The following slides are for the personal educational use of attendees of the 3rd Psychiatry and HIV Symposium held in Barcelona on 7 May 2010

Neurocognitive Impairment
Risk Factors, Diagnosis, and Treatment

Scott Letendre, M.D.

Associate Professor of Medicine

University of California, San Diego

Barcelona, España

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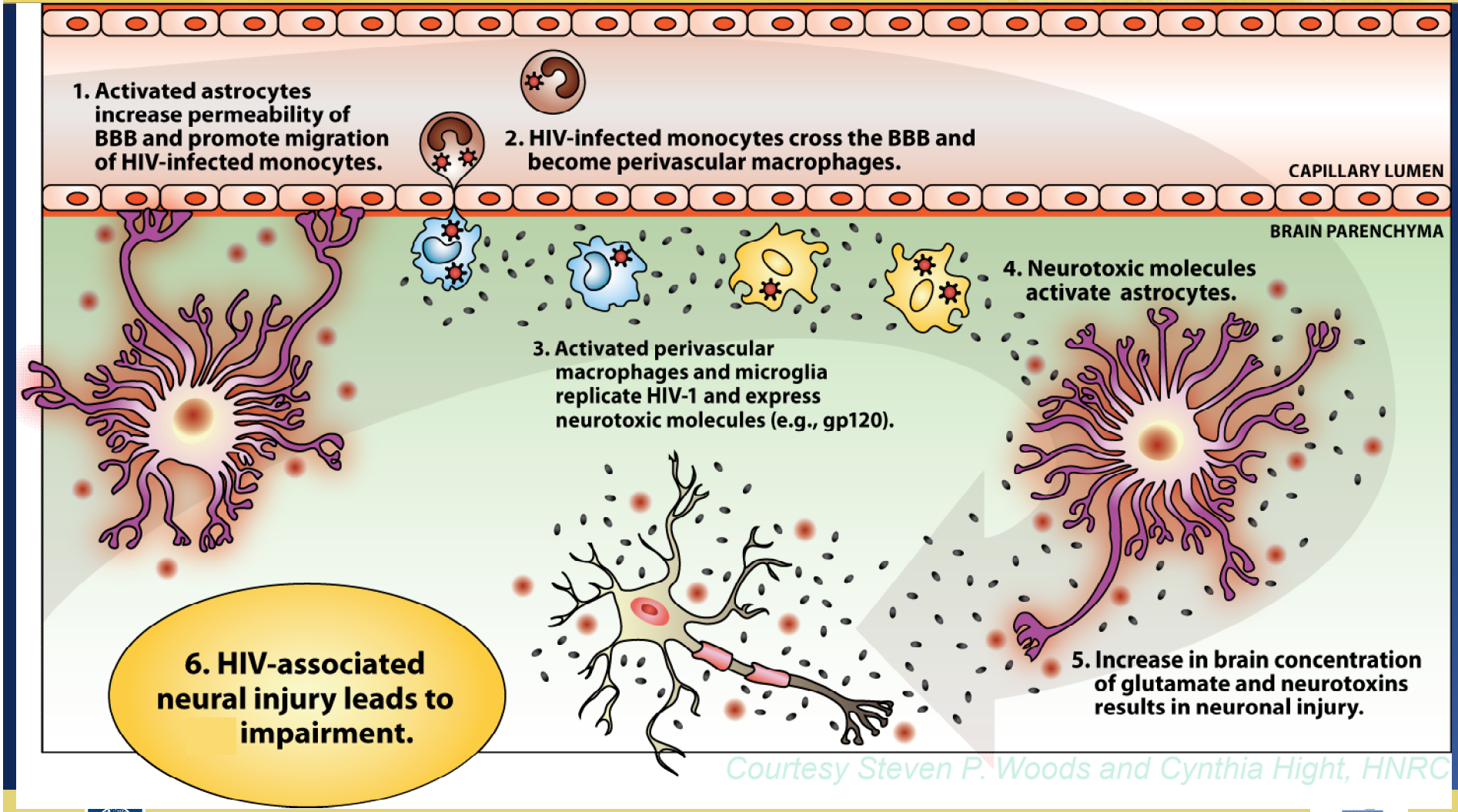
Model of HIV Neuropathogenesis



Courtesy Steven P. Woods and Cynthia Hight, HNRC

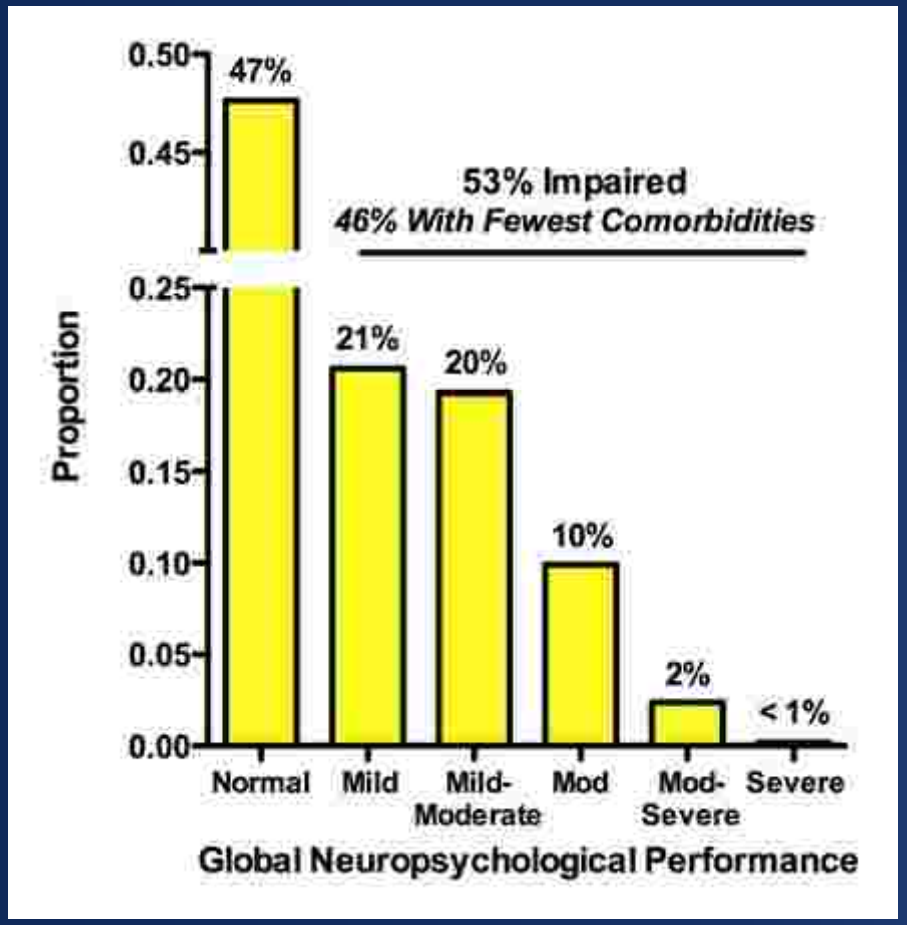
Clinical Definition of HIV-Associated Neurocognitive Disorders

	Acquired Impairment in ≥ 2 Cognitive Abilities	Interferes with Daily Functioning	No Current Severely Confounding Condition	No Pre-existing Cause	Delirium Absent
Asymptomatic Neurocognitive Impairment (ANI)	✓	No	✓	✓	✓
Mild Neurocognitive Disorder (MND)	✓	Mild	✓	✓	✓
HIV-Associated Dementia (HAD)	Marked	Marked	✓	✓	✓

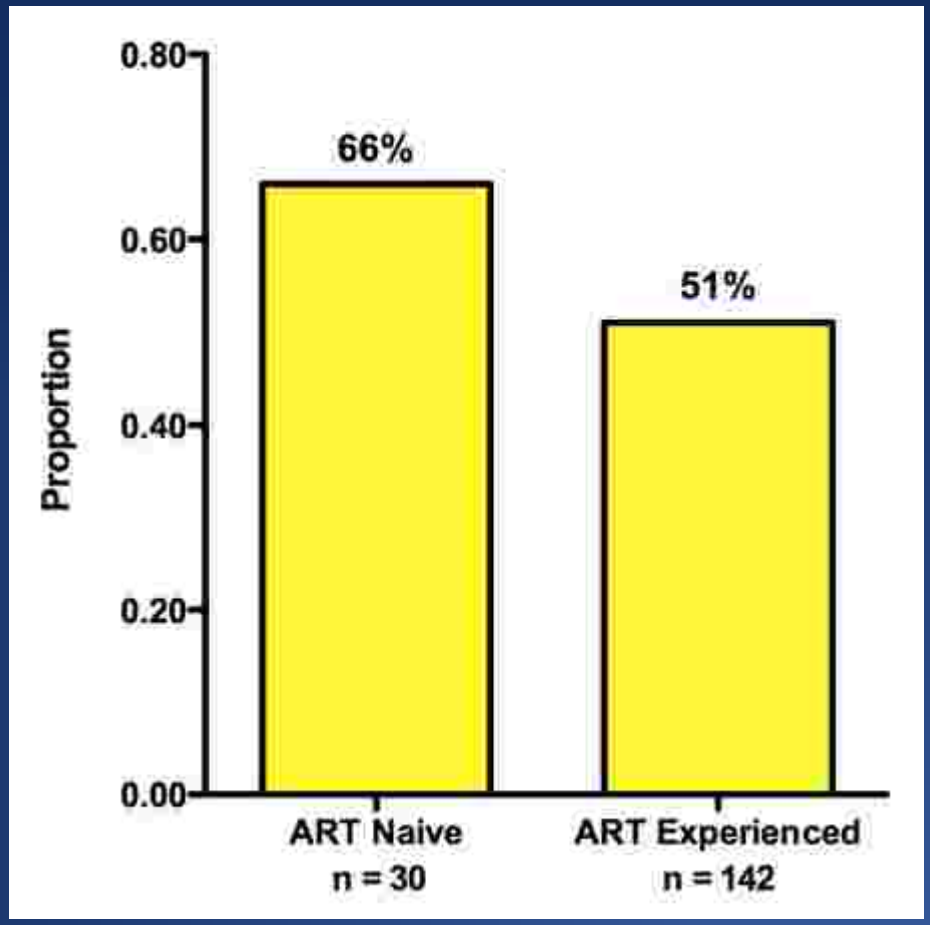
Antinori et al, Neurology 2007, 69: 1789-99

HAND is Common in U.S. and in Spain

Findings from CHARTER & FLSIDA



Heaton RH, et al. 16th CROI, 2009, Abstract 154



Muñoz-Moreno, et al. 17th CROI 2010 Abstract 416

Risk Factors for HAND Can be Used to Increase Clinical Suspicion

Host

- AIDS, Malnutrition
- Anemia, Thrombocytopenia
- Age, Gender
- Metabolic Syndrome
- Stimulants
  - » Methamphetamine
  - » Cocaine
- Genetics
  - » Chemokines

Non-Host

- HIV
  - » Neuroadaptation
  - » Clade-Subtype
  - » Resistance
- Chronic co-infections
  - » Hepatitis C
- Microbial translocation

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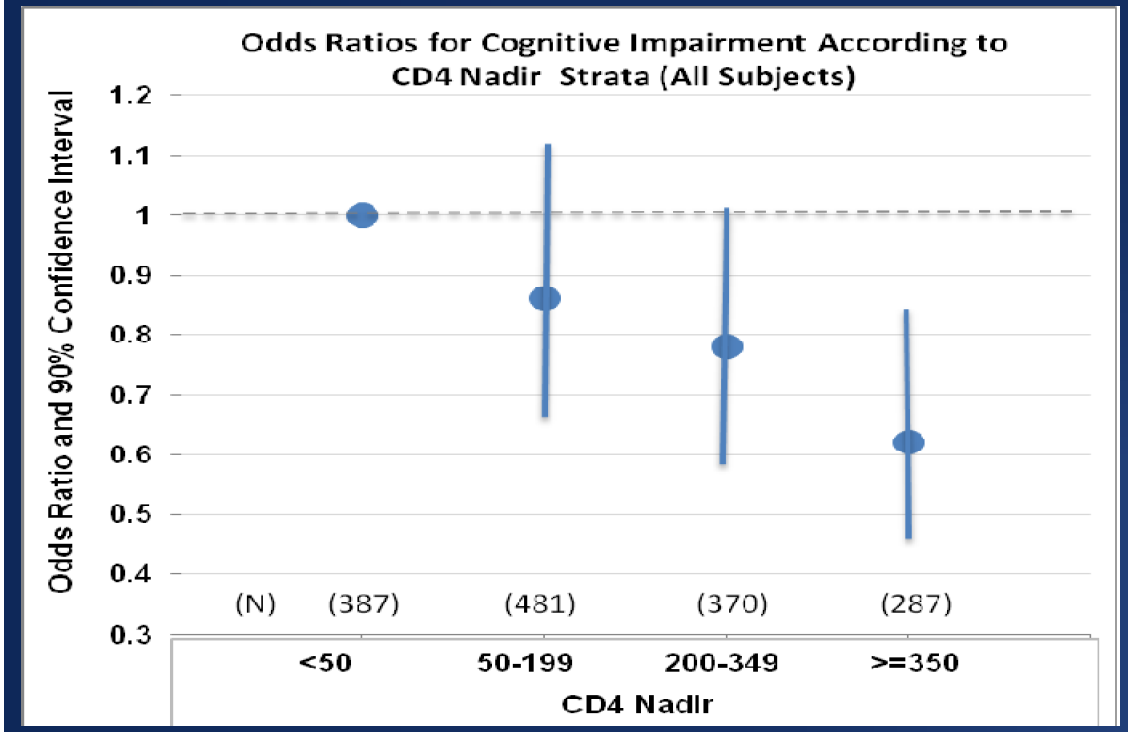
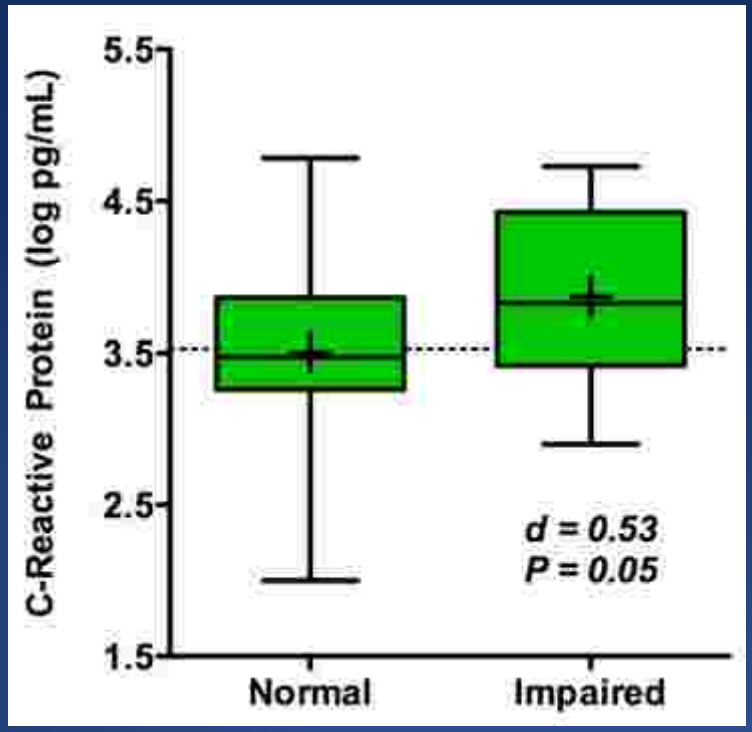
Valcour et al, Neurology, 2004, 63: 822-7; Valcour et al, JAIDS, 2006, 43: 405-10; Cherner et al, Neurology, 2005, 64: 1343-7; Gonzalez et al, PNAS, 2002, 99: 13795-800; Ranga et al, J Virol, 2004, 78: 2586-90; Letendre et al, J Infect Dis, 2007, 196: 361-70; Hightower et al, Virology, 2009; Ancuta et al, PLoS ONE, 3(6): e2516

HAND May be Associated with Lower CD4 Nadirs and Higher C-Reactive Protein Levels



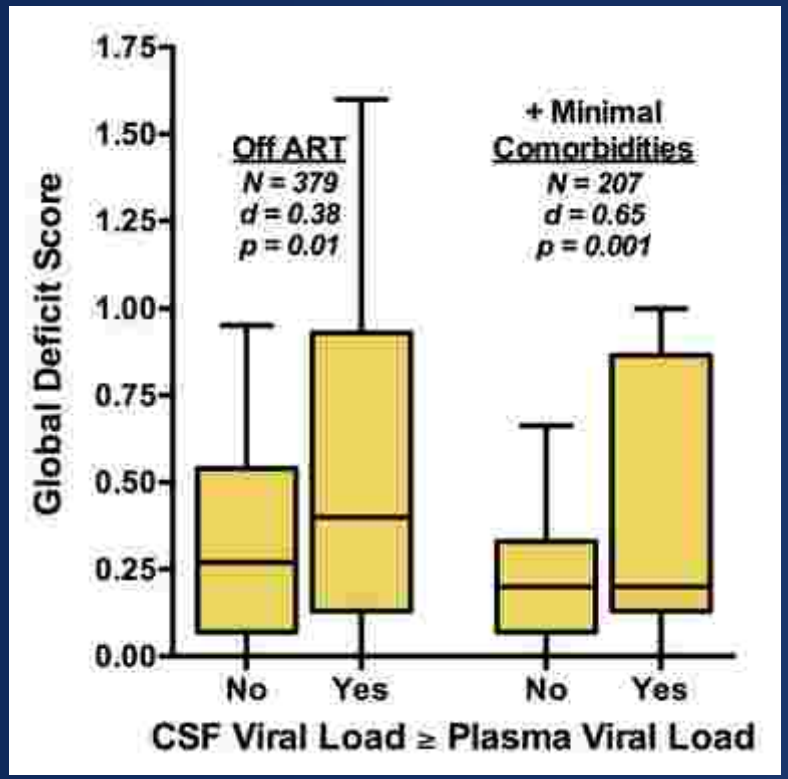
Ellis et al, 17th CROI 2010, Abstract 429



Unpublished CHARTER Data

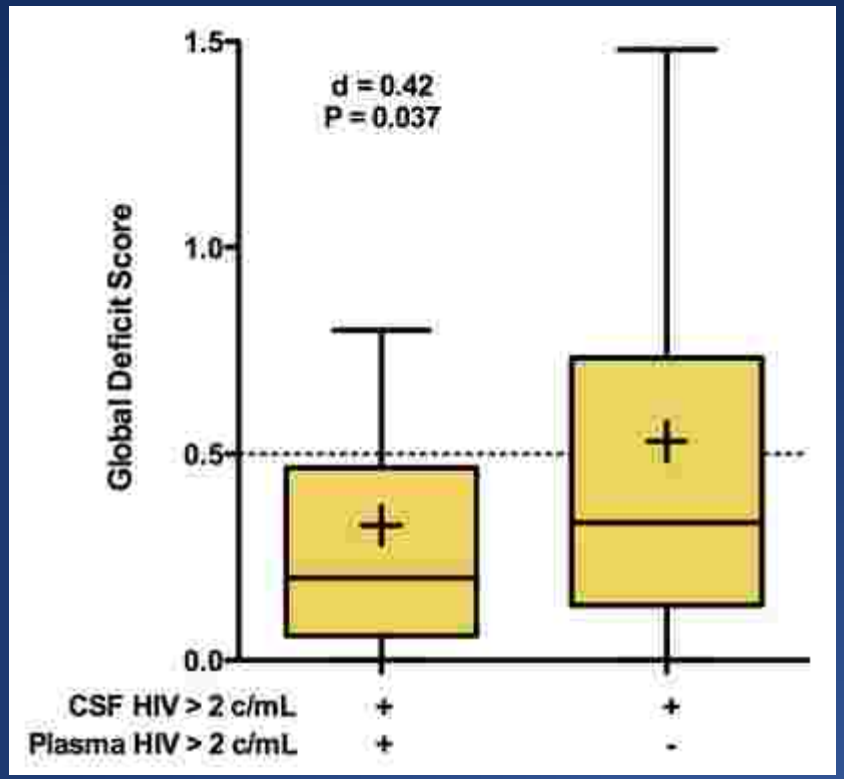
CSF Viral Loads Are Associated with HAND, but Only When Compared to Plasma Viral Loads

Without ART



Letendre et al, 17th CROI 2010, Abstract 172

With ART



Letendre et al, 16th CROI 2009, Abstract 484b

EACS Recommended Screening for Neurocognitive Impairment

Any HIV-infected person complaining of disturbances in his/her memory (comprehension, clarity or speed) should be evaluated extensively, including neurological examination, neuropsychological assessment, cerebrospinal examination and imaging of the brain.

- Patients without such symptoms that should be targeted for screening
  - Uncontrolled HIV infection (detectable plasma HIV RNA)
  - Use of antiretroviral agents with limited CNS penetration
  - Low CD4 nadir (<200 cells/mm3)
  - Ongoing depression
- Screening tool
  - International HIV Dementia Scale (IHDS)[i]
- Interventions if neurocognitive impairment detected:
  - If patient is not on ART:
    - Consider initiation of ART in which at least 2 drugs penetrate CNS[ii]
    - Consider risk for antiretroviral resistance if prior virological failure
  - If patient is already on ART:
    - Consider changing antiretroviral treatment to active drugs with better CNS penetration[iii]
    - Consider genotyping of plasma and CSF HIV RNA whenever feasible prior to changing ART

European AIDS Clinical Society, Guidelines, Prevention and Management of Non-Infectious Co-Morbidities

Assessment Methods

Symptom Questionnaire → **Screening Tests** → **Brief NP Testing** → **Comprehensive NP Testing**

- MOS-HIV
- PAOFI

- HIV Dementia Scale
- International HIV Dementia Scale

- ALLRT Brief Neurocognitive Screen
- Grooved Pegboard
- Action Fluency
- Computerized Testing

- At least 5 cognitive abilities
- At least 2 tests per ability

PATIENT'S ASSESSMENT OF OWN FUNCTIONING

Memory Scale

	Almost Always	Very Often	Fairly Often	Once In A While	Very Infrequenty	Almost Never
1. How often do you forget something that has been told to you within the last day or two?	1	2	3	4	5	6
2. How often do you forget events which have occurred in the last day or two?	1	2	3	4	5	6
3. How often do you forget people whom you met in the last day or two?	1	2	3	4	5	6
4. How often do you forget things that you knew a year or more ago?	1	2	3	4	5	6
5. How often do you forget people whom you knew or met a year or more ago?	1	2	3	4	5	6
6. How often do you lose track of time, or do things either earlier or later than they are usually done or are supposed to be done?	1	2	3	4	5	6
7. How often do you fail to finish something you start because you forgot that you were doing it? (Include such things as forgetting to put out cigarettes, turning off the stove, etc.)	1	2	3	4	5	6

Chelune et al, Advances in Clinical Neuropsychology, 1983, pp 95-126

MOS-HIV Cognitive Functional Status Scale

How much of the time during the **past 4 weeks**:	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
A. Did you have difficulty reasoning and solving problems, for example making plans, making decisions, learning new things?	1	2	3	4	5	6
B. Did you forget things that happened recently, for example, where you put things, appointments?	1	2	3	4	5	6
C. Did you have trouble keeping your attention on any activity for long?	1	2	3	4	5	6
D. Did you have difficulty doing activities involving concentration and thinking?	1	2	3	4	5	6

Slide Courtesy Karl Goodkin

Knippels, et al. AIDS. 2002;16:259-267

Designated Screening Tests

- **Mini Mental Status Exam**
  - » Limited usefulness given its emphasis on cognitive abilities impaired due to posterior neocortical functions
- **HIV Dementia Scale**
  - » Developed specifically to target cognitive abilities reliant on frontostriatal circuitry that are typically affected in HAND
  - » Attention, Episodic memory, Psychomotor speed, Construction
- **International HIV Dementia Scale**
  - » Developed to be simpler and less dependent on language tasks

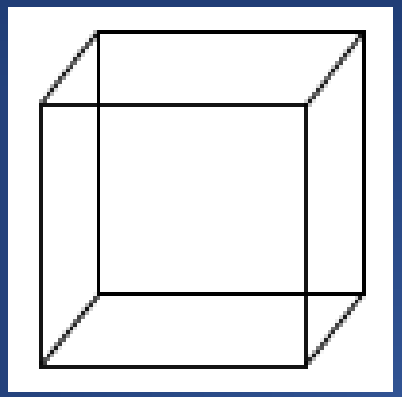
Slide Courtesy Steven Paul Woods

Components of the HIV Dementia Scale

- Antisaccadic errors

- Written alphabet (timed)

- Recall of four words
  - Dog
  - Hat
  - Green
  - Peach
- Cube Copy (timed)



Slide Courtesy Steven Paul Woods

Power et al. J Acquir Immune Defic Hum Retrovirol. 1995; 8:273-278

International HIV Dementia Scale

- Memory: Word Recall
- Motor Speed: Finger tapping
- Psychomotor Speed: Alternating hand movements

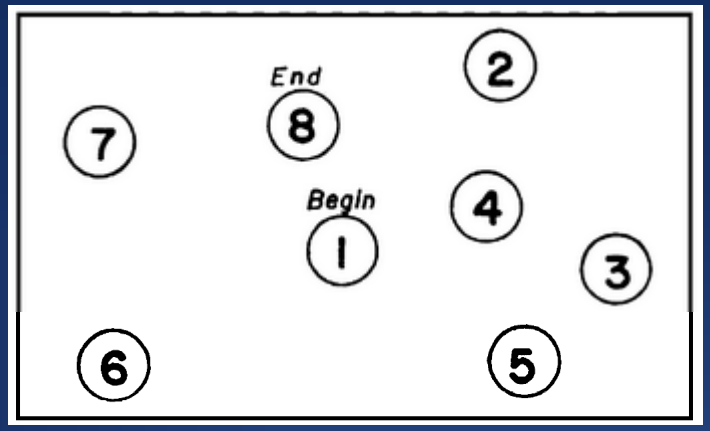
- **IHDS Score**
  - Maximum score is 12 points
  - Score of ≤ 10: Possible dementia

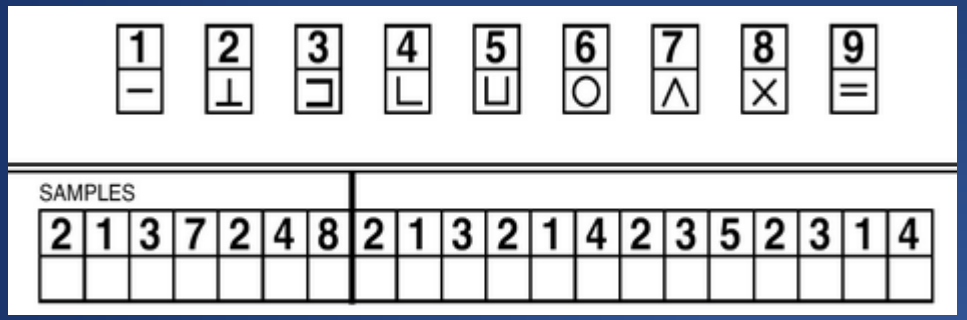
US cohort			Uganda cohort		
	Sens	Spec		Sens	Spec
12.0	100%	0%	12.0	100%	0%
11.5	92%	22%	11.5	100%	20%
11.0	92%	31%	11.0	96%	23%
10.5	83%	52%	10.5	88%	48%
10.0	80%	57%	10.0	80%	55%
9.5	71%	79%	9.5	64%	71%
9.0	63%	88%	9.0	60%	79%
8.5	46%	95%	8.5	40%	89%
8.0	46%	100%	8.0	36%	89%
			7.5	20%	95%

Sacktor N, et al. AIDS. 2005; 19: 1367-74

Brief Neuropsychological Testing

- Brief Neurocognitive Screen (ALLRT)
  - » Trailmaking A & B
  - » Digit Symbol Test
    - Sensitivity up to 65%
    - Specificity up to 84%
- Grooved Pegboard
- Computerized Testing



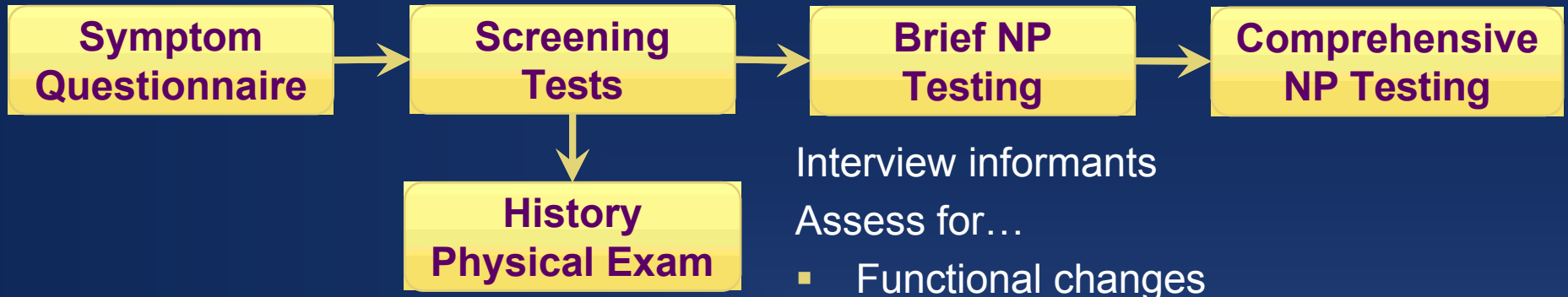


Woods SP et al, Neuropsychologia. 2005; 43:1144-51
Ellis RJ, et al. J Neurovirol 2005; 11: 503-11

Brief Assessment of HAND
Summary of Advantages and Disadvantages

	Advantage	Disadvantage
Symptom Questionnaires	Good sensitivity Inexpensive Self-administered	Limited Specificity
HIV Dementia Scale	Very good specificity Inexpensive Minimal training	Variable sensitivity
International HIV Dementia Scale	Very good sensitivity Inexpensive Minimal training	Moderate Specificity Limited validation
Brief NP Testing	Very good sensitivity Very good specificity	Requires training Must be administered May be copyrighted

Approach to Screening and Diagnosis

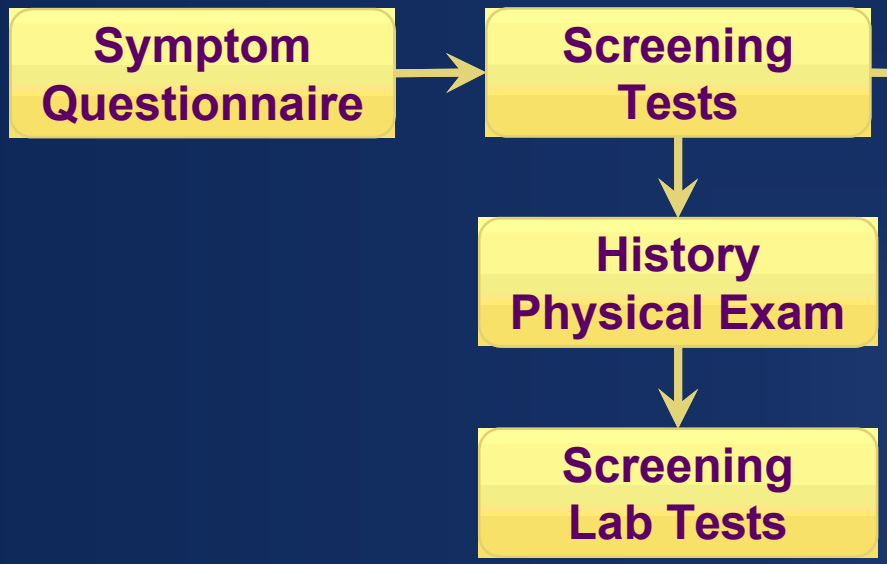


Interview informants

Assess for…

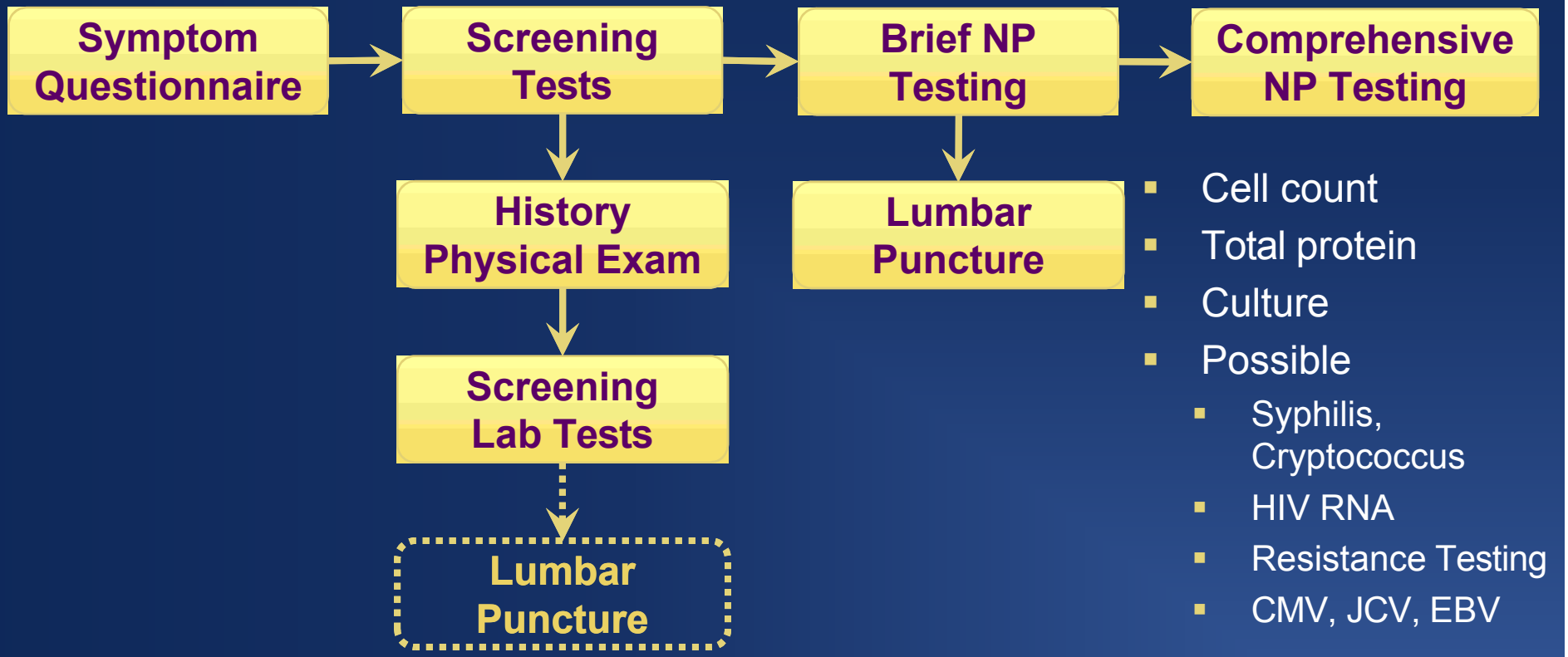
- Functional changes
- Mood changes
- Sleep disorders
- Alcohol and recreational drug use
- Prescribed and OTC drugs
- Focal neurologic signs

Approach to Screening and Diagnosis



- Chemistry Panel
- Complete Blood Count
- Glucose, Lipids
- TSH, B12
- Oxygen saturation
- Toxicology
- HCV, HBV, Syphilis, Cryptococcus
- PPD (possible)

Approach to Screening and Diagnosis



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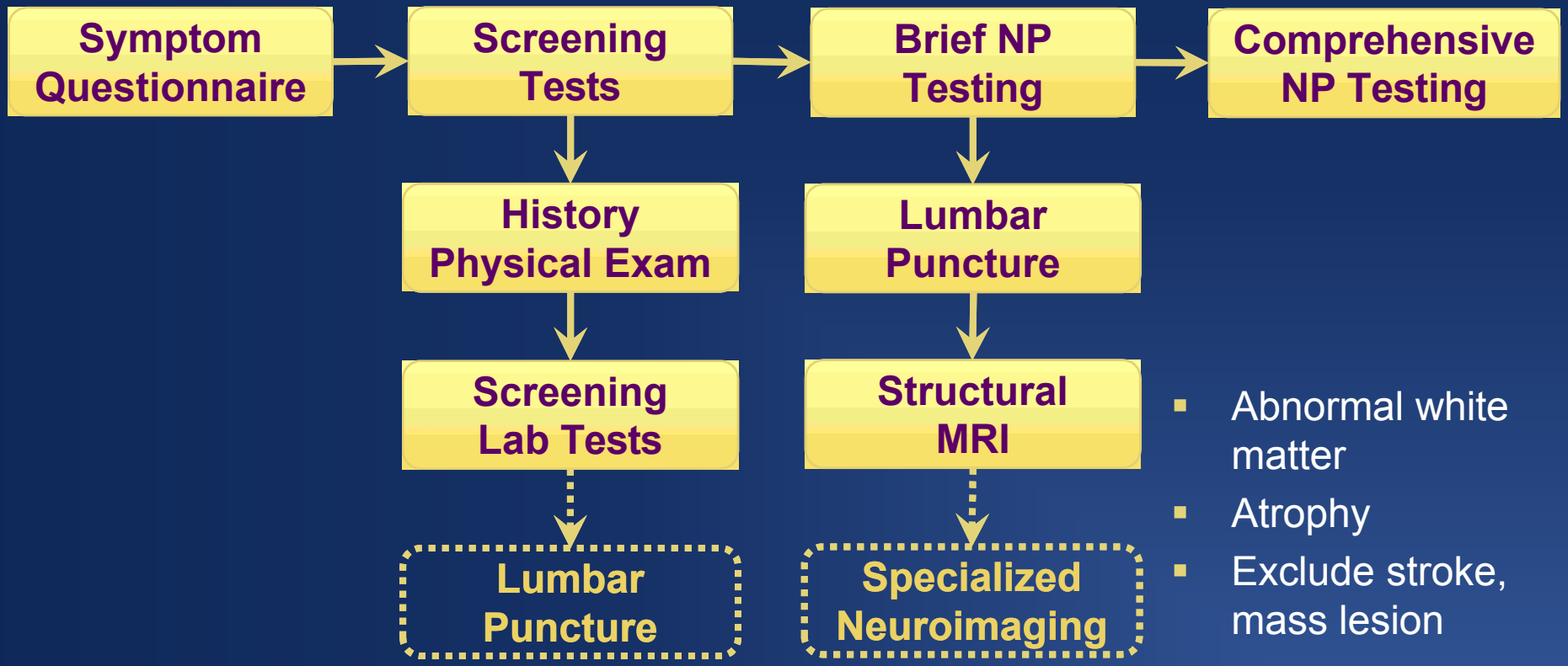
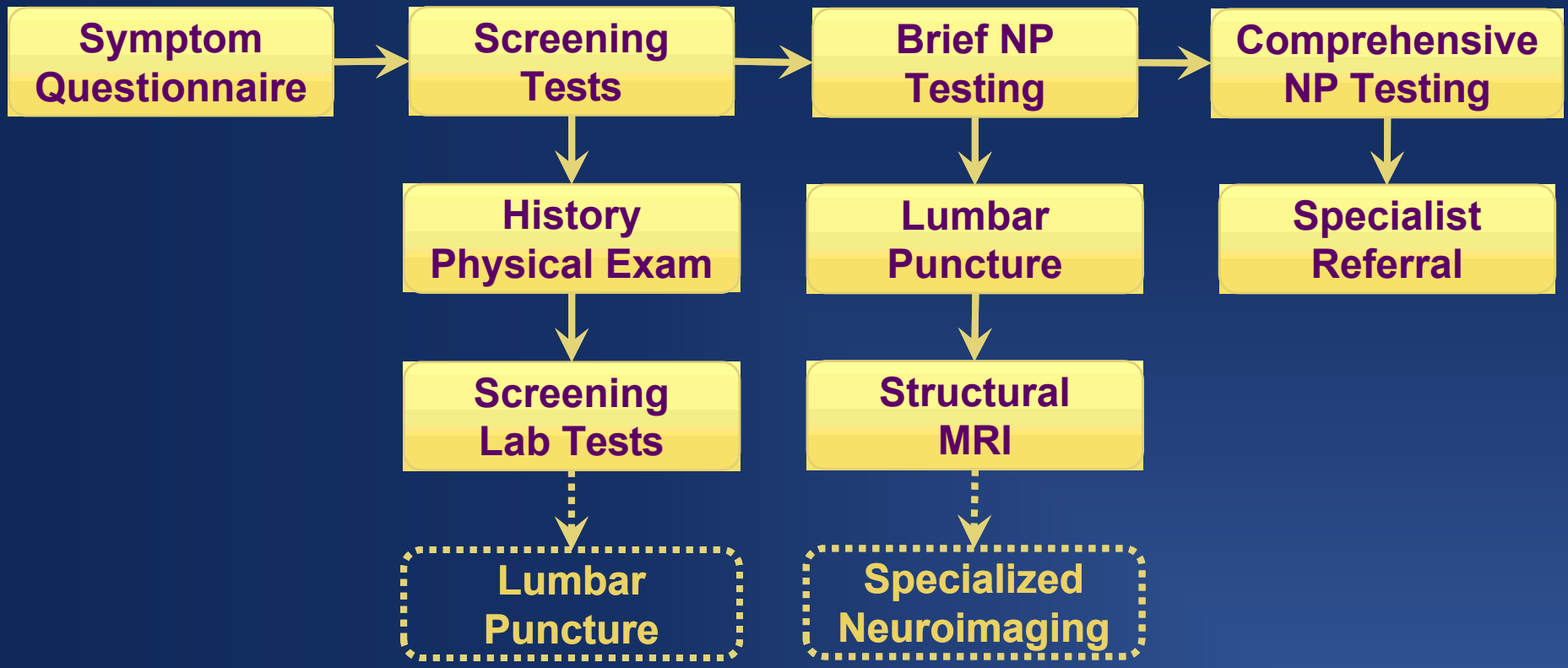


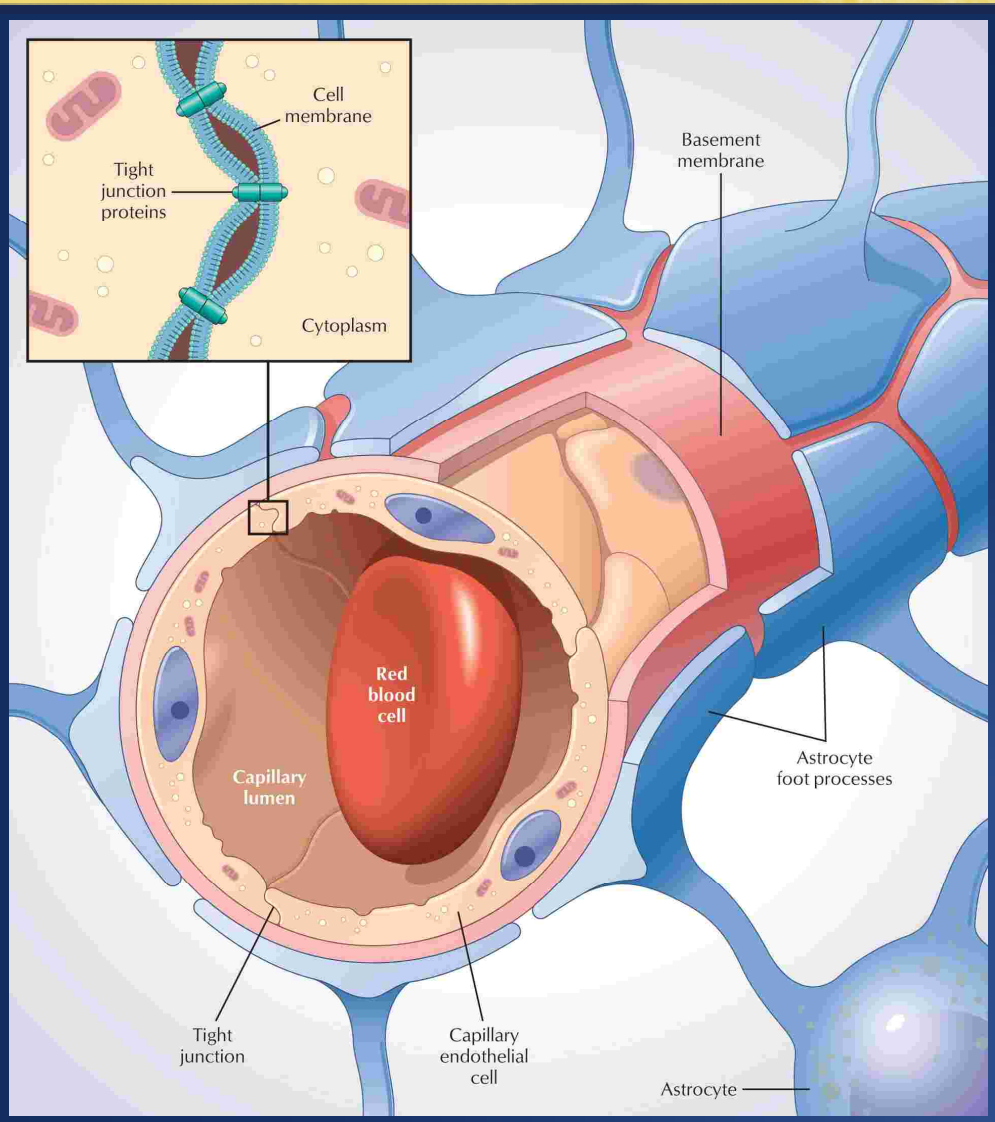
- Abnormal white matter
- Atrophy
- Exclude stroke, mass lesion

Approach to Screening and Diagnosis



Antiretroviral Treatment

Structure of the Blood-Brain Barrier



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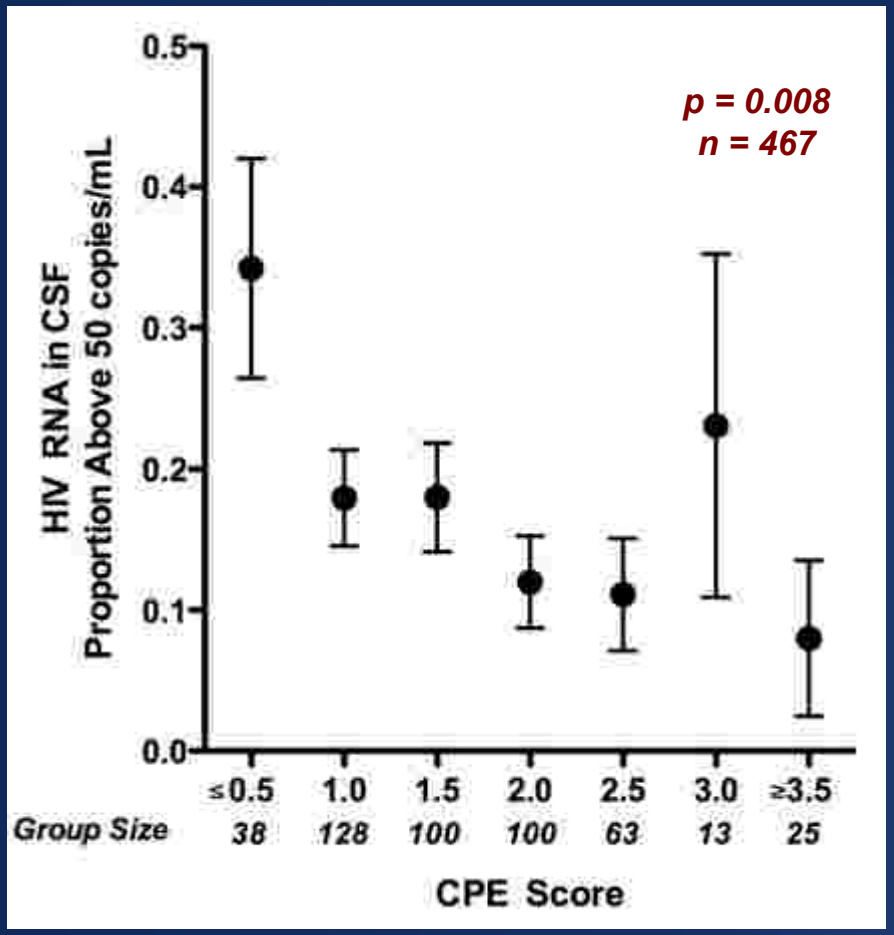
CNS Penetration-Effectiveness Ranks 2010

	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

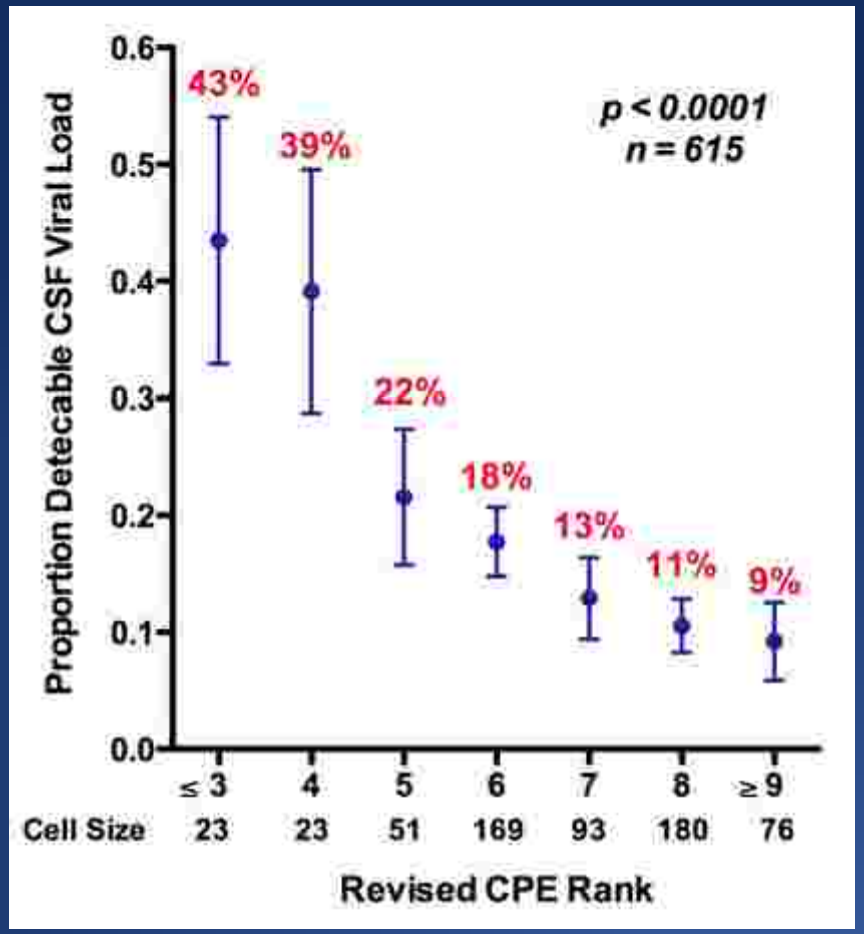
Letendre et al, 17th CROI 2010, Abstract 172

Estimation of Penetration-Effectiveness in CNS

Better Penetration = Lower CSF Viral Loads



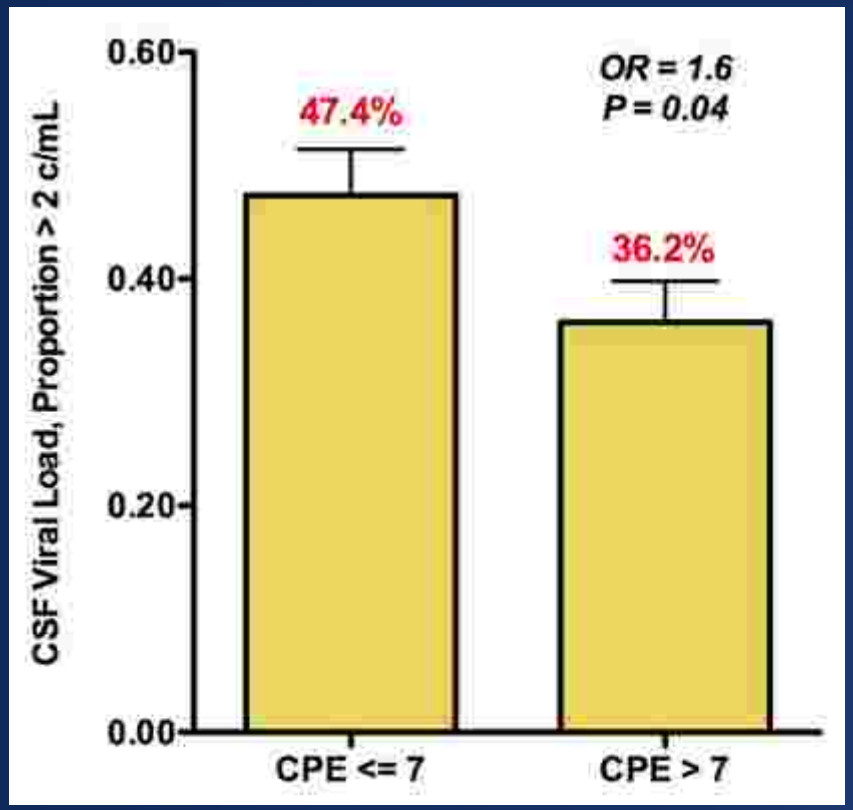
Letendre S, et al. Arch Neurol 2008; 65:65-70



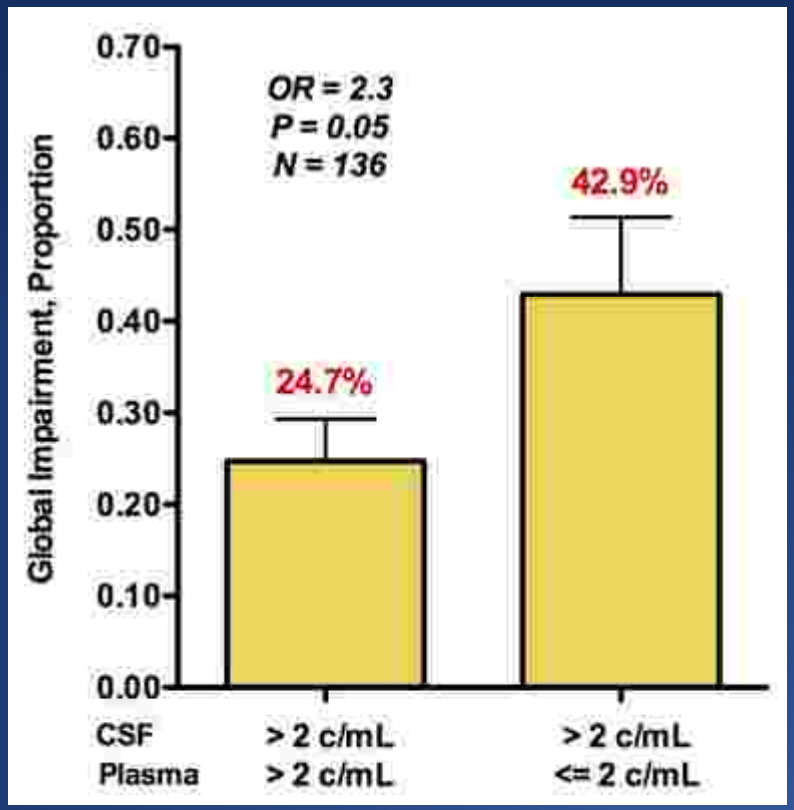
Letendre et al, 17th CROI 2010, Abstract 172

CSF Viral Loads Are Associated with HAND When Compared to Plasma Viral Loads

ART Penetration vs. Low-Level HIV



Low-Level HIV vs. Performance



Letendre et al, 16th CROI 2009, Abstract 484b

Recent Findings Supporting Penetration are Consistent but Not Uniformly

	Cysique	Tozzi	Ellis	Marra
Study	UCSD CIT	NIID	ALLRT	ACTG 736
Sample Size	37	185	2,636	26
CPE: CSF VL	**Lower VL**	No CSF	No CSF	**Lower VL**
Number of NP Tests	6	15	3	4
CPE: NP Tests	**Better**	**Better**	**Better**	***Less Improvement***
Prospective	Yes	Yes	Yes	Yes
Controlled	No	No	No	No
Norms for NP Change	**Yes**	No	No	No

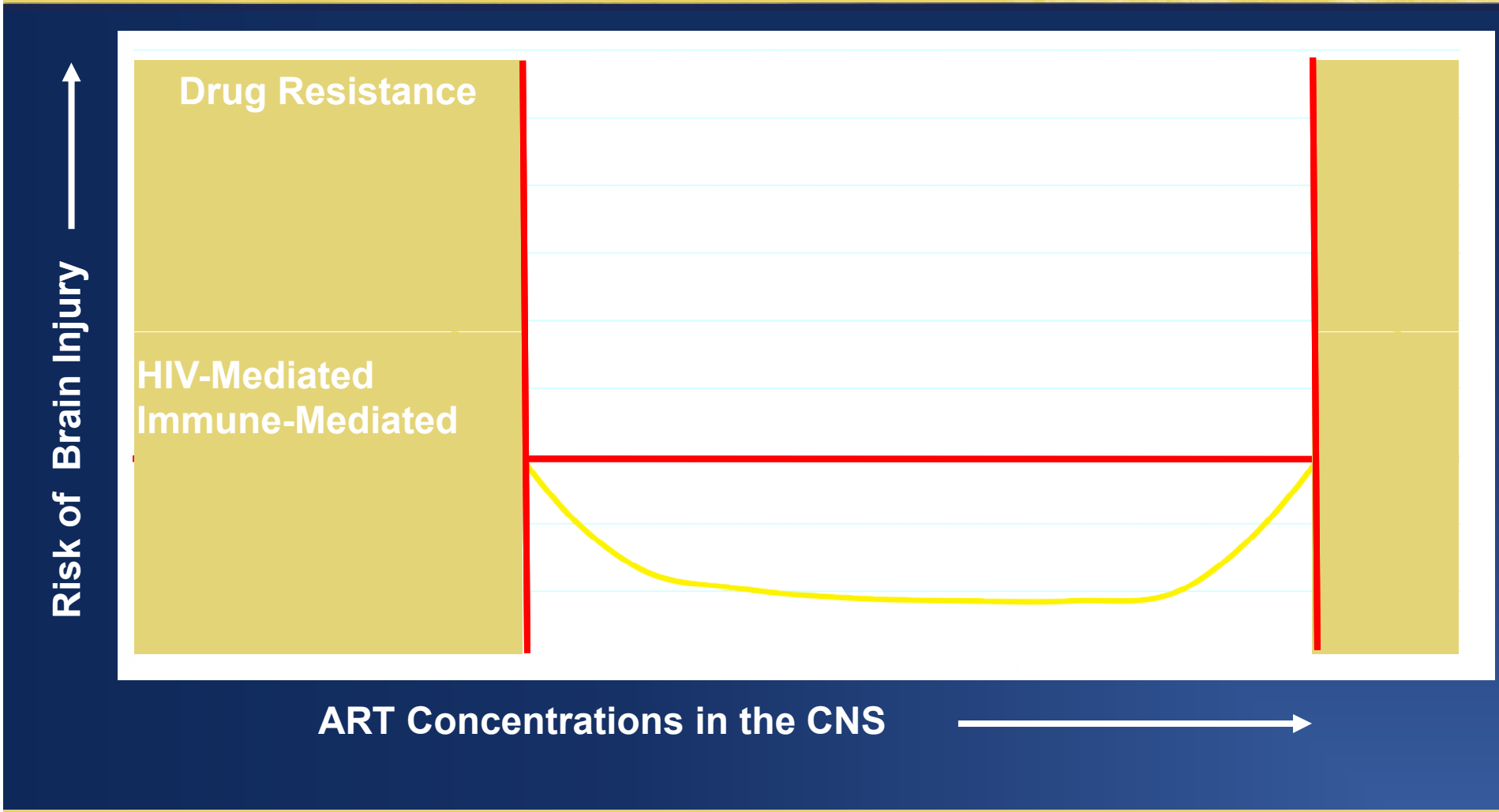
Cysique et al, Neurology 2009, 73(5):342-8; Tozzi et al, J Acquir Immune Defic Syndr 2009;52:56–63; Ellis et al, Annual Meeting American Neurological Association 2009; Marra et al, AIDS 2009, 23(11):1359-66

Better Distribution into the Nervous System may have Other Benefits

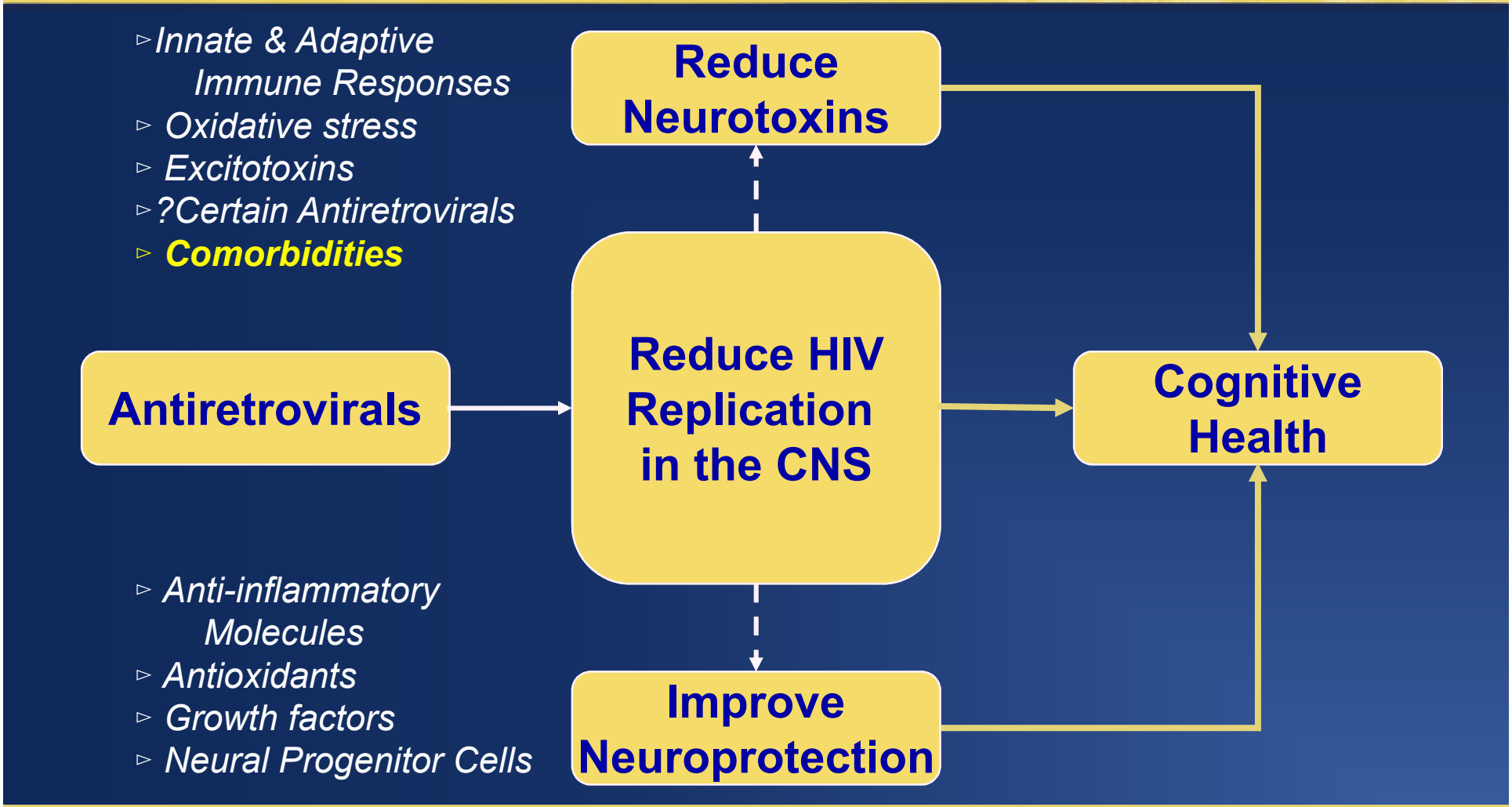
- Better mood
  - » Even after accounting for antidepressant use and neuropsychological performance
- Better survival
  - » In a study of nearly 20,000 adults in the UK
  - » In more than 2,000 perinatally infected children
  - » In individuals with CNS opportunistic infections

Unpublished CHARTER Data;
Garvey et al, 17th CROI, 2010, Abstract 427
Patel et al, AIDS 2009, 23(14):1893-901;
Gasnault et al, 15th CROI, 2008, Abstract 385

Conceptual Therapeutic Window in the Nervous System



Treatments Other than ART May be Necessary



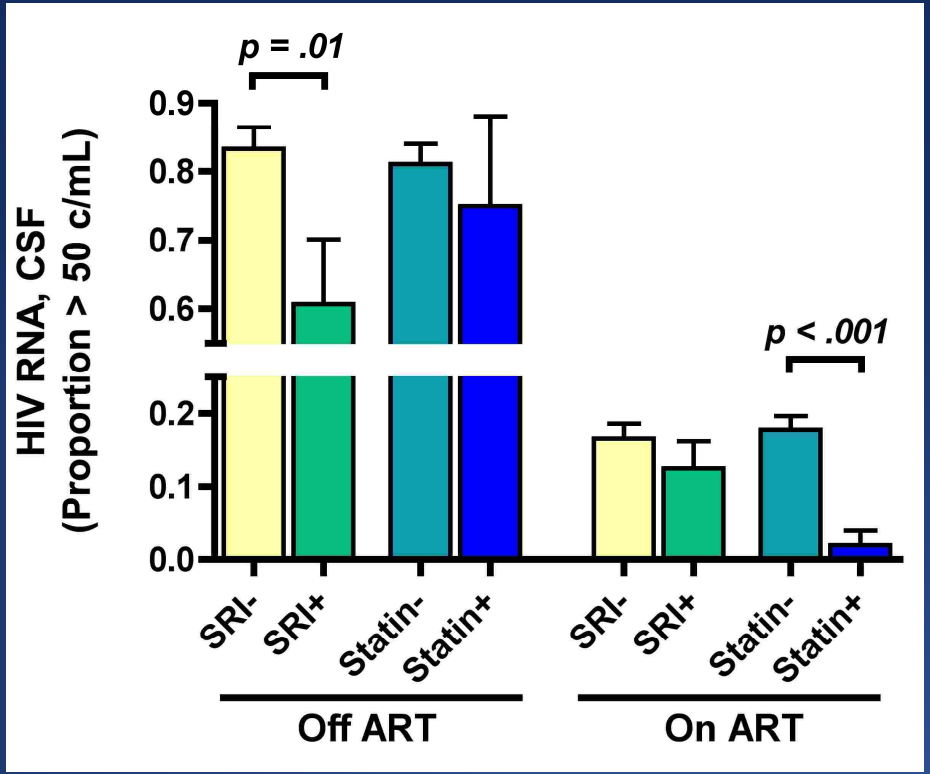
Treatments Other than ART are Unproven

- Potential Modifiers of Neuronal Injury
  - » Glutamate: Memantine
  - » Serotonin: SSRIs / SNRIs
  - » Dopamine: Methylphenidate, Bupropion
  - » Choline: Donepezil
- Growth factors
  - » Erythropoietin (if anemic)
- Anti-inflammatories
  - » Minocycline
  - » Statins (HMG CoA Reductase Inhibitors)
  - » NSAIDs
- Glycogen synthase kinase-3β inhibitors
  - » Lithium

Zink et al, JAMA, 2005;293(16):2003-11
Letendre et al, AIDS, 2006, 20:1885–1888
Schiffito et al, J Neurovirol 2009, iFirst: 1-11
Zhao et al, HIV Clin Trials 2010;11(1):59–67
Digicaylioglu et al, Nature. 2001;412(6847):641-7
Letendre et al, J Neuroimm Pharmacol, 2007, 2(1):120-127

Possible Impact of Other Therapies

- 658 CHARTER participants
- Serotonin reuptake inhibitors and Statins were each associated with lower CSF viral loads
- SRIs were also associated with better NP performance



Letendre et al, J Neuroimm Pharmacol 2007, 2(1): 120-7

Prevention is Unproven

- Earlier initiation of ART
  - » Earlier may be better: At least above 350 cells/mm^3
  - » ART reduced the incidence of HAD but better penetrating ART is unproven in preventing HAND
- Diagnose and treat comorbidities
  - » Mood disorders
  - » Stimulant abuse
  - » Co-infections
  - » Metabolic and lipid disorders
  - » Vascular disorders
- Measure biomarkers to raise suspicion and increase surveillance when abnormal
  - » **None are clinically validated**
  - » CD4 count, hemoglobin, platelets, C-reactive protein
  - » CSF viral load ≥ plasma viral load
  - » ApoE, MCP-1, soluble CD14

Recommendations

- **Counsel** patients on HAND and antiretroviral penetration to enable them to make informed treatment choices
- **Question** patients about cognitive symptoms and activities of daily living at routine visits and before initiating ART
- **Screen for and treat other conditions** that could account for nervous system complaints
  - » Co-infections, substance use, mood disorders, vascular and metabolic disease
  - » Consider lumbar puncture and neuroimaging
- **Consider using better penetrating ART** since data support that it better reduces HIV in CSF and may lead to better neurocognitive performance
  - » Recent US treatment guidelines may lead to undertreatment of the CNS
- **Continue to monitor** effectively treated patients
  - » Cognitive impairment might persist or even occur for the first time in treated individuals

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- David Simpson
- Ben Gelman

National Institutes of Health

- …Mental Health
- …Drug Abuse
- …Neurological Disorders and Stroke

Pharma

- Boehringer-Ingelheim
- Abbott Laboratories
- ViiV Healthcare
- Merck, Inc.
- Tibotec