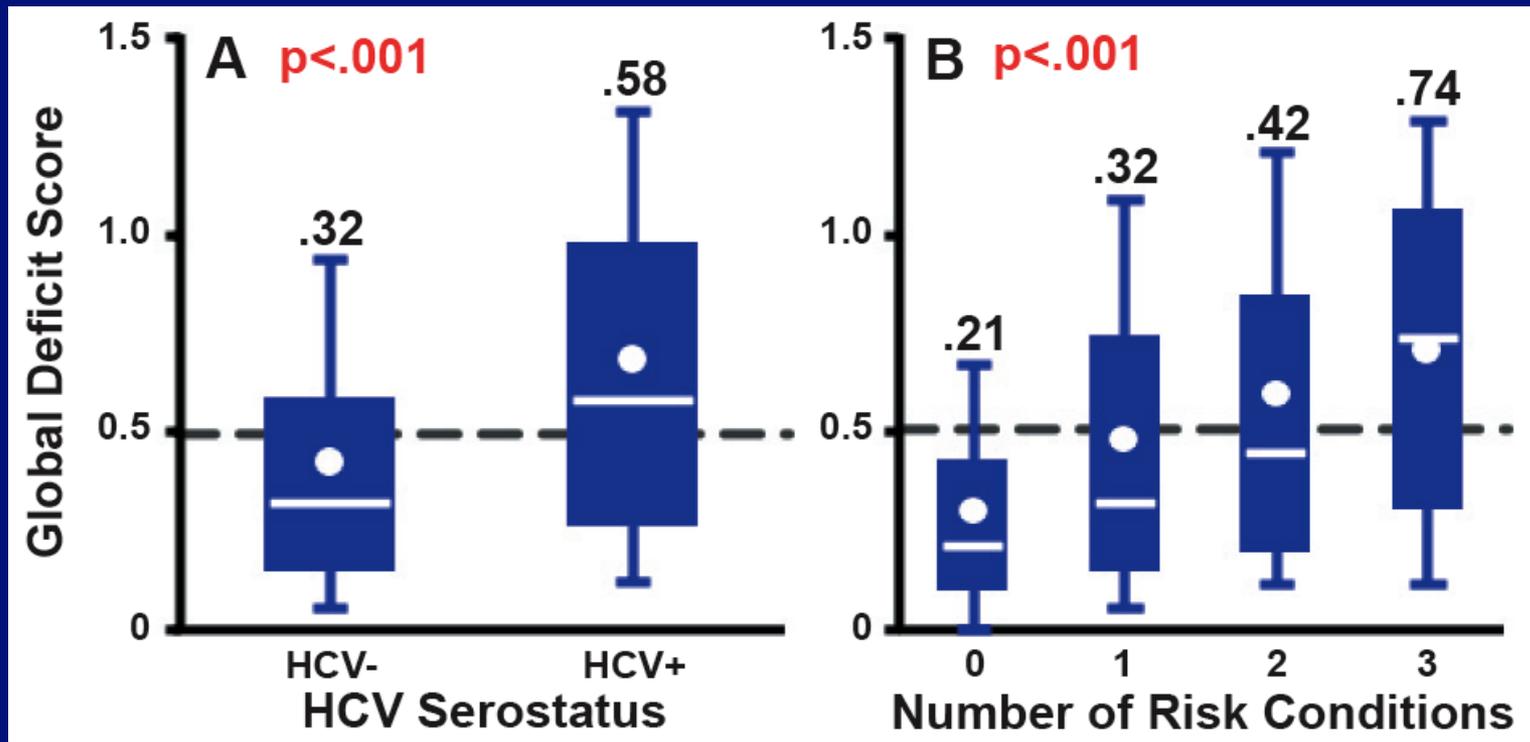
- Drug Abuse - example of methamphetamine
- Coinfections - example of Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments



# Rate of Neurocognitive Impairment in HCV+ Persons in Anhui, China



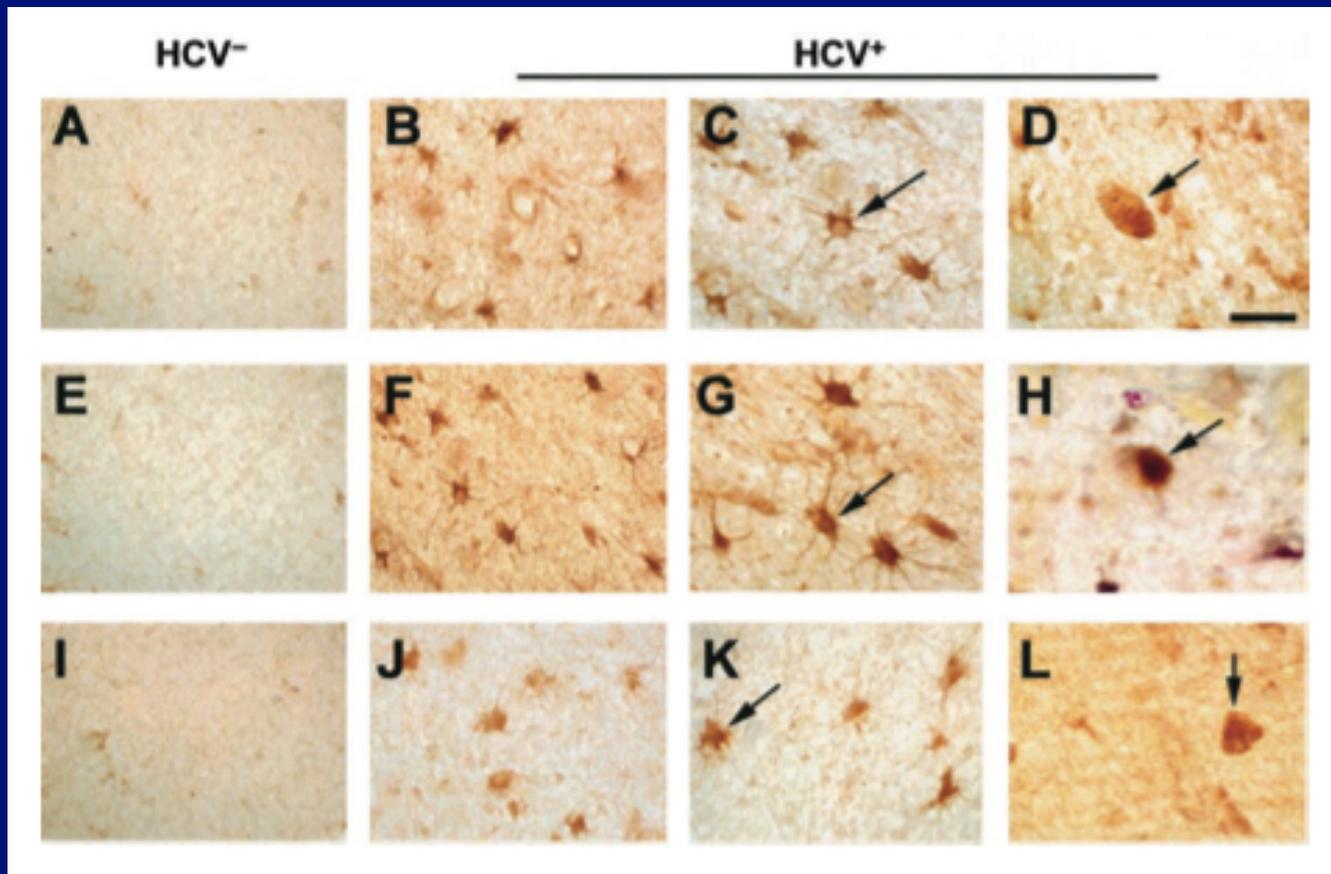
# NNTC Clinical Cohort Shows that Hepatitis C virus Confers Risk for Neurocognitive Impairment



Panel A shows worse neurocognitive score in HCV+ vs HCV-

Panel B shows as the number of comorbid conditions increases, neurocognitive performance worsens. The risks, in various combinations include HIV, HCV, and methamphetamine dependence

# Cellular Localization of HCV in NNTC Brains



Polyclonal antibody  
to HCV NS5A  
structural protein

Monoclonal  
antibody to NS5A

Monoclonal  
antibody to HCV  
core antigen

Astrocytic localization

Macrophage  
localization

# Neurobehavioral Effects of HIV infection in China

Robert Heaton, Ph.D. and Colleagues

- UCSD

- L. Cysique
- J. Hampton Atkinson
- Donald Franklin
- Igor Grant
- Hua Jin
- Deborah Lazzaretto
- Scott Letendre
- Thomas Marcotte
- Ofilio Vigil

- China

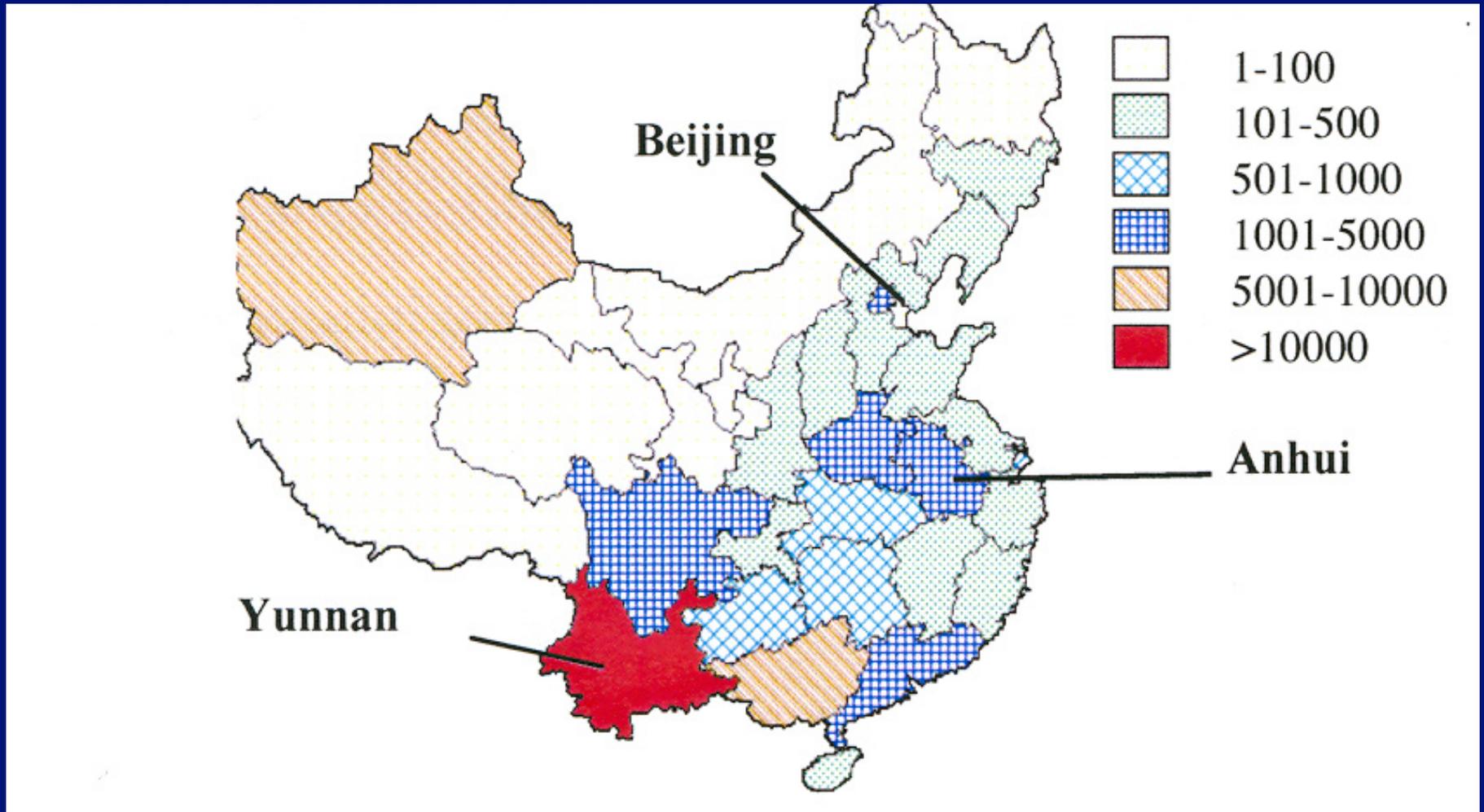
- Zunyou Wu <sup>1</sup>
- Xin Yu <sup>2</sup>
- Chuan Shi <sup>2</sup>
- Yun Gao <sup>1</sup>
- Ning Dong <sup>1</sup>
- Yihua Fan <sup>2</sup>

<sup>1</sup> China CDC, NCAIDS

<sup>2</sup> Peking University, Institute  
of Mental Health



# HIV/AIDS Cases by Geographic Region and Proposed Data Collection Sites in China



# Anhui Cohort

- 400 participants were enrolled
- 198 HIV- and 202 HIV+
- Primary risk factor for HIV was blood product donations (former plasma donors)



# Overview of Methods

- Neuropsychological battery: 15 tests covering 7 ability domains
- Standardized medical/neurological history and examination
- Psychiatry: structured assessments of substance use disorders and affective disorders



# Demographic Characteristics of Anhui Cohort: All Former Plasma Donors

|                           | HIV-<br>(n = 198) | HIV+<br>(n = 202) |
|---------------------------|-------------------|-------------------|
| Age                       | 40.3 ± 6.3        | 40.2 ± 6.4        |
| Education                 | 5.8 ± 2.1         | 5.5 ± 2.3         |
| Male                      | 60.6%             | 60.9%             |
| Lifetime plasma donations | 13.2 ± 23.8       | 52.3 ± 95.6 ***   |

\*\*\* $p < .0001$



# Demographic Characteristics (2)

|                          | HIV-      | HIV+      |
|--------------------------|-----------|-----------|
| Speaks Fuyang dialect    | 100%      | 100%      |
| Speaks Mandarin          | 13%       | 14%       |
| Han Ethnicity            | 99.5%     | 99.5%     |
| Grew up in rural area    | 100%      | 99%       |
| Resides in rural area    | 100%      | 99.5%     |
| # family members in home | 5.2 ± 1.2 | 5.1 ± 1.4 |
| Married *                | 95.5%     | 88.6%     |
| Widowed *                | 4.5%      | 10.9%     |



# HIV Disease Characteristics

|   | HIV+ Anhui<br>N = 202                  |
|---|--|
| % AIDS                                      | 56.4%                                  |
| Current CD4                                 | 350 ± 194                              |
| <i>nadir</i> CD4                            | 252 ± 157                              |
| Log <sub>10</sub> HIV RNA plasma* (N = 131) | 4.2 (IQR = 3.5-4.7) [Min- Max 2.1-5.5] |

\* NucliSens EasyQ HIV-1 from bioMérieux  
EasyQ assay uses real-time NASBA amplification and molecular beacon detection technology and has a range of 50 to 3 million IU(copies)/mL.



# CDC Stages in HIV+

| CDC Stage | N  | Percent | Current CD4 Mean |
|-----------|----|---------|------------------|
| A1        | 15 | 7.4     | 637              |
| A2        | 52 | 26      | 393              |
| A3        | 44 | 22      | 292              |
| B1        | 1  | 0.5     | 610              |
| B2        | 20 | 10      | 372              |
| B3        | 40 | 20      | 271              |
| C2        | 7  | 3.5     | 609              |
| C3        | 23 | 11      | 199              |



# HIV Treatment Regimens

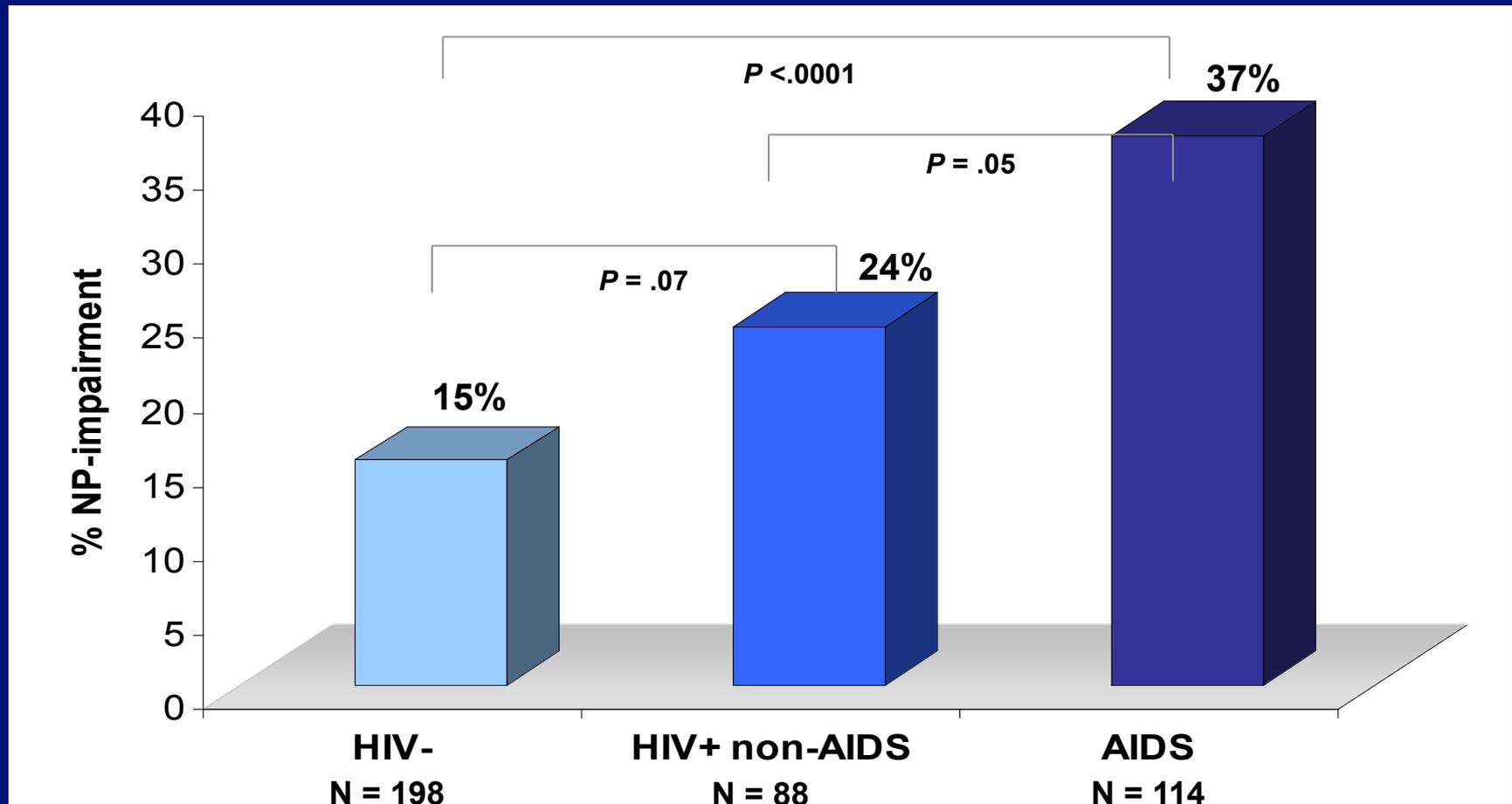
|                              | HIV+<br>N = 202 |
|------------------------------|-----------------|
| HIV+ on ART (N = 115) *      | 57%             |
| Percent on HAART **          | 88%             |
| Percent on Dual-therapy      | 9%              |
| Percent Monotherapy          | 3%              |
| Treatment duration (months)  | 15 ± 9          |
| Reported “adherence always”  | 98.3%           |
| Chinese traditional medicine | 2.5%            |

\*On ART for AIDS = 77%; Non-AIDS = 31%

\*\* HAART = composed of at least 3 ART



# Proportion of NP Impairment among HIV-, HIV+ and AIDS Participants



NP Impairment was defined as GDS  $\geq 0.5$



# HIV Disease History and NP Impairment

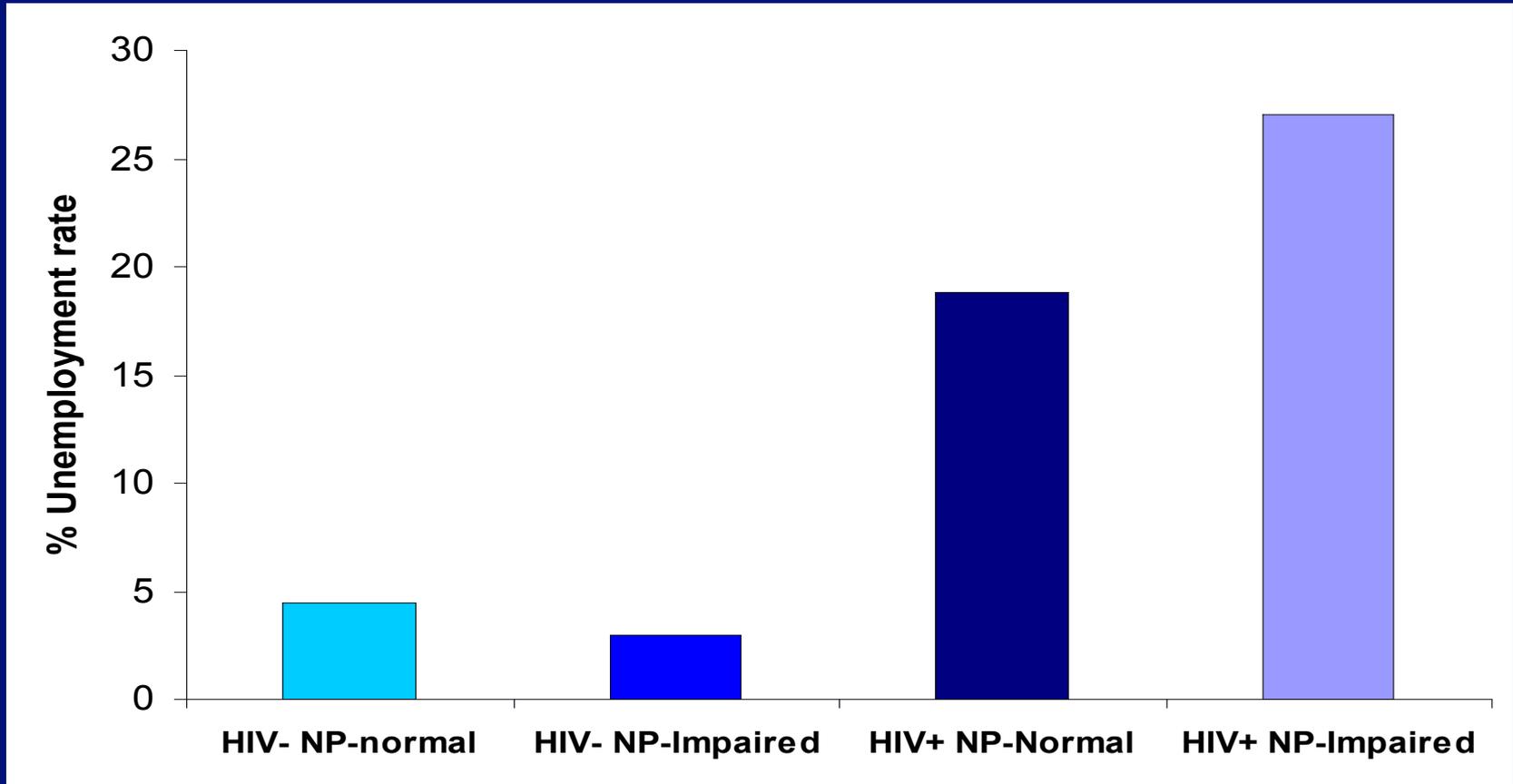
|                            | NP Impaired<br>HIV+ (n = 63) | NP Normal<br>HIV+ (n = 139) |
|----------------------------|------------------------------|-----------------------------|
| Current CD4 below 200      | 34%                          | 22.5%                       |
| <i>Nadir</i> CD4 below 200 | 64%                          | 46% *                       |
| Currently on ART           | 75%                          | 49% **                      |

**No correlation between NP impairment (GDS) and Log<sub>10</sub> HIV RNA, or Log<sub>10</sub> Beta-2 microglobulin**

\*  $p < .05$  \*\*  $p < .001$



# HIV Status, NP Impairment and Unemployment



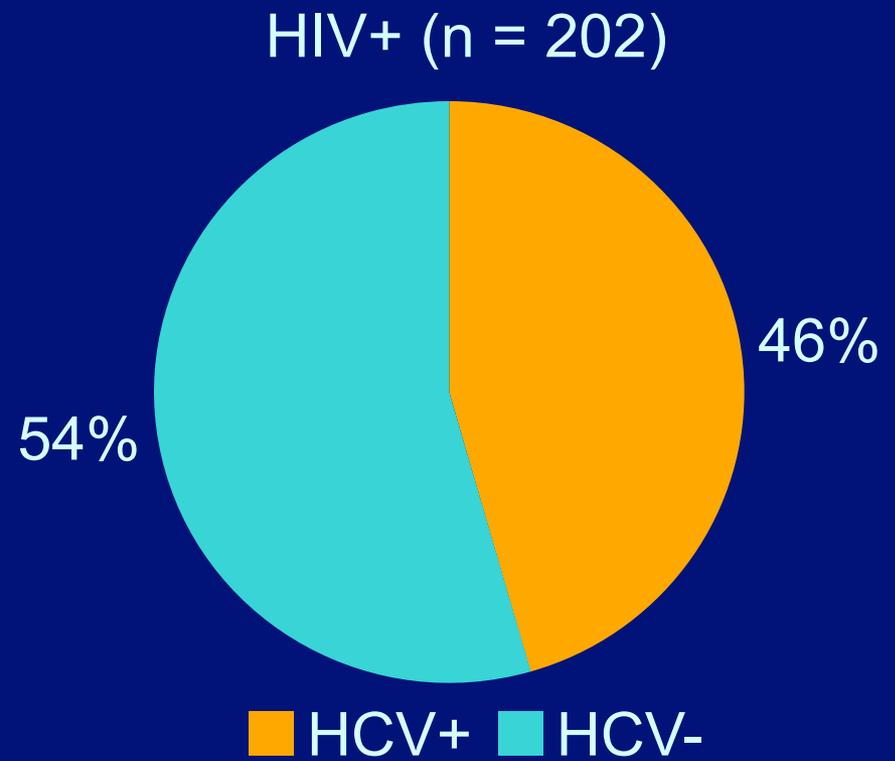
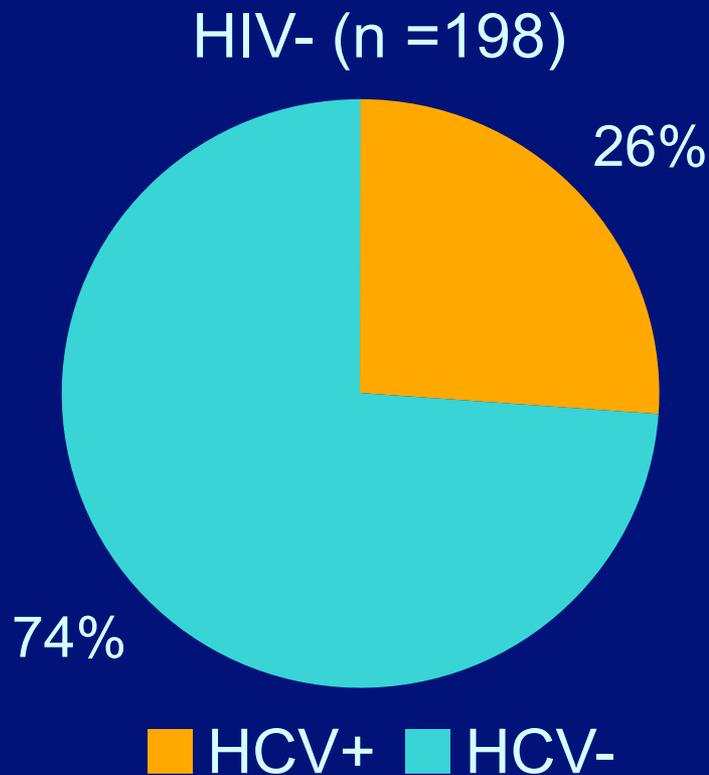
HIV effect:  $p < .0001$

NP Impairment: effect  $p = .40$

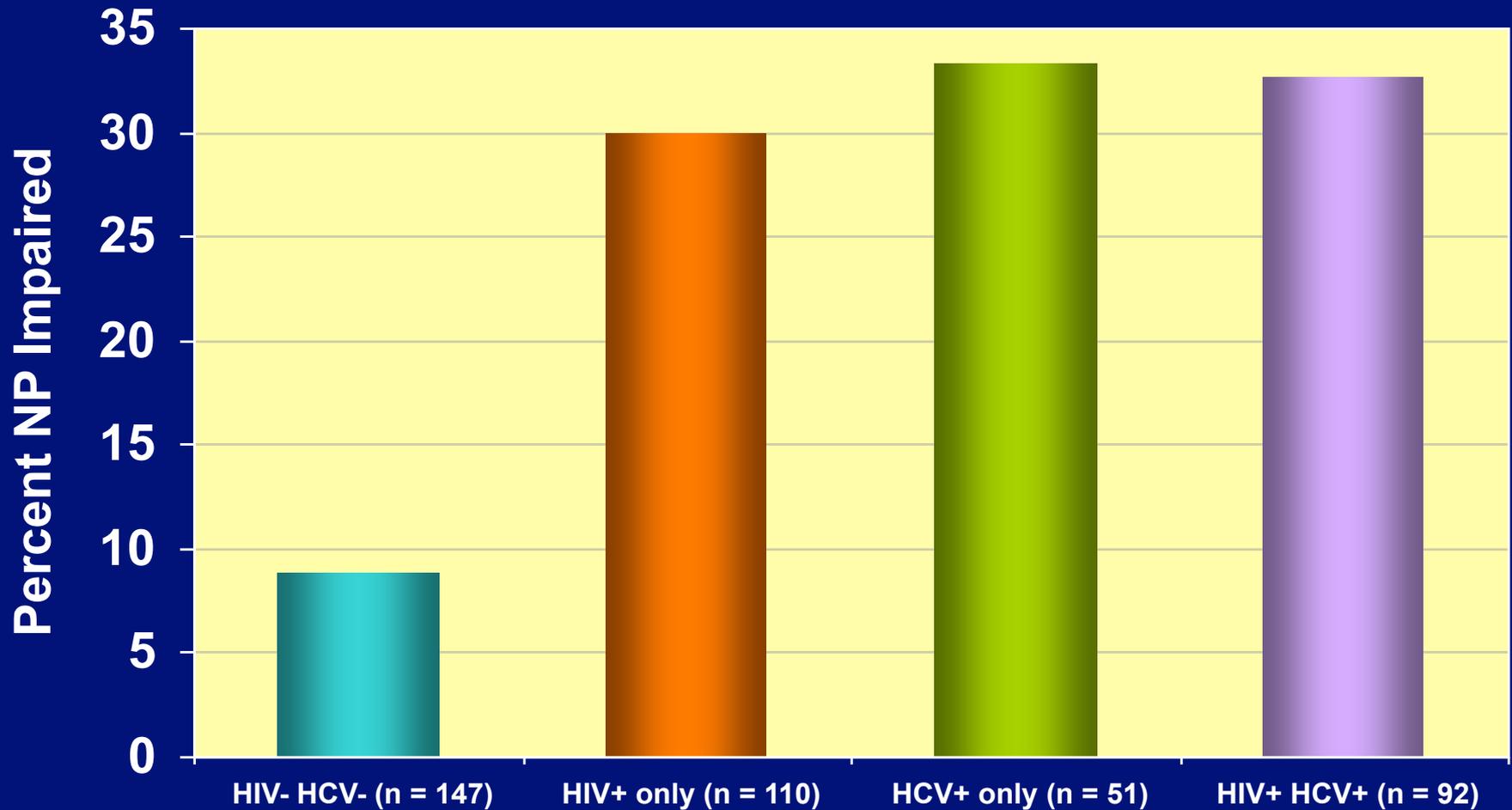
Interaction:  $p = .24$



# Prevalence of HCV Infection Among Anhui Participants



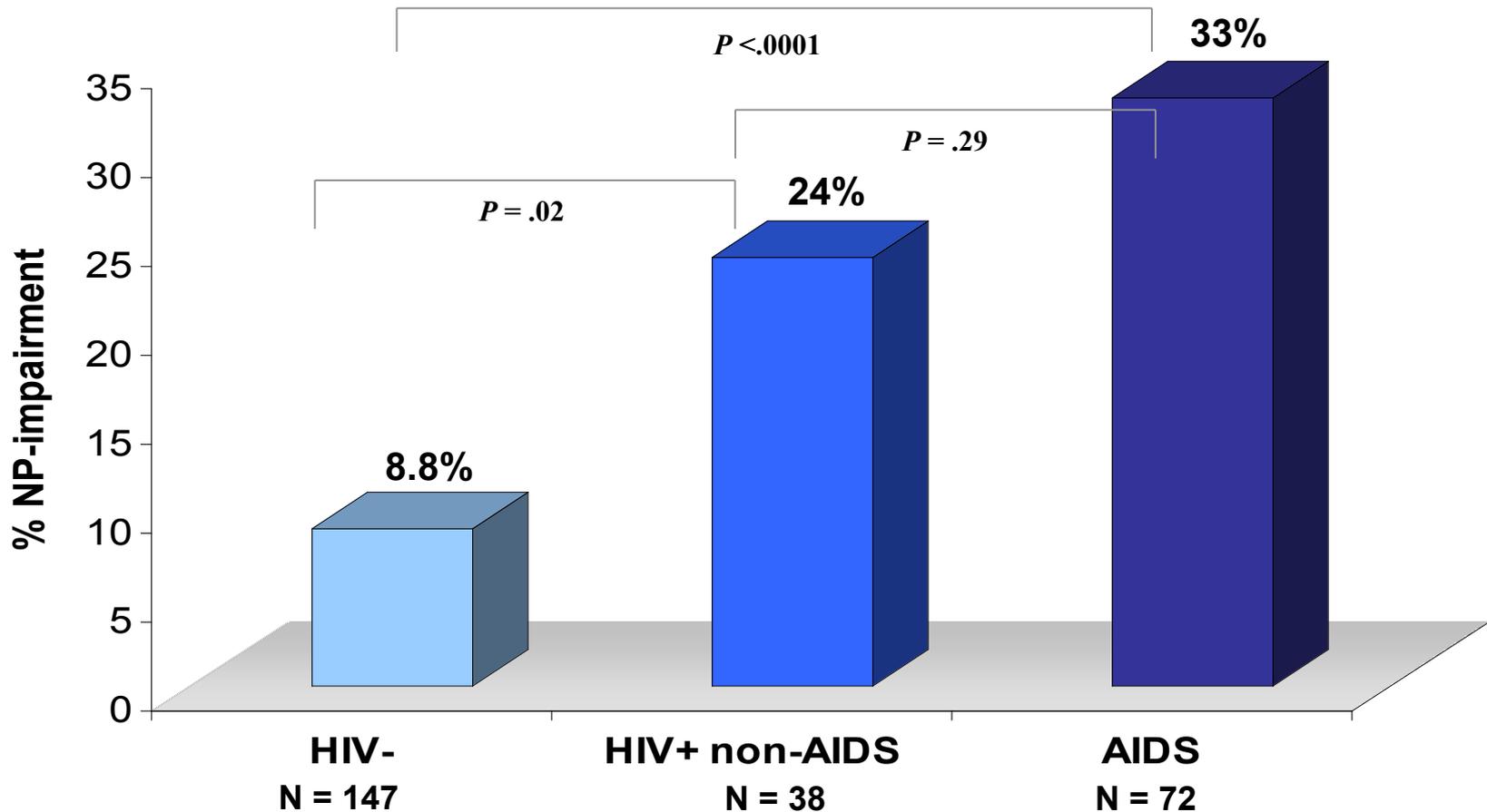
# Individual and Combined Effects of HIV and HCV on NP Status



\*\*\*  $p < .001$



# Proportion of NP Impairment Among HIV-, HIV+ and AIDS Participants (HCV- Only)



# Acknowledgments

The HIV Neurobehavioral Research Center (HNRC) is supported by  
Center award MH 62512 from NIMH

The San Diego HIV Neurobehavioral Research Center (HNRC) Group is affiliated with  
the University of California, San Diego, the Naval Hospital, San Diego, and  
the Veterans Affairs San Diego Healthcare System,

and includes:

Director: Igor Grant, M.D.;

Co-Directors: J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., and  
J. Allen McCutchan, M.D.;

Center Manager: Thomas D. Marcotte, Ph.D.; Heather Bentley, CCRA; Melanie Sherman; Naval Hospital San Diego:  
Braden R. Hale, M.D., M.P.H. (P.I.);

Neuromedical Component: Ronald J. Ellis, M.D., Ph.D. (P.I.), J. Allen McCutchan, M.D., Scott Letendre, M.D., Edmund  
Capparelli, Pharm.D., Rachel Schrier, Ph.D.;  
Jennifer Marquie-Beck; Terry Alexander, R.N.; Janis Durelle;

Neurobehavioral Component: Robert K. Heaton, Ph.D. (P.I.), Mariana Cherner, Ph.D., Steven Paul Woods, Psy.D., David  
J. Moore, Ph.D.; Matthew Dawson;

Neuroimaging Component: Terry Jernigan, Ph.D. (P.I.),  
Christine Fennema-Notestine, Ph.D., Sarah L. Archibald, M.A., John Hesselink, M.D.,  
Jacopo Annese, Ph.D., Michael J. Taylor, Ph.D., Brian Schweinsburg, Ph.D.;



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The San Diego HIV Neurobehavioral Research Center (HNRC) Group is affiliated with  
the University of California, San Diego, the Naval Hospital, San Diego, and  
the Veterans Affairs San Diego Healthcare System,

and includes:

Neurobiology Component: Eliezer Masliah, M.D. (P.I.),  
Ian Everall, FRCPsych., FRCPsych., Ph.D., Cristian Achim, M.D., Ph.D.;

Neurovirology Component: Douglas Richman, M.D., (P.I.), David M. Smith, M.D.; International Component: J. Allen  
McCutchan, M.D., (P.I.);

Developmental Component: Ian Everall, FRCPsych., FRCPsych., Ph.D. (P.I.),  
Stuart Lipton, M.D., Ph.D.;

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# HIV, HCV, Drug Abuse and the Brain

*Thank You for Your Attention!*

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