Controversies: Screening for and Management of HAND

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Acknowledgements & Conflicts

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- …Drug Abuse
- …Allergy and Infectious Diseases

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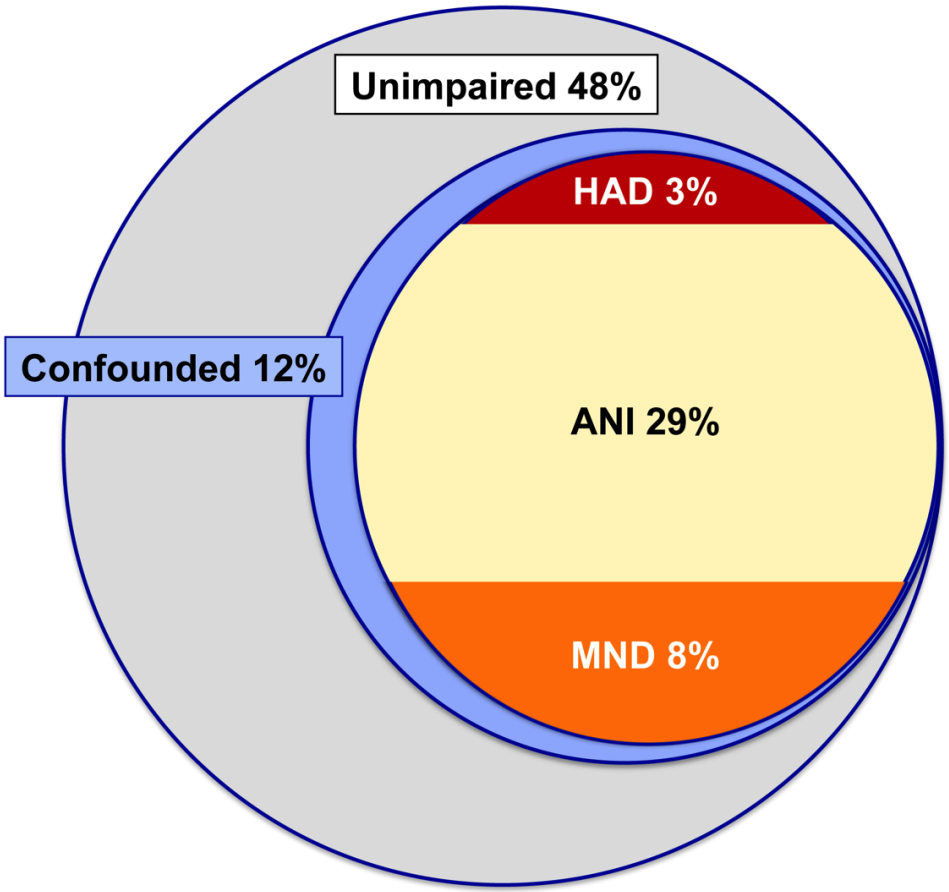
- ViiV
- Merck, Inc.
- Janssen
- Biogen IDEC

Should Clinicians Screen for HAND?

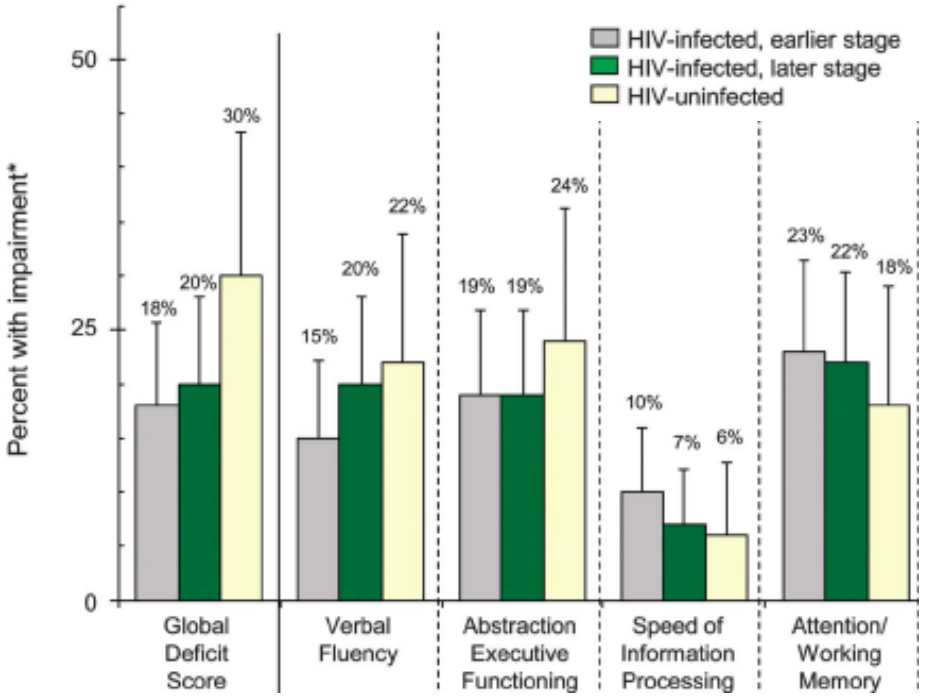
Should Clinicians Screen for ~~HAND?~~ Neurocognitive Impairment?

Is Neurocognitive Impairment in People with HIV Disease Common and Clinically Important?

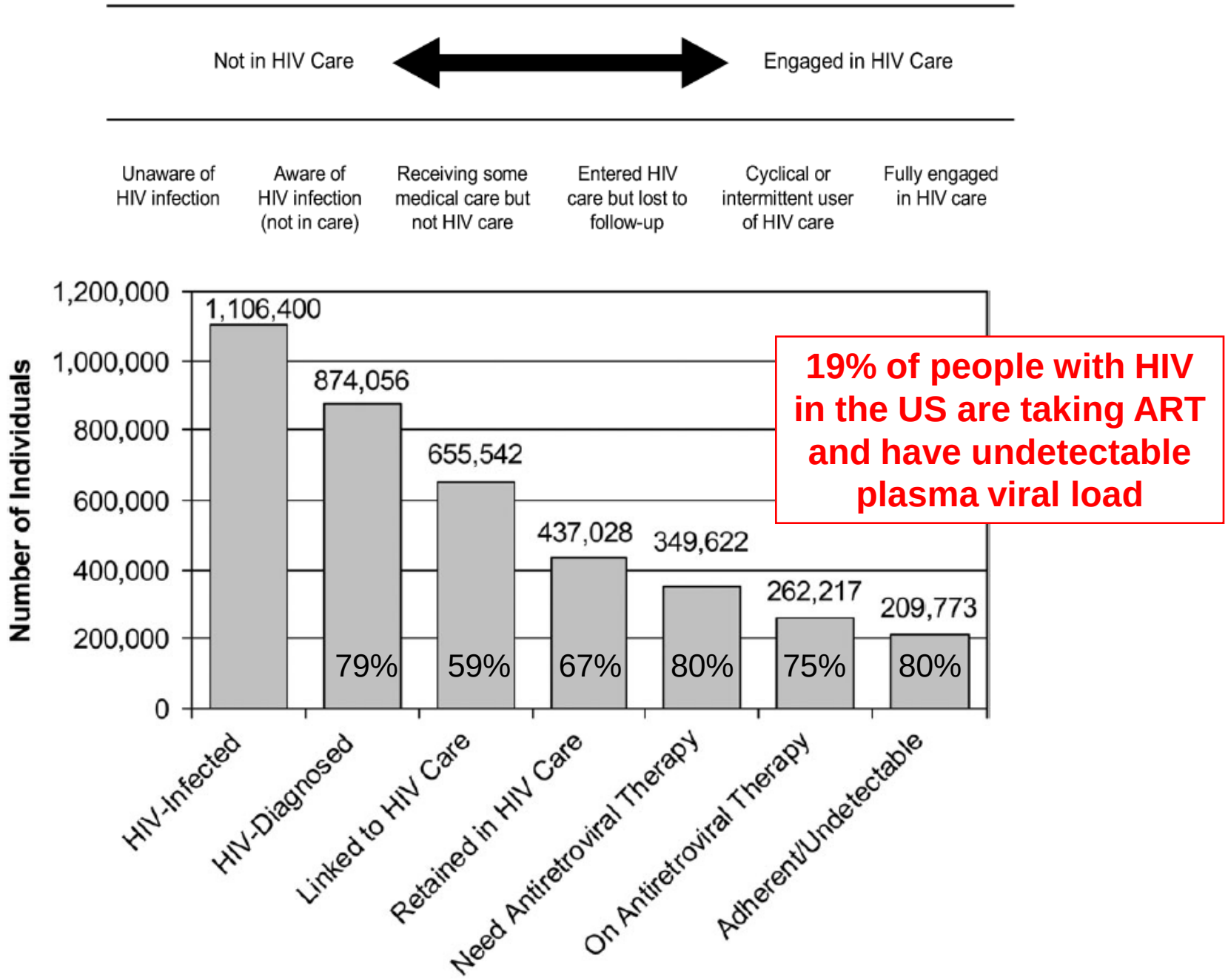
Neurocognitive Impairment is Common in Most – But Not All – Reports



Heaton, et al. Neurology 2010, 75:2087-96

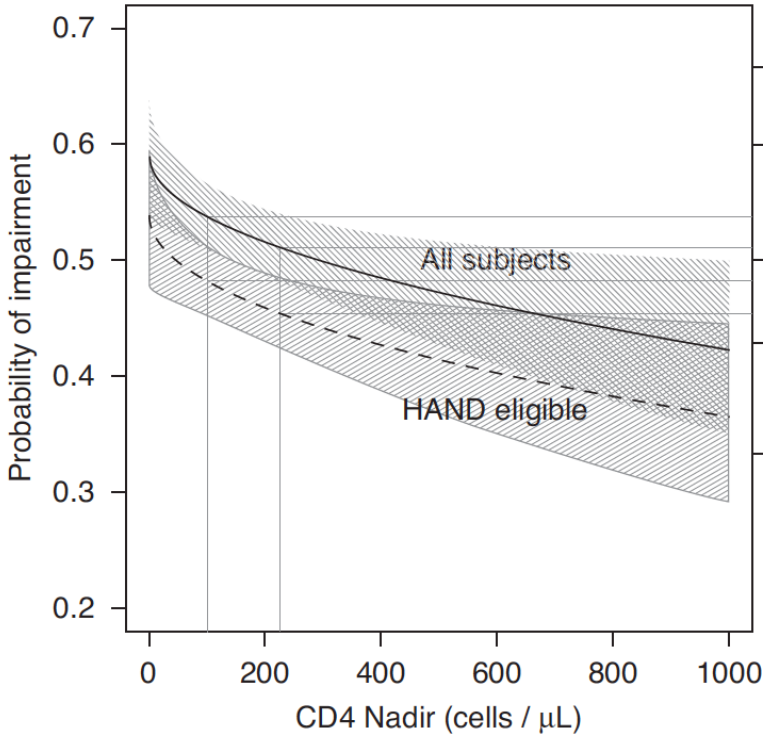


Crum-Cianflone, et al. Neurology 2013, 80:371–379

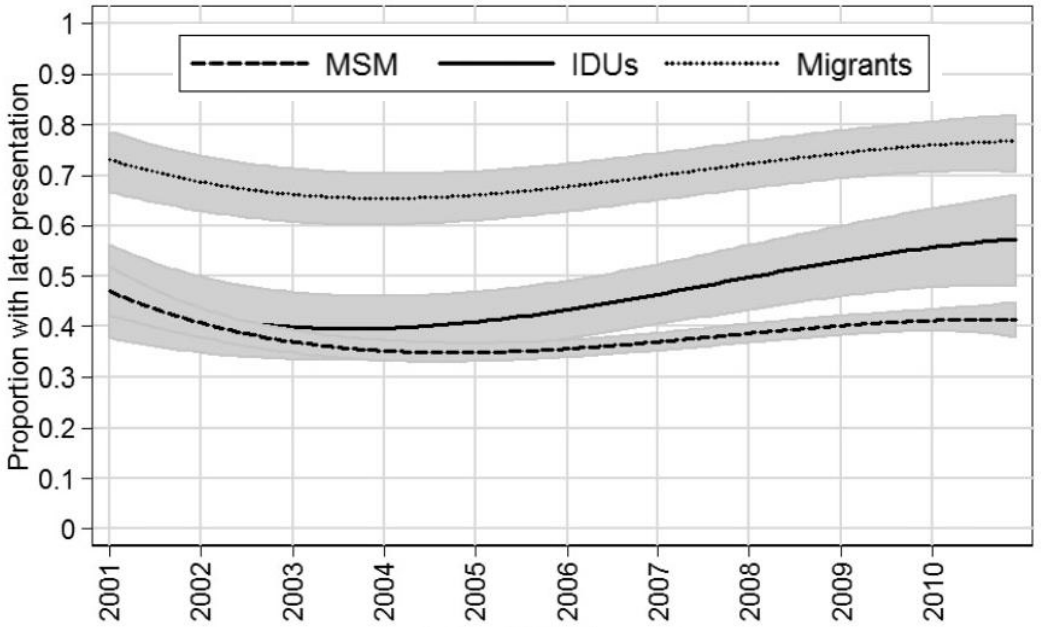


Gardner et al, Clin Infect Dis. 2011; 52(6):793-800

Neurocognitive Impairment is Associated with Advanced Immune Suppression

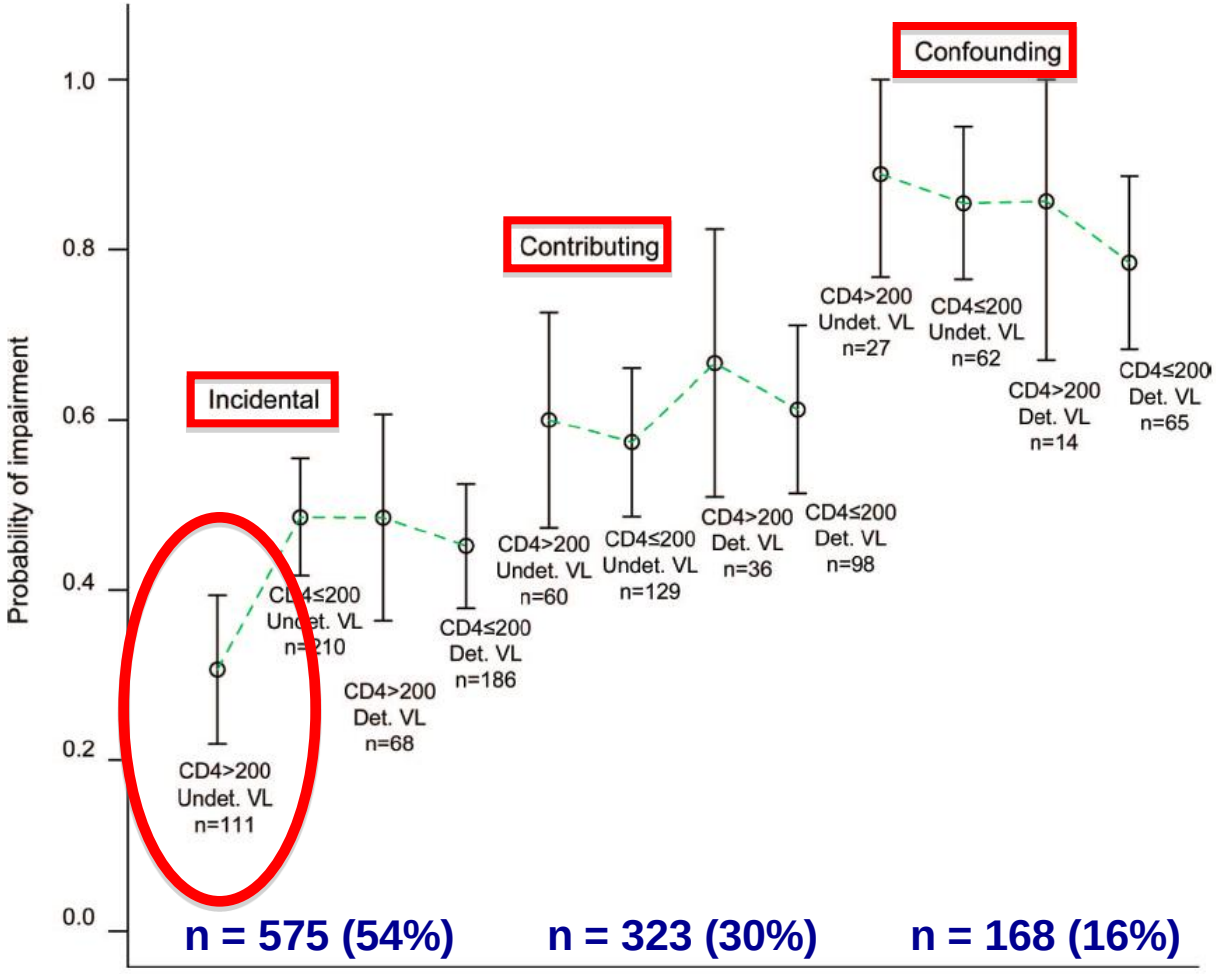


Ellis, et al. AIDS, 2011, 25: 1747-51

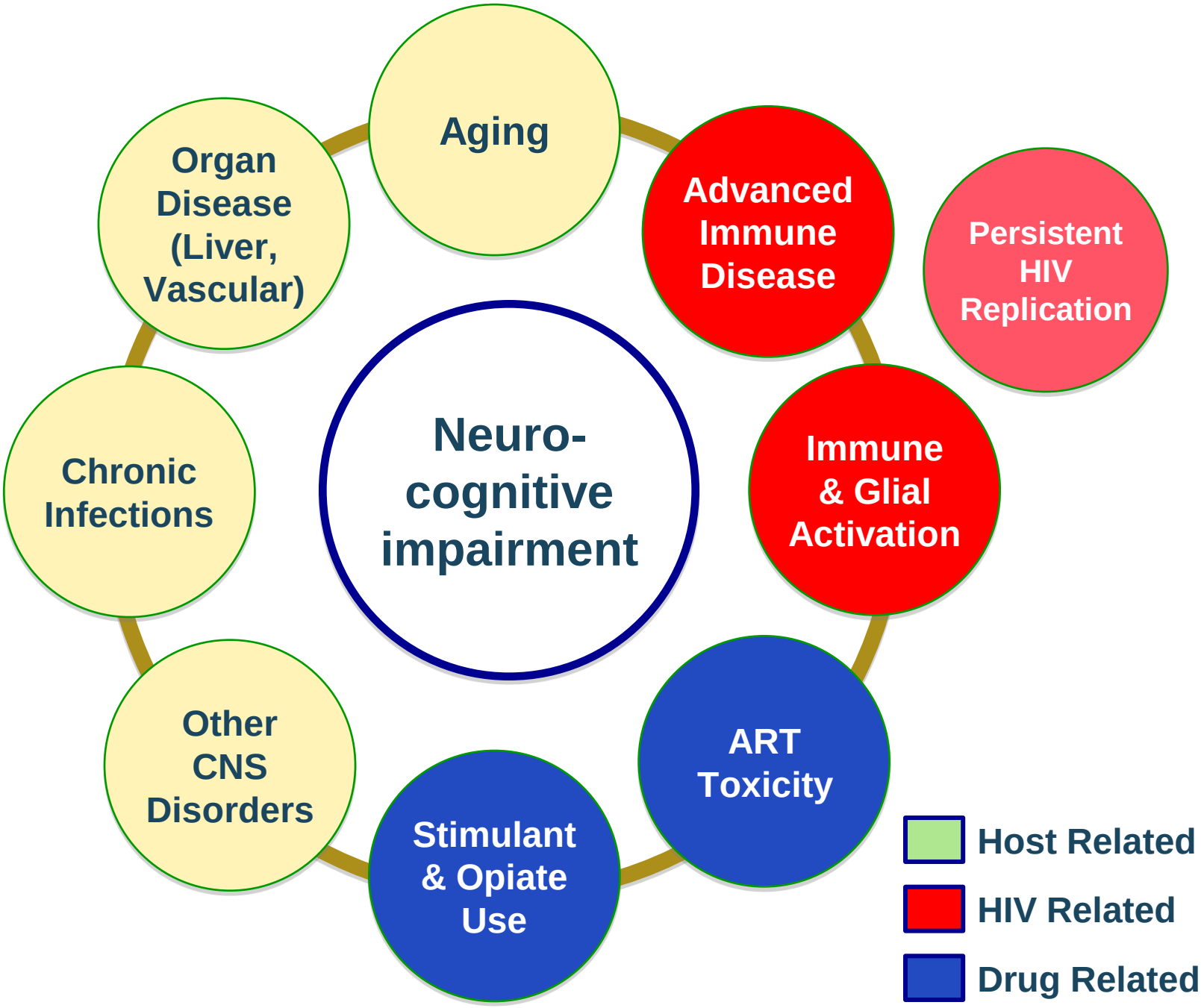


Zoufaly, et al. HIV Medicine, 2012, 13: 172-181

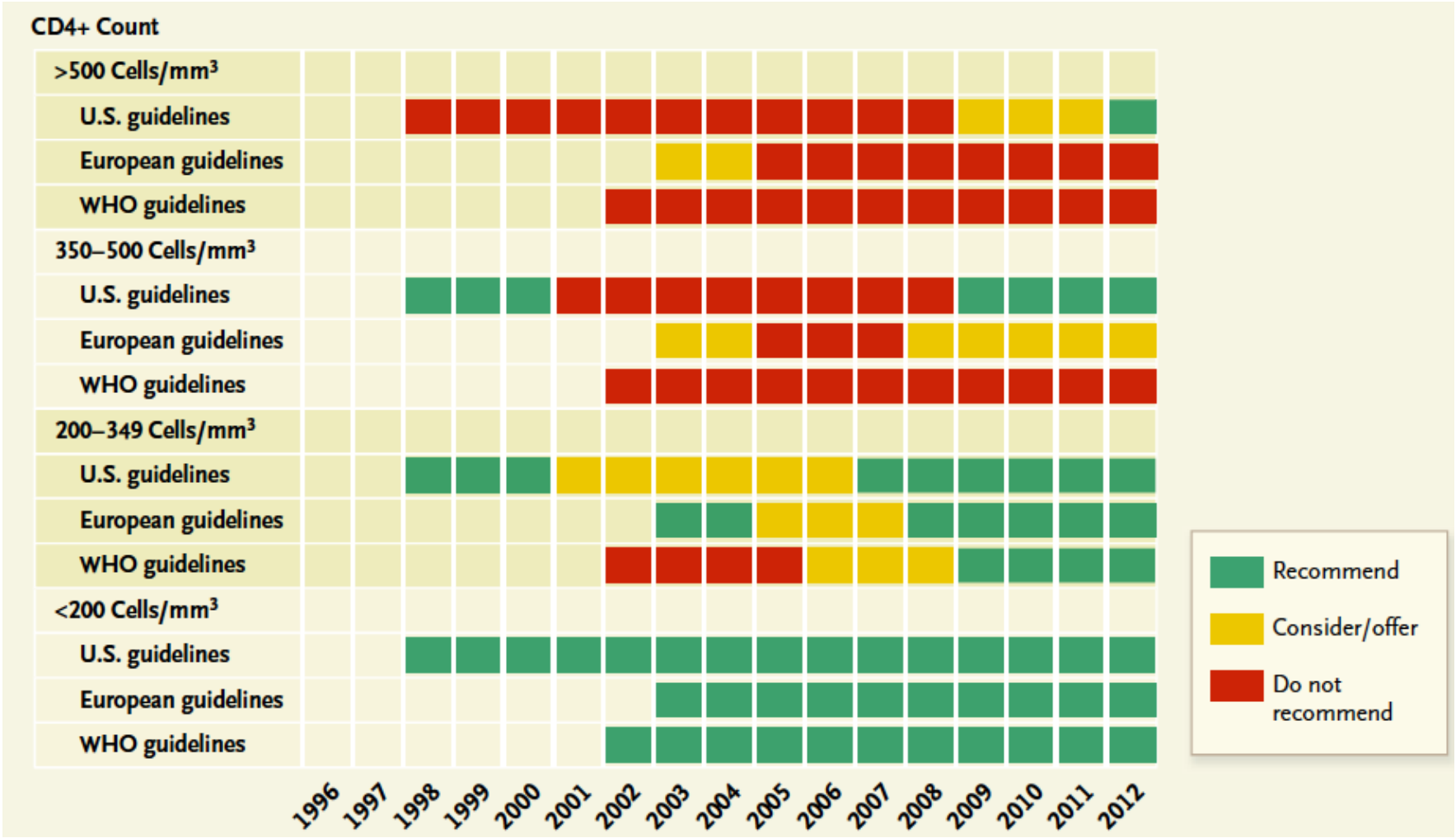
CNS Impact of HIV is Most Evident in the Absence of Other Conditions



Heaton, et al. Neurology, 2010, 75:2087–2096

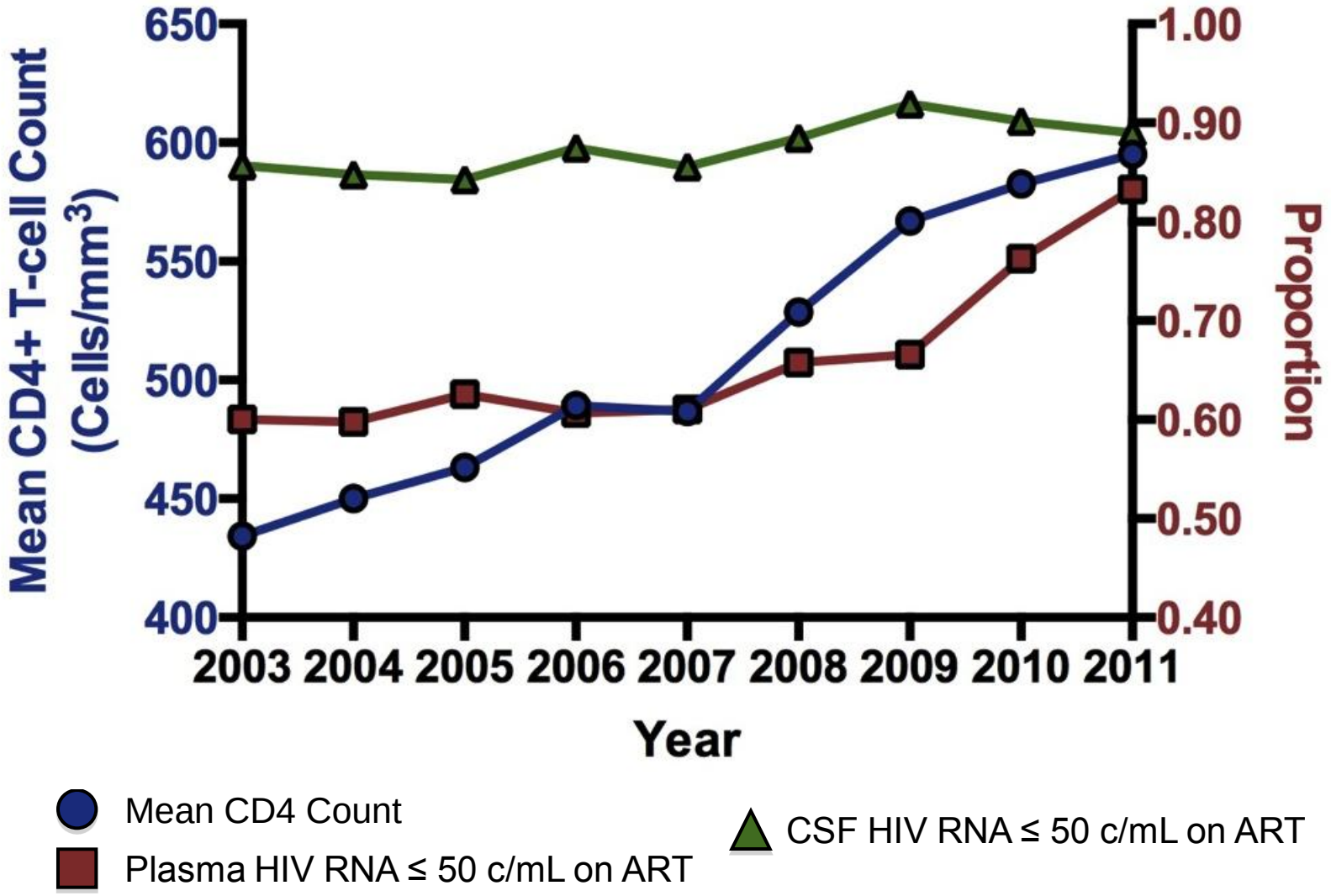

Aging
Organ Disease (Liver, Vascular)
Advanced Immune Disease
Persistent HIV Replication
Chronic Infections
Neuro-cognitive impairment
Immune & Glial Activation
Other CNS Disorders
ART Toxicity
Stimulant & Opiate Use
Host Related
HIV Related
Drug Related

Guidelines Continue to Evolve to Favor Earlier Initiation of ART



De Cock and El-Sadr, New England Journal of Medicine, 2013; :DOI: 10.1056/NEJMp1300458

CD4 Counts and Plasma Viral Loads Improve Over Time in CHARTER



Many Functional Abilities Can Be Affected by Neurocognitive Impairment

Lawton IADLs

- Shopping and Food preparation
- Medications
- Transportation
- Financial management
- Job performance

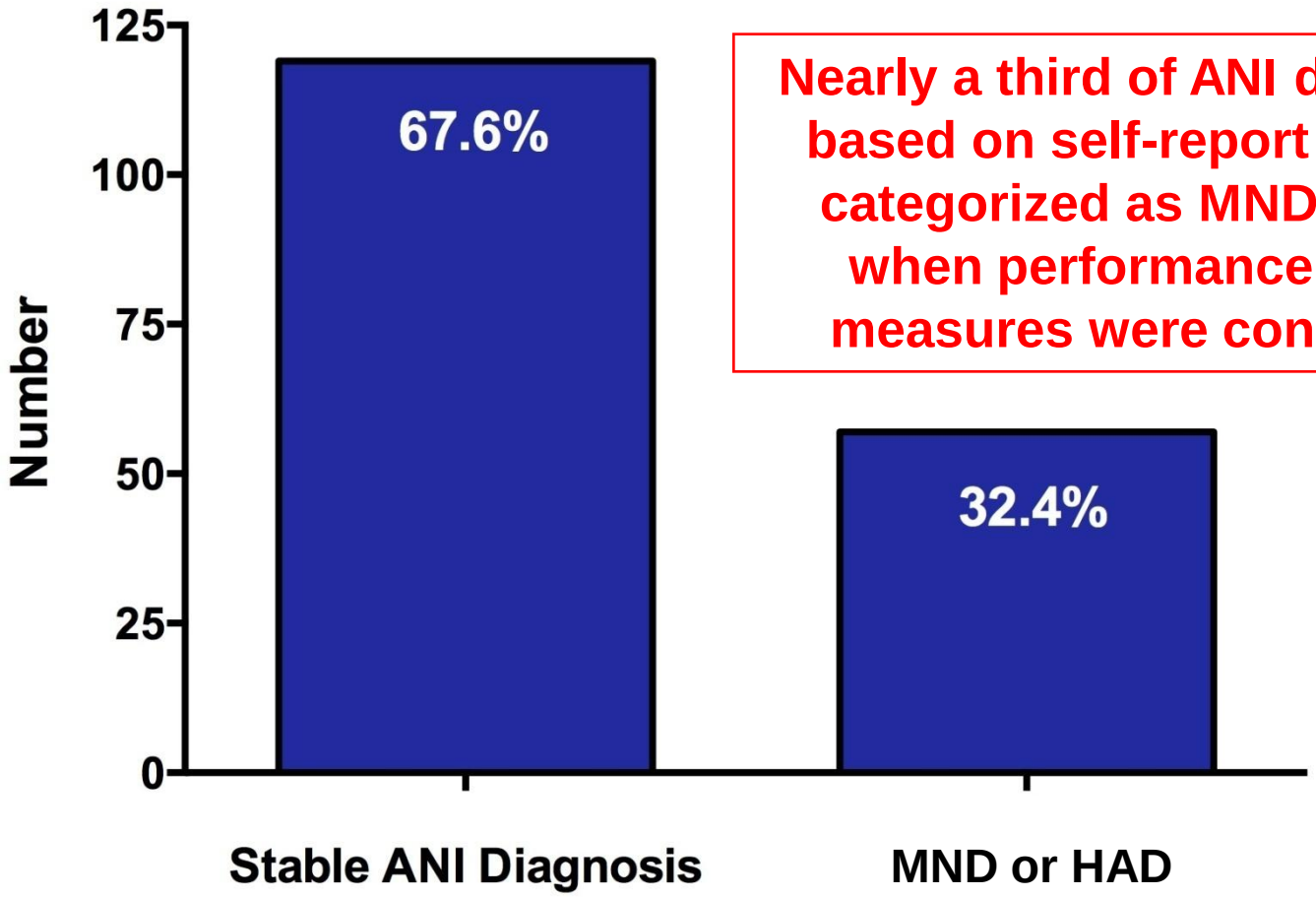
Lawton MP, Brody EM. Gerontologist. 1969;9(3):179-186.

Other Effects

- Traffic accidents
- Worse Survival

Marcotte et al, J Clin Exp Neuropsych, 28: 13
Ellis et al, Arch Neurol. 1997;54(4):416-24
Wilkie et al, J Neuropsychiatry Clin Neurosci. 1998;10(2):125-32

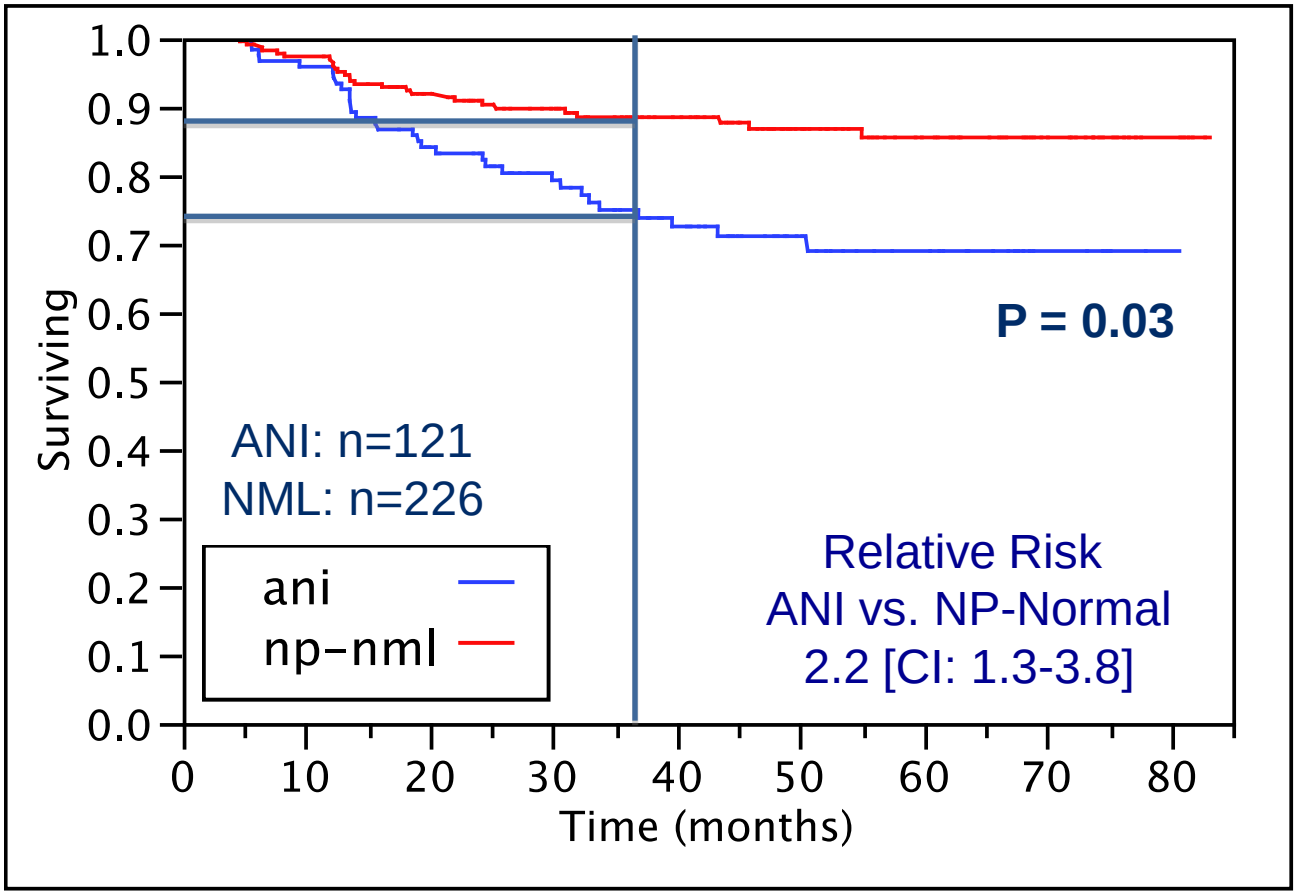
Symptoms and Functioning Varies Based on the Type of Assessment



Nearly a third of ANI diagnoses based on self-report were re-categorized as MND or HAD when performance-based measures were considered

Heaton, et al. 19th CROI 2012, Abstract 77

People with ANI are at Greater Risk for Progression to More Severe HAND



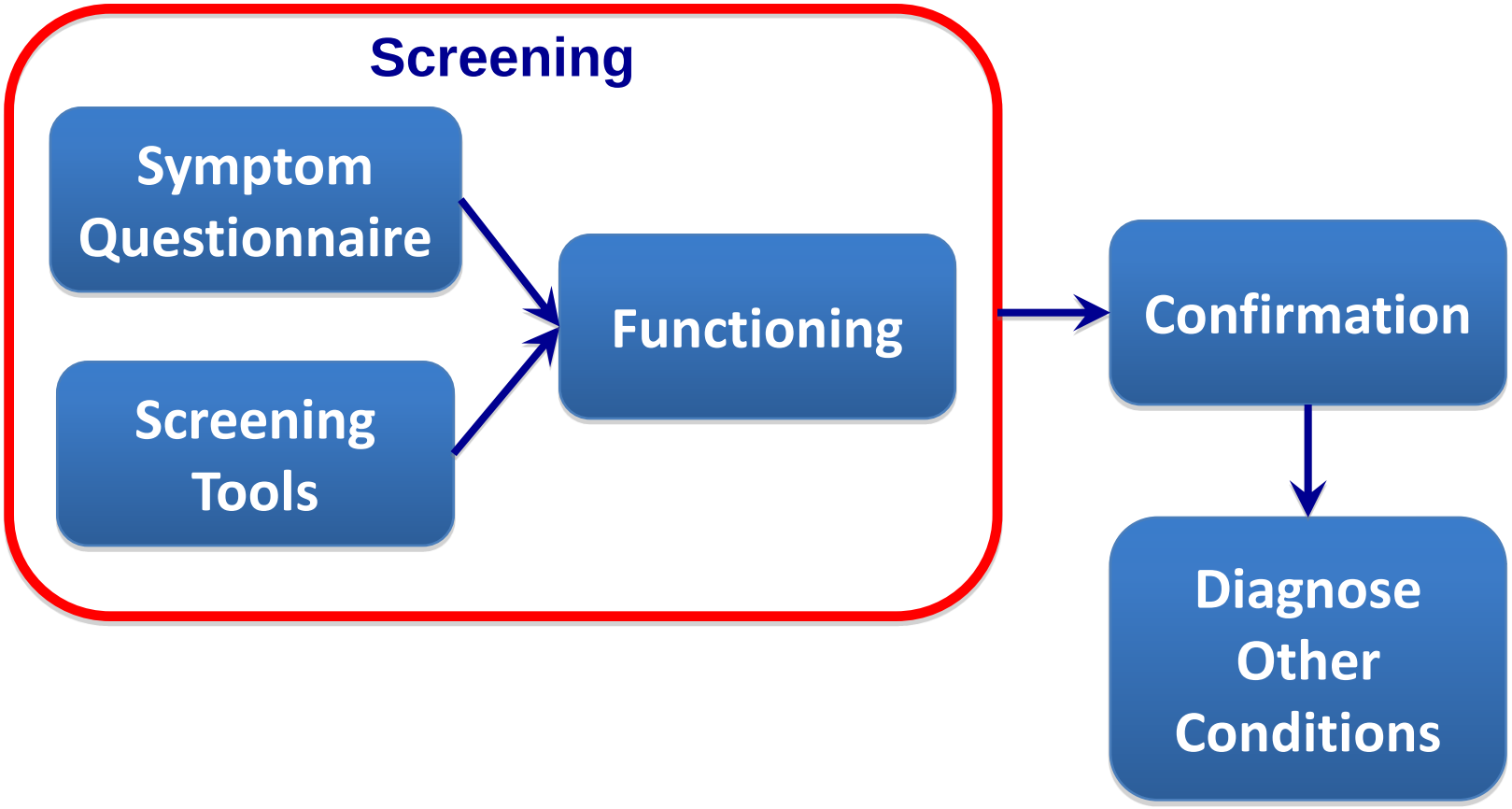
Heaton, et al. 19th CROI 2012, Abstract 77

Which patients should be screened for HAND? How often should screening occur?

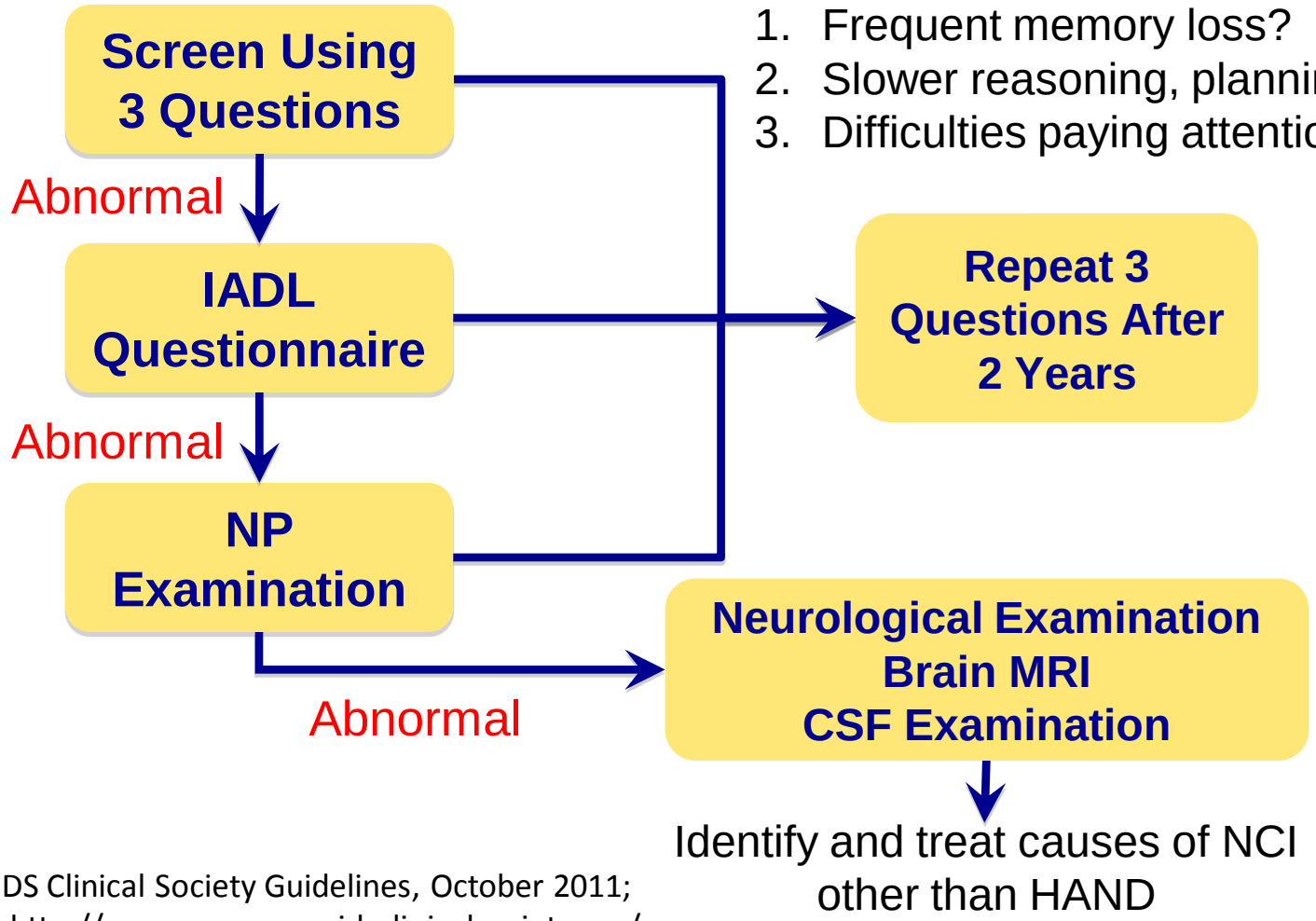
- **Assess all patients** with HIV disease (CEBM 5; GOR D)
  - Assessment can assist in treatment and management decisions, provide reassurance, and detect cognitive, behavioural and mood changes before symptoms arise or are acknowledged (CEBM 2b)
  - No rationale for screening only symptomatic patients (CEBM 2b)
- Assess neurocognitive functioning early in disease **using a sensitive screening tool** (CEBM 5, GOR D)
- All patients with HIV should be screened for HAND **within 6 months of diagnosis** (CEBM 5; GOR D)
- Screening should take place **before initiation of ART** (CEBM5; GOR D)

Mind Exchange Working Group, Clin Infect Dis. 2013; 56(7):1004-17

Basic Approach to Screening and Diagnosis



2011 European AIDS Clinical Society (EACS) Guidelines



European AIDS Clinical Society Guidelines, October 2011; Available at: http://www.europeanaidsclinicalsociety.org/ [accessed 15 Nov 2011]

Which tools should be used for screening?

- **No single HAND screening tool is suitable across all practice settings** (CEBM 1b; GOR B)
- **Choice of screening tool depends on several factors**, including:
  - Availability of a neuropsychologist
  - The cost of testing and the time available for testing
  - The characteristics of the population in which it will be used (CEBM 5; GOR D)
- Where a neuropsychologist is available and suitable population norms are available, a combination of two neuropsychological tests have shown good sensitivity, including to the milder forms of HAND (CEBM 2b; GOR B)
- Repeated screening may be beneficial to detect changes over time

Mind Exchange Working Group, Clin Infect Dis. 2013; 56(7):1004-17

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Mind Exchange Working Group, Clin Infect Dis. 2013; 56(7):1004-17

Tool	Benefits	Limitations
HIV Dementia Scale (HDS)	Very brief Specific for HAD	Insensitive for mild HAND Requires trained examiner
International HDS	Very brief, Sensitive & specific for HAD, No trained examiner	Insensitive for mild HAND
Total Recall of HVLT-R	Very brief, Alternate forms reduce practice effect	Requires trained examiner Normative data
Grooved Pegboard	Very brief, Sensitive to motor dysfunction	Requires trained examiner Normative data
Executive Interview	Good internal consistency Correlates w/other measures	Less sensitive than HDS Unknown accuracy in mild HAND
Cognitive functional subscale of MOS-HIV	Sensitive to motor dysfunction	Insensitive for attention or memory functioning
Brief NeuroScreen	Brief	Requires trained examiner Less sensitive for mild HAND
CogState, CANTAB	Automated	Limited validation for screening in HIV disease
Montreal Cognitive Assessment	Brief Multiple languages	Sensitivity 63%

Mind Exchange Working Group, Clin Infect Dis. 2013; 56(7):1004-17, Ellis et al, Journal of Neurovirology, 11: 503–511, 2005, Overton et al, J. Neurovirol 2013, 19:109–116

Screening Summary

In Favor of Screening

- **Identifies people earlier in neurocognitive disease**
  - May be more responsive to intervention
- **Identifies treatable neuropsychiatric diseases**
  - Infections e.g., syphilis
  - Substance use
  - Depression
- **Enables clinics to provide needed social and medical assistance**

Not In Favor of Screening

- **No single tool is sensitive in all settings**
- **Uses clinical resources, which are limited**
  - Resources to confirm screening findings may not available
- **Increases anxiety**
  - Only 25% of ANI patients progress over 3 years
  - No proven treatments
- **Leads to interventions that could worsen disease**

If you do not have the resources to complete the diagnosis of HAND, should you screen?

Management of HAND

If the Effects of ART Drugs Differ in the CNS, Can We Translate this into Clinical Practice?

Estimates of higher drug distribution into the CNS are associated with:

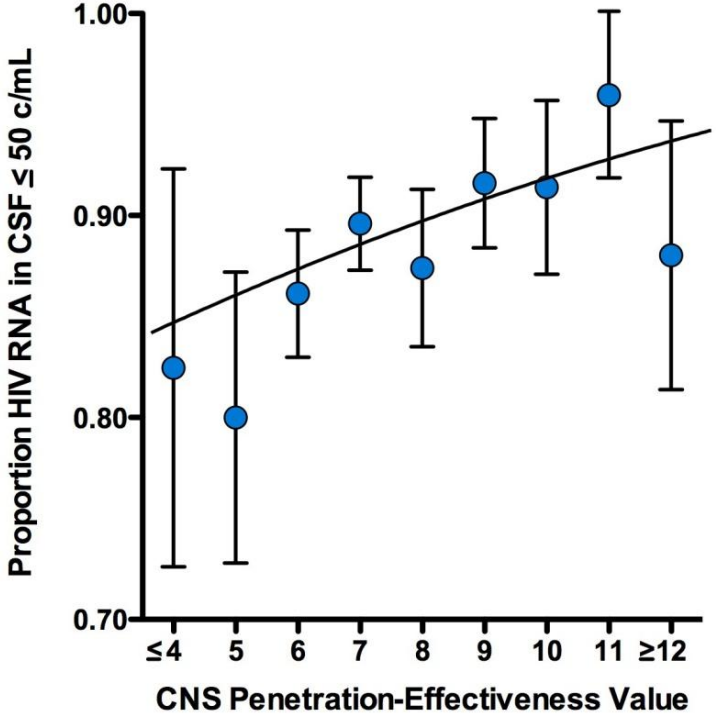
- Lower HIV RNA levels in CSF
- Lower soluble biomarker levels in CSF
- Lower frequency of neurocognitive impairment in some <u>but not all</u> analyses

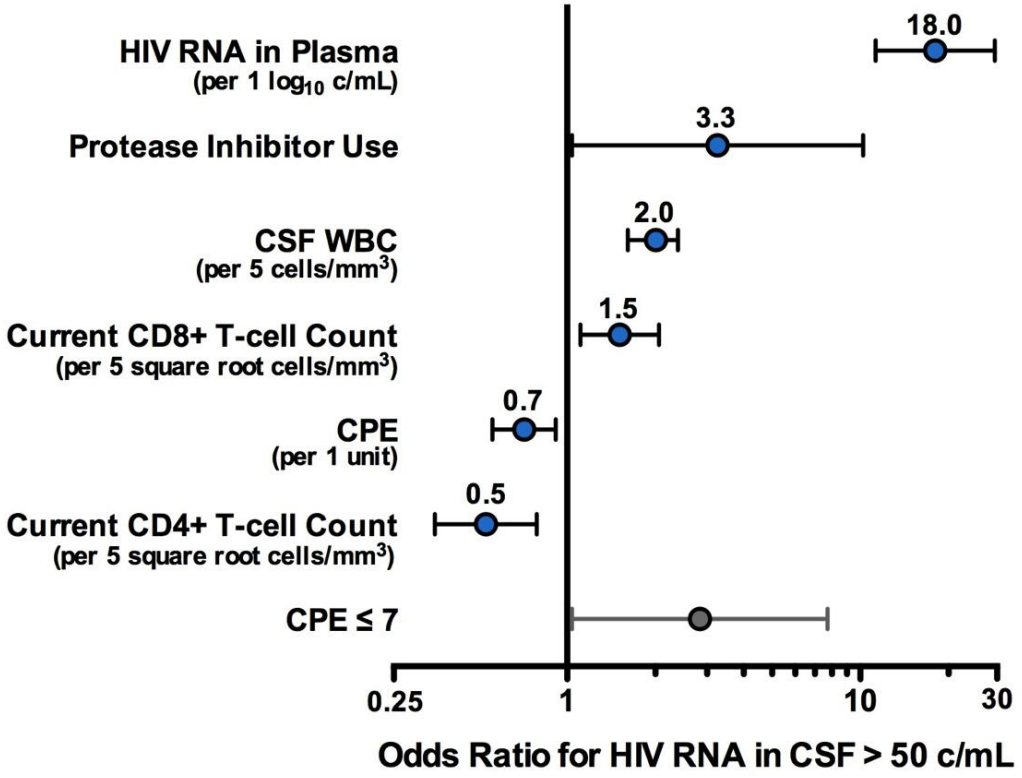
	50 c/mL Assay	2 c/mL Assay
Cross-sectional	Yes[1]	Yes[3]
Longitudinal	Yes[2]	No[4]
Comment	Included patients with plasma HIV RNA > 50	HIV RNA 2-50 c/mL associated with NCI

Letendre et al, [1]CROI 2010, [2]CROI 2012, [3]CROI 2009, [4]CROI 2013

Higher CPE Values Correlate with Undetectable HIV RNA in CSF Over Time

2,207 CSF Viral Loads in 413 Volunteers in CHARTER





Letendre et al, 19th CROI, 2012, Abstract 473

In CHARTER, CPE Values Correlate with Other Variables

Variable	Direction (Higher CPE)		p value
HIV RNA in CSF*	Lower	^{2} = 10.8	.001
Number of ART drugs	More	r = .71	< .0001
Age	Older	r = .12	< .0001
Duration of Regimen	Longer	r = .13	< .0001
VACS Values	Higher	r = .10	.001
Duration of HIV	Longer	r = .05	.10

- Not: HCV serostatus, Neuropsychiatric comorbidities, ethnicity, gender, AIDS, nadir or current CD4

*** Association with HIV RNA in CSF remains statistically significant in multivariable regression models that include these covariates**

Higher CPE Values Correlate with Lower IP-10, sCD14, and Neopterin in CSF During HIV Suppression

	All on ART			HIV RNA Plasma ≤ 50			Multivariable
CSF Biomarker	N	r	p value	N	r	p value	p value
SDF-1α	144	-0.26	0.001	83	-0.20	0.07	0.07
IP-10	255	-0.18	0.004	140	-0.22	0.008	0.006
sTNFR-II	87	-0.30	0.005	52	-0.26	0.06	0.26
IL-6	256	-0.12	0.05	140	-0.15	0.08	0.10
Neopterin	45	-0.29	0.056	29	-0.38	0.04	0.04
TNF-α	256	-0.12	0.058	140	-0.17	0.05	0.16
MCP-1	283	-0.06	0.28	157	-0.09	0.28	0.20
sCD14	59	-0.02	0.88	35	-0.35	0.04	0.02

ART Characteristics Are Also Associated with CSF Viral Escape

First Author	Sample Size	% with CVE	ART Correlates	CSF Correlates	Other Correlates
Rawson (2012)	142	21%	↓ CPE		↑ Plasma HIV RNA ↓ Age
Cusini (2012)	60	6.7%	↓ CPE	↑ Protein	↑ Peak Plasma HIV RNA, ↑ Age
Eden (2010)	69	11%	Absence of ZDV	↑ Neopterin	
Perez-Valero (2012)	1,264	4.4%	PI/r Use ATV Use	↑ WBCs	↑ Duration of HIV ↑ Platelets ↑ Serum Protein
Weighted Median (IQR)		8.8% (5.0%-18.5%)			

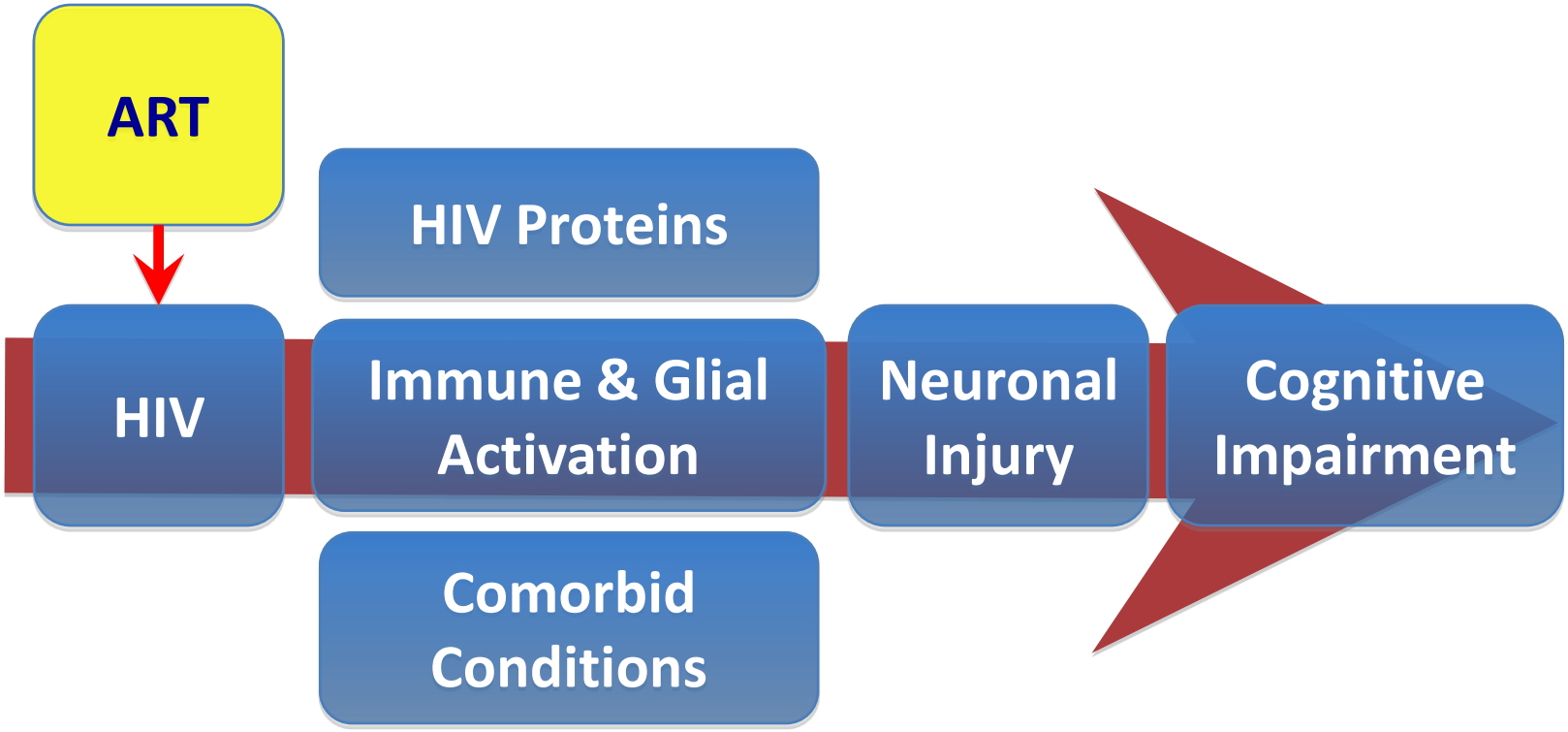
Two published case series also supported a role for ART characteristics in CVE; Canestri et al, CID 2010; Peluso et al, AIDS 2012

How Well Do These Findings Translate to Cognition?

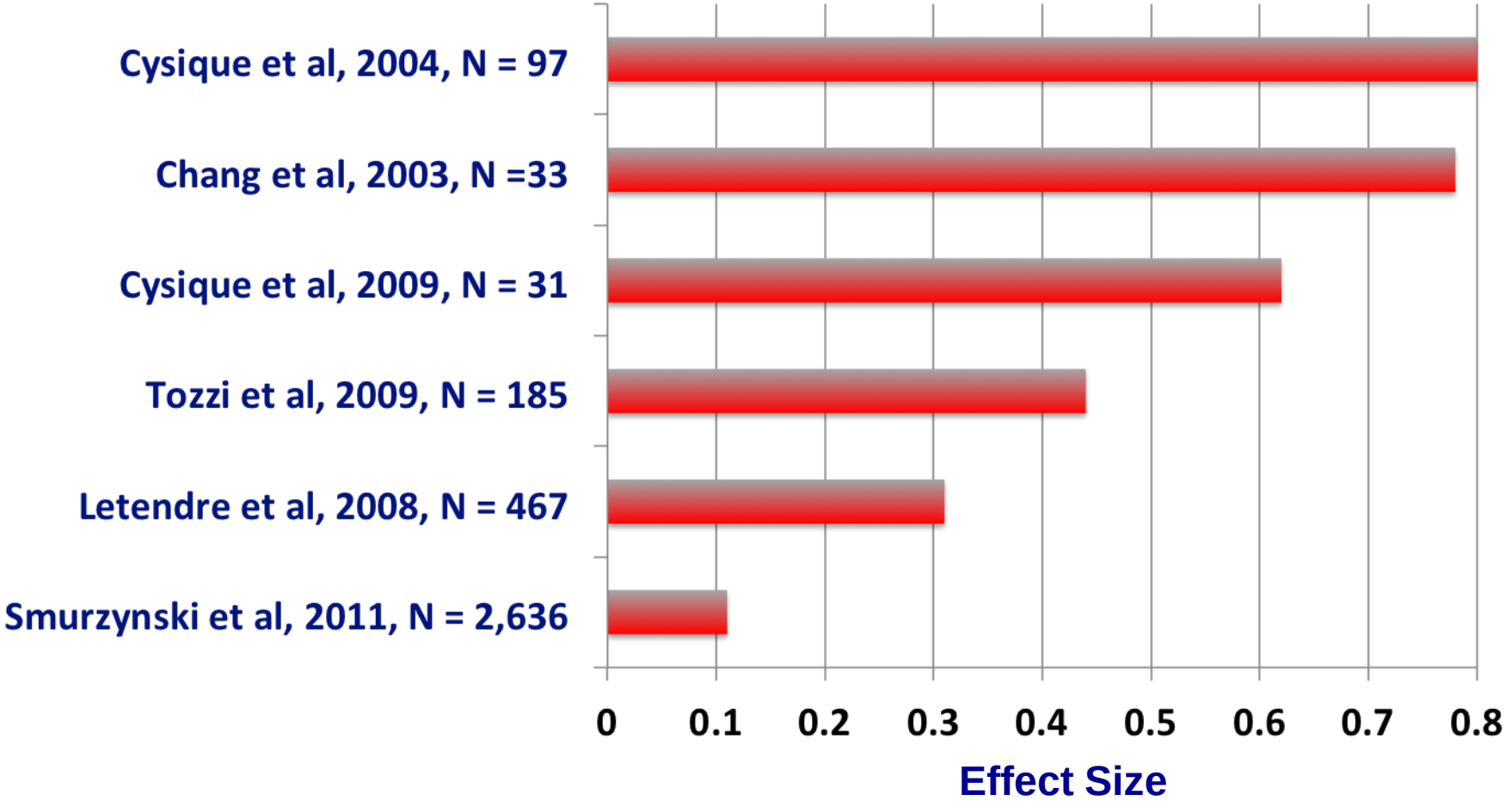
Important considerations:

1. **Susceptibility to neurocognitive impairment varies between patients**
   - Balance between ART safety and effectiveness likely differs between patients
2. **Not all neurocognitive impairment is due to HIV**
   - ART would not benefit NCI due to non-HIV causes
3. **Pathogenesis of ANI, MND, and HAD may differ**
   - The 3 conditions may not respond similarly to ART

ART Affects an Early Step in HAND Pathogenesis… Later Steps May Not Respond As Well



Published Reports with Higher Quality Methods Found Associations with CPE



Cysique et al, BMC Neurology, 2011;11:148

CPE-Related Reports in 2013

		N	NP	Duration	Finding	Comment
Ciccarelli	C-S	101	C	-	↑ CPE associated with better functioning	2010 version stronger than 2008 version
Rourke	C-S	417	C	-	↑ CPE associated with better functioning	
Fabbiani	C-S	215	C	-	Adjusted CPE associated with better functioning	Adjusted CPE using GSS
Vassallo	L	96	C	22 months	↑ CPE associated with better functioning	
Ellis	RCT	49	C	16 weeks	No overall statistically significant benefit; Benefit in subgroup	Planned enrollment 120
Kahouadji	C-S	93	B	-	↑ CPE associated with worse FAB scores	Substantial methodologic flaws

C-S = Cross-sectional, L = Longitudinal, RCT = Randomized clinical trial, C = Comprehensive, B = Brief

Ciccarelli et al, Antiviral Therapy 2013, 18: 153-160; Rourke et al, 2013, Submitted; Vassallo et al, 20th CROI 2013, Abstract 449; Ellis et al, 20th CROI 2013, Abstract 20; Fabbiani et al, 20th CROI 2013, Abstract 405; Kahouadji et al, HIV Medicine 2013, 14: 311-5

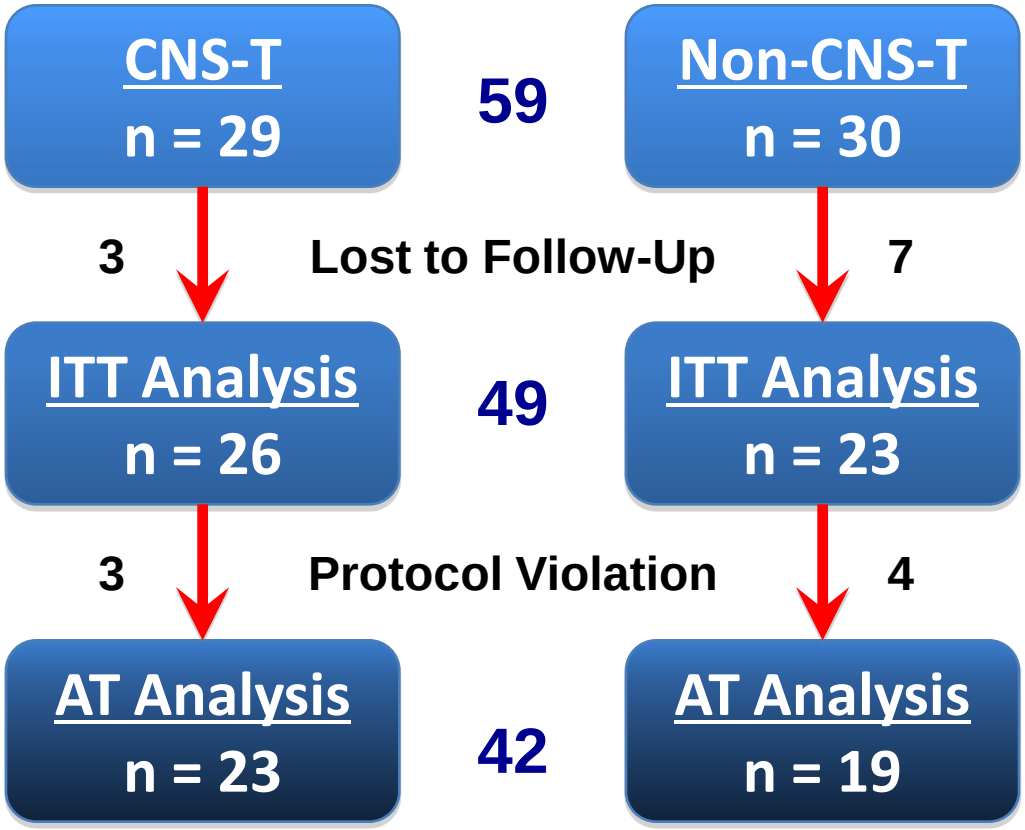
Recent Reports
Cognitive Intervention Trial 2

- Multicenter, NIH-funded clinical trial randomizing people with HAND to initiating or changing to either CNS-targeted or untargeted ART
- Primary endpoint: 16 weeks of ART
- Adaptive randomization to balance:
  - ART experience (naive vs. experienced)
  - Entry CD4+ T-cell count (<200 vs. ≥200)
  - Severity of impairment (mild vs. moderate-severe)
  - HCV serostatus

Ellis et al, 20th CROI, 2013, Abstract 20

Enrollment and Disposition

Planned Enrollment: 120



ITT = Intent-to-treat
AT = As treated

Ellis et al, 20th CROI, 2013, Abstract 20

Potentially Influential Differences Occurred Between Arms at Baseline

	CNS-T	Non-CNS-T	p
ARV Naive	12 (35%)	13 (26%)	> 0.20
Plasma VL (< 50 c/mL)	7 (27%)	6 (26%)	> 0.20
Entry CD4	214 [5, 964]	306 [3, 1224]	> 0.20
Nadir CD4 < 200	16 (67%)	8 (38%)	**0.08**
HCV seropositivity	9 (35%)	3 (13%)	**0.10**
Randomized Treatment			
Number ARVs	4	3	**0.06**
Relative PSS	1	0.95	0.19
ARVs most different between arms	NVP, LPV/r ZDV, ABV, FTC	ETR, DRV/r, TDF, 3TC	--

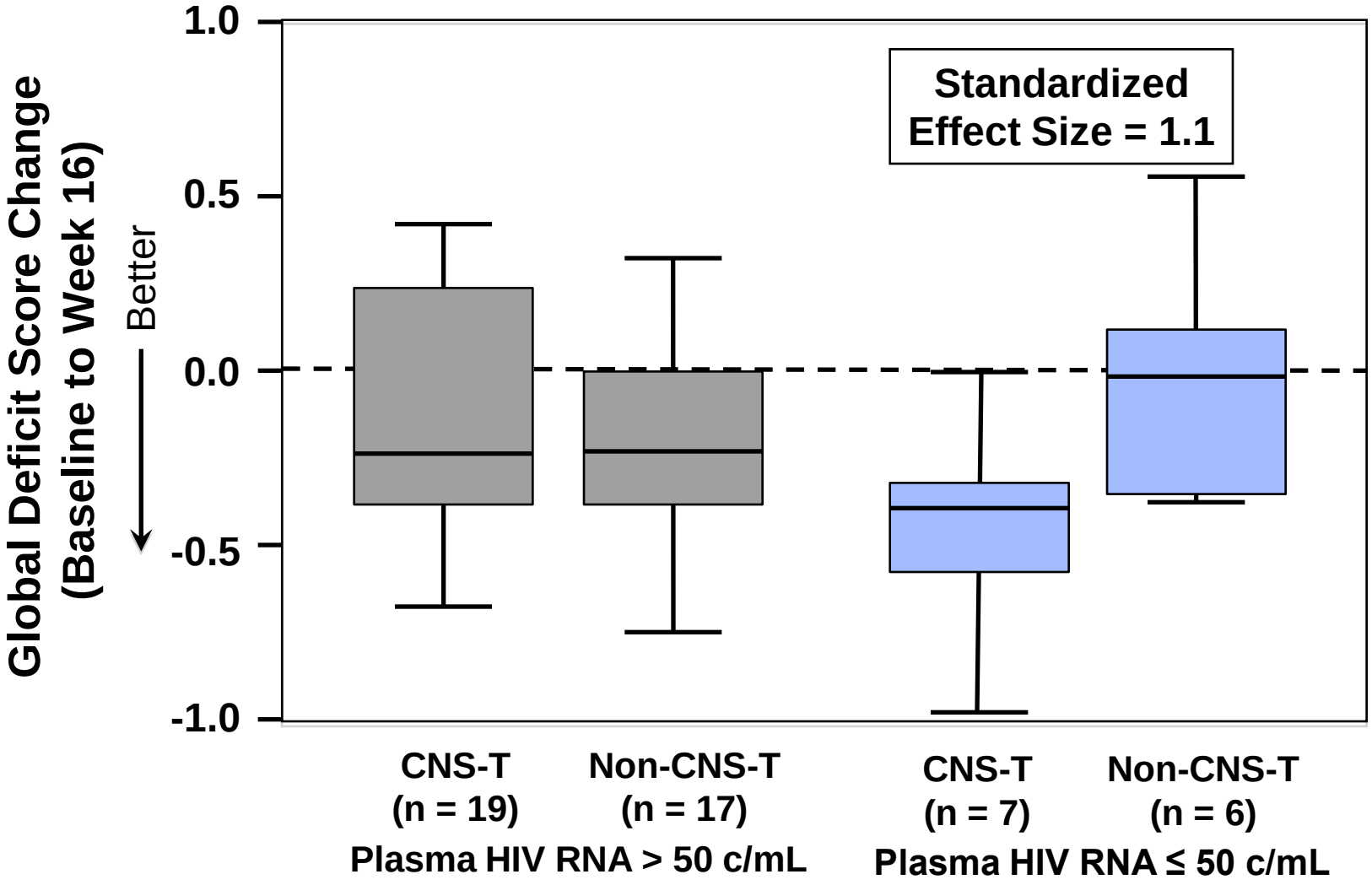
Ellis et al, 20th CROI, 2013, Abstract 20

The Primary Outcome Did Not Differ At Week 16

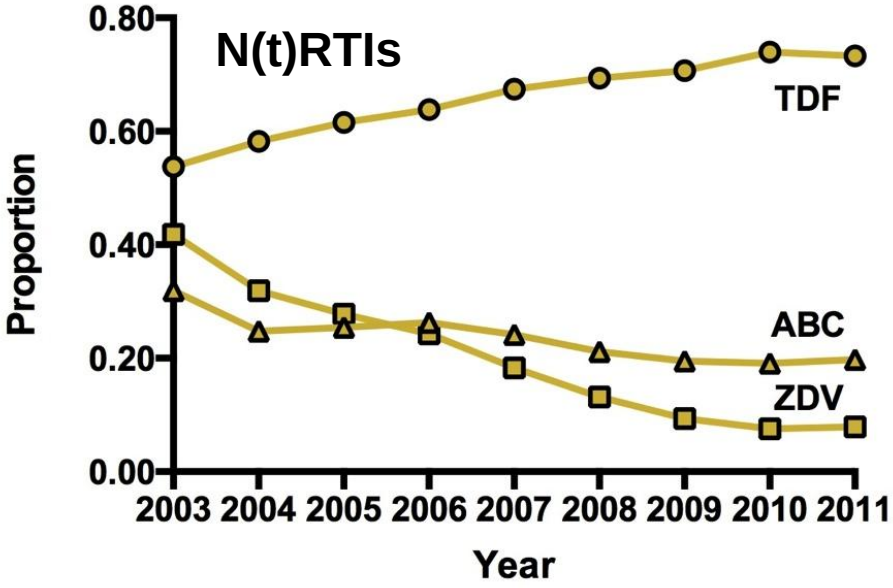
	CNS-T (N = 26)	Non-CNS-T (N = 23)	p
Adjusted GDS change (mean, SD)	-0.14 (0.54)	-0.07 (0.43)	> 0.20
Plasma VL < 50 c/mL (%)	54%	82%	**0.06**
CSF VL < 50 c/mL (%)	68%	87%	0.17
Change in CD4+ T-cells (mean, SD)	+41 (104)	+55 (154)	0.33

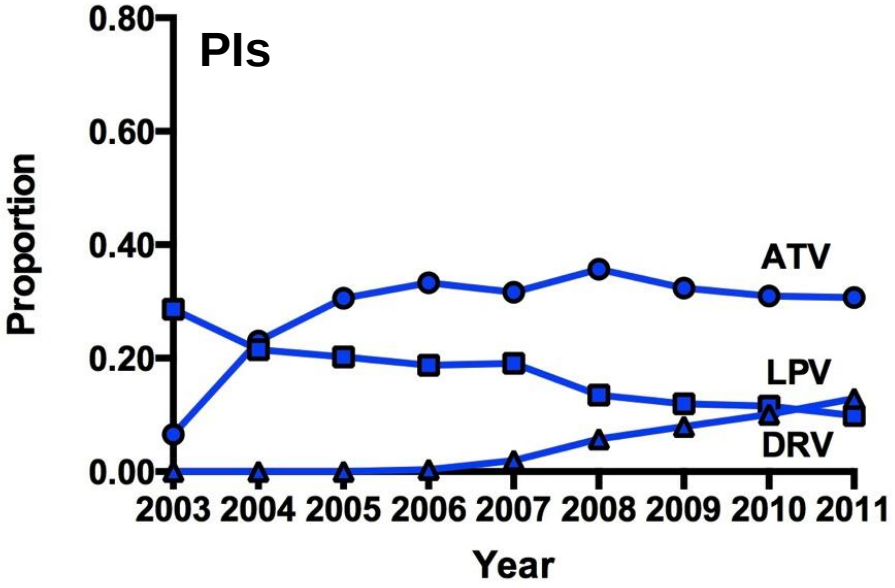
Ellis et al, 20th CROI, 2013, Abstract 20

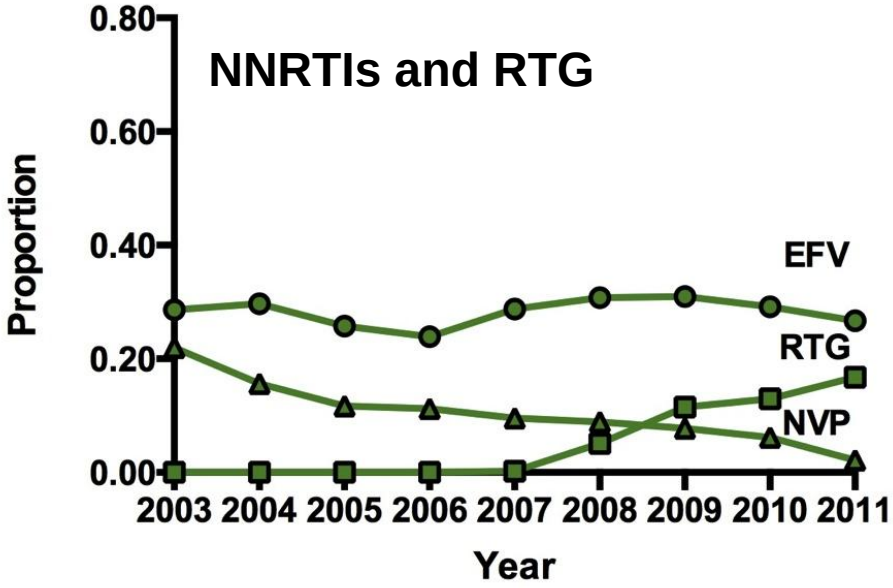
In a Planned Secondary Analysis, Those Who Enrolled with Suppressed HIV RNA May Have Benefitted from CNS-T ART



ART Use Continues to Evolve



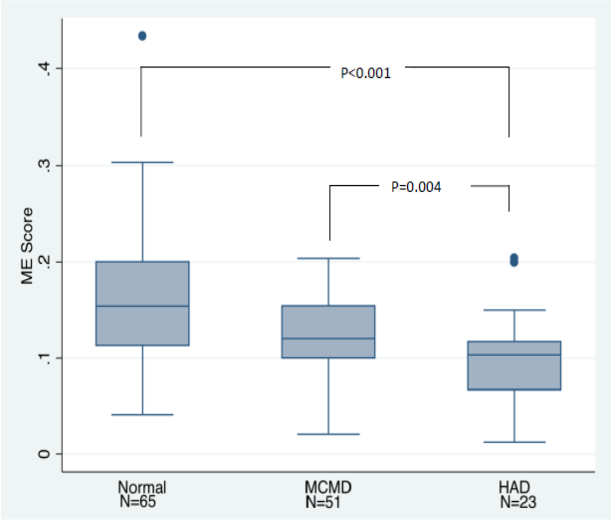




CHARTER
Unpublished Data

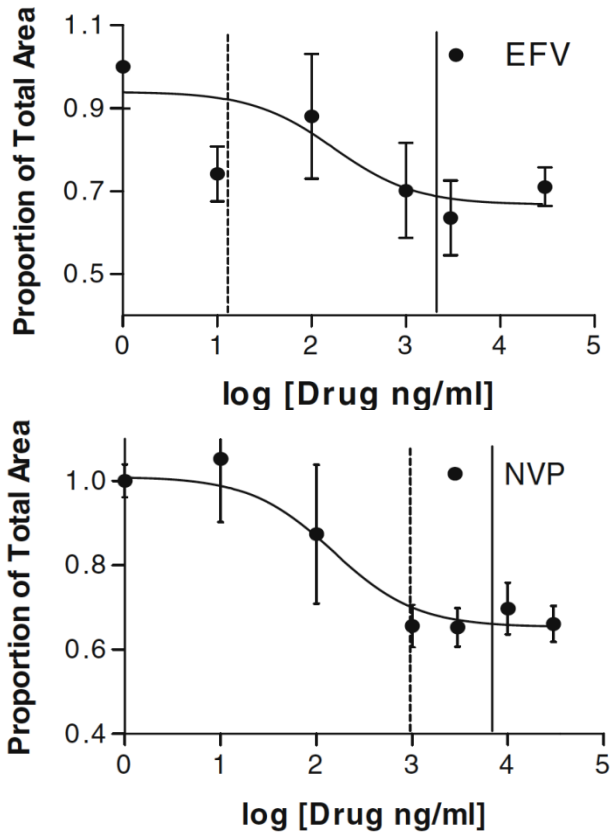
Several Other Characteristics May Influence Neurocognitive Functioning

Monocyte Efficacy



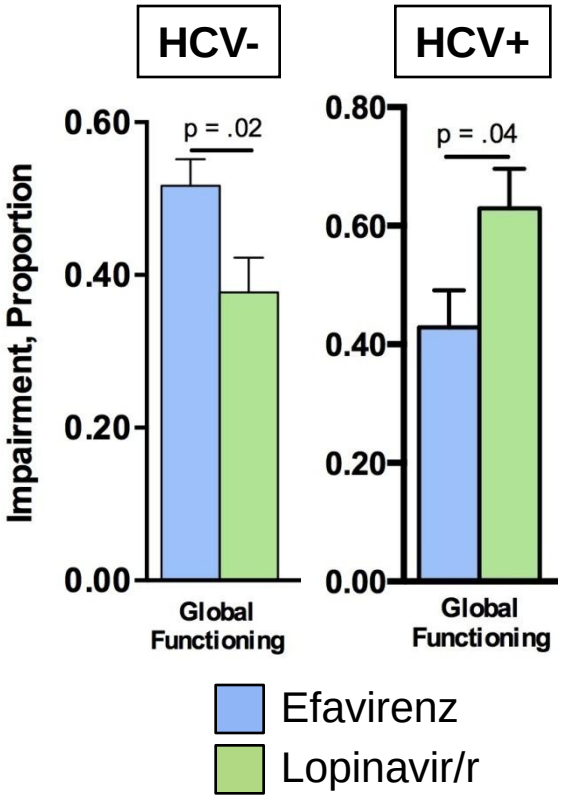
Shikuma et al, Antiviral Therapy 2012, 17: 1233-42

Neuronal Toxicity



Robertson et al, J Neurovirol 2012, 18: 388-299

HCV Co-infection



Letendre et al, 20th CROI, 2013, Abstract 407

Mind Exchange Guidance Regarding ART

- No evidence supports initiation of therapy with better CNS-penetrating regimens in **neurocognitively normal patients** (CEBM 5; GOR D)
- In the treatment of **existing neurocognitive impairment**, better neurocognitive performance has generally been observed in patients receiving higher CPE cART regimens (CEBM 2b)
  - Evidence base is limited and some of the data are contradictory regarding the potential benefits of CPE cART (CEBM 2b)

Mind Exchange Working Group, Clin Infect Dis. 2013; 56(7):1004-17

Clinical Infectious Diseases

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

Kenneth H. Mayer, Section Editor

The Mind Exchange Working Group

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Clin Infect Dis. (2013) 56 (7): 1004-1017.
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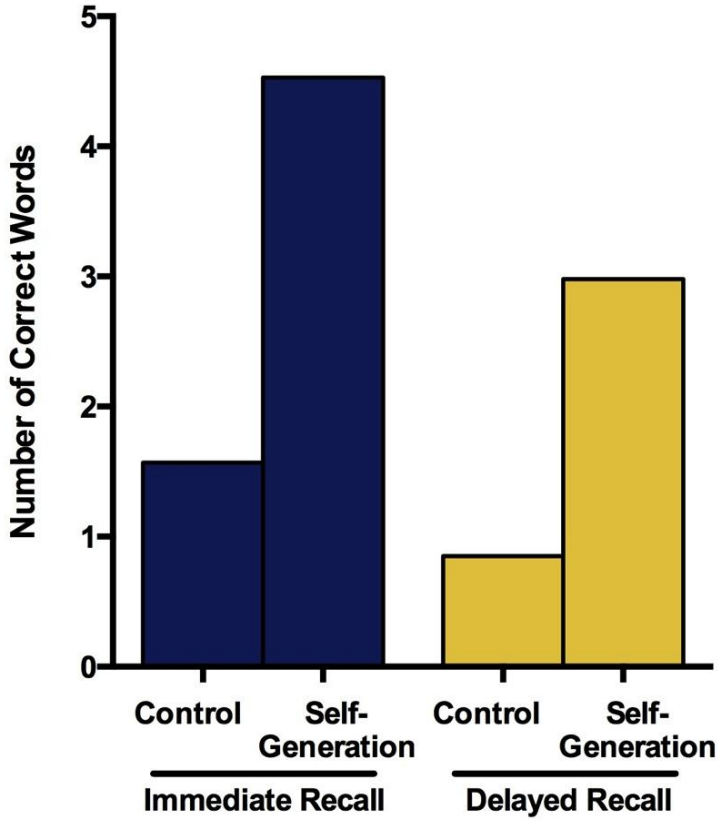
» Abstract ***Free***
Full Text (HTML)
Full Text (PDF)
Supplementary Data

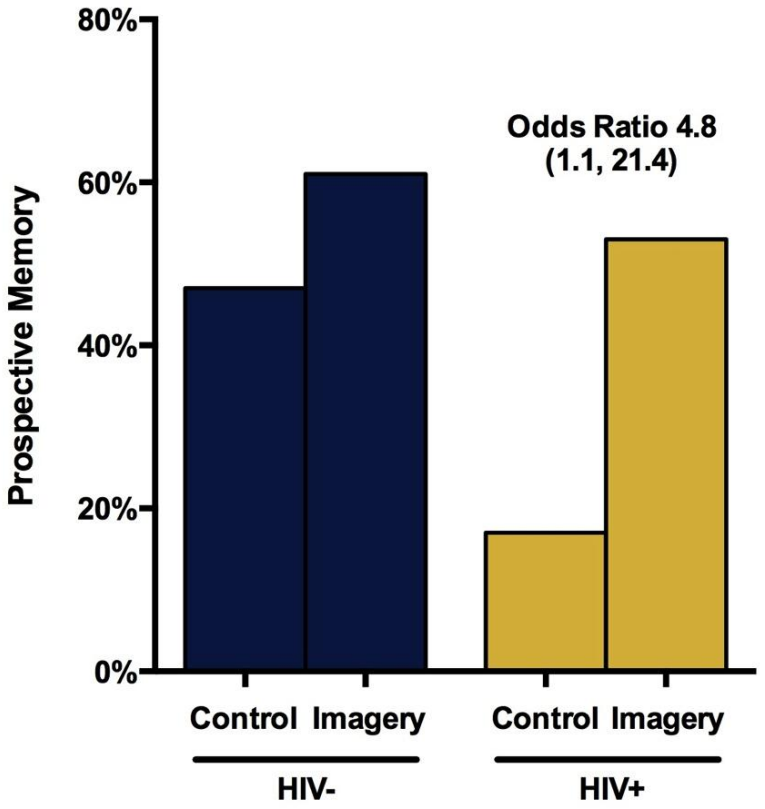
Even if Some Drugs Are More Safe and Effective in the CNS than Others,
Treatment Decisions Should Not be Made Without Considering Other Conditions Affecting the Patient

When Treating the CNS,
Focus First on Conditions that
Have Well Defined Treatments

Cognitive Rehabilitation for HAND

HIV-associated neurocognitive deficits can be improved using cognitive rehabilitation techniques such as self-generation, cueing, and strategic visualization/imagery





Weber et al., J Int Neuropsychol Soc. 2012 Jan;18(1):128-33
Weber et al., Neuropsychol Rev 2013, DOI 10.1007/s11065-013-9225-6

Summary & Conclusions

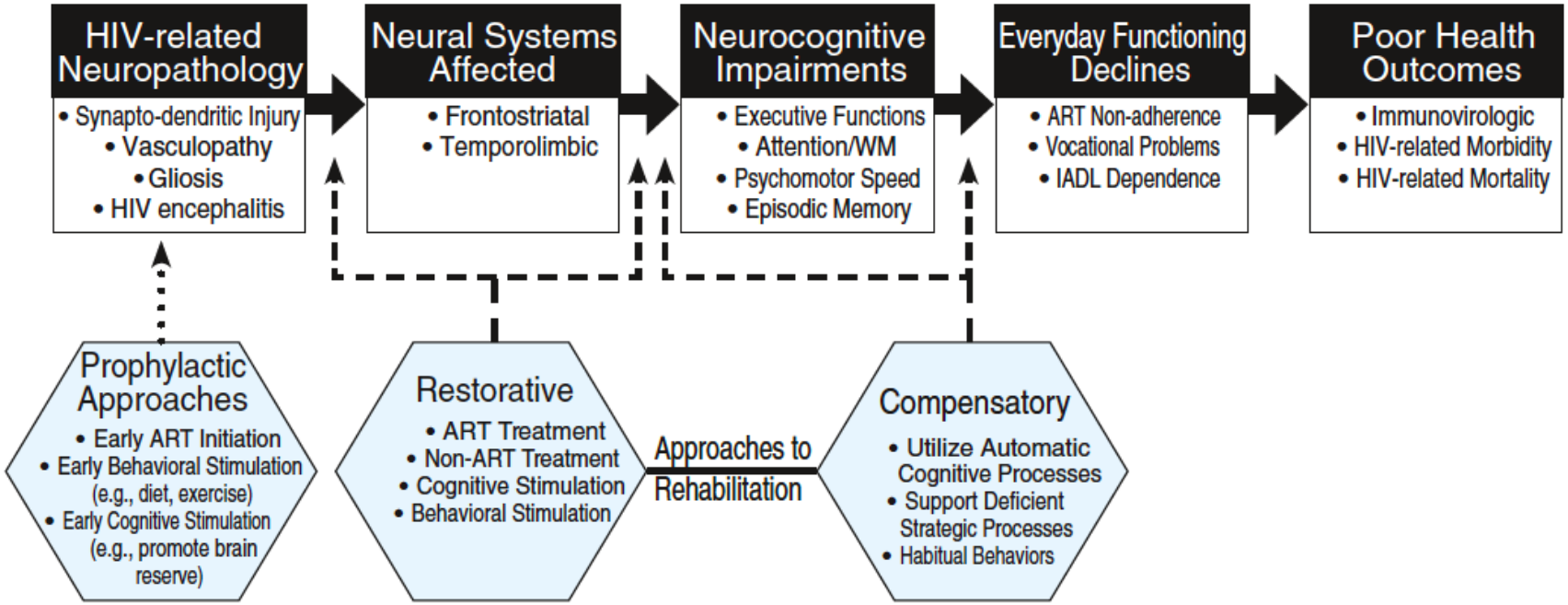
- **Neurocognitive impairment is common in people with HIV but not all neurocognitive impairment is due to HIV disease**
- **Screening tools for neurocognitive impairment are available but confirmatory assessments are not available in all clinics**
  - Self-report of symptoms alone may underestimate prevalence
  - Do not change ART based solely on screening results
  - Diagnose and treat what you can
- **ART that has better CNS distribution might better treat neurocognitive impairment due to HIV disease**
  - Supportive observational and non-randomized interventional data
  - Inconclusive randomized clinical trial: Benefit may be greatest in people who have already achieved viral suppression
  - In addition to drug distribution, neurotoxicity and monocyte activity may be important to consider

Summary & Conclusions

- **Further strengthen efforts to…**
  - Identify people earlier in disease (reduce late presenters)
  - Initiate therapy earlier in disease
- **Clinical management of CNS complications of HIV disease requires a multifaceted approach**
  - More guidance is available to assist clinicians than in the past
  - Test and treat…for neurocognitive impairment
  - Provide social and medical support
  - Monitor for worsening disease

Cognitive Neurorehabilitation of HIV-associated Neurocognitive Disorders: A Qualitative Review and Call to Action

Erica Weber • Kaitlin Blackstone • Steven Paul Woods



Weber et al., Neuropsychol Rev 2013, DOI 10.1007/s11065-013-9225-6

- When you’re a hammer, everything looks like a nail…
- But sometimes a nail is a nail

Choosing Not to Screen for Neurocognitive Impairment is Like Throwing the Baby Out With the Bathwater

<u>Reasons to screen for neurocognitive impairment</u>

- HAND is clinically important
- Screening does not require substantial resources
- No randomized trial has demonstrated a safe and effective therapy for HAND

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

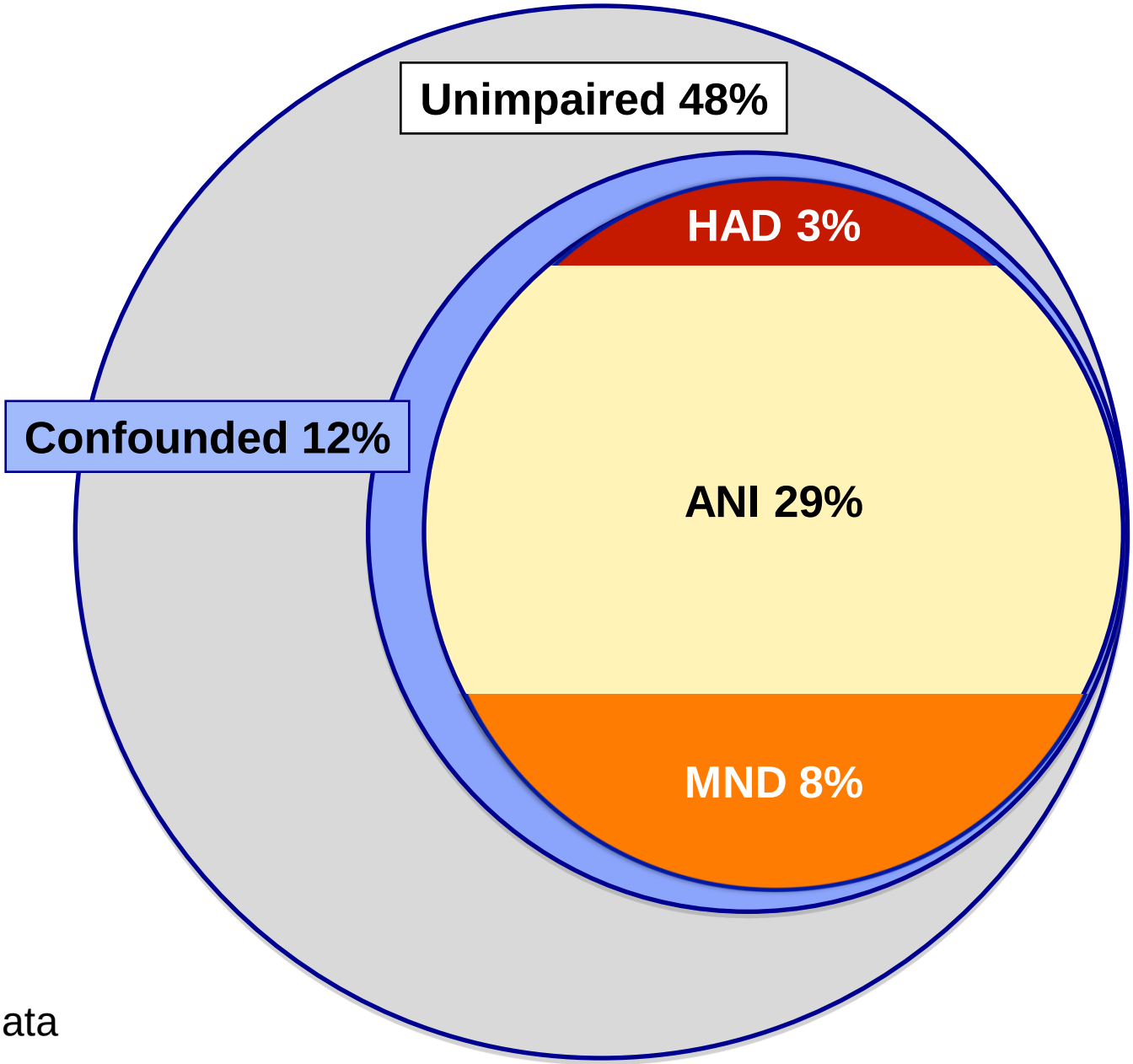
The Mind Exchange Working Group

Many practical clinical questions regarding the management of human immunodeficiency virus (HIV)–associated neurocognitive disorder (HAND) remain unanswered. We sought to identify and develop practical answers to key clinical questions in HAND management. Sixty-six specialists from 30 countries provided input into the program, which was overseen by a steering committee. Fourteen questions were rated as being of greatest clinical importance. Answers were drafted by an expert group based on a comprehensive literature review. Sixty-three experts convened to determine consensus and level of evidence for the answers. Consensus was reached on all answers. For instance, good practice suggests that all HIV patients should be screened for HAND early in disease using standardized tools. Follow-up frequency depends on whether HAND is already present or whether clinical data suggest risk for developing HAND. Worsening neurocognitive impairment may trigger consideration of antiretroviral modification when other causes have been excluded. The Mind Exchange program provides practical guidance in the diagnosis, monitoring, and treatment of HAND.

Keywords. AIDS dementia complex; HIV-associated dementia (HAD); HIV-associated neurocognitive disorder (HAND); HIV encephalopathy; neurocognitive impairment.

The Mind Exchange Working Group
Clinical Infectious Diseases 2013, PMID: 23175555

Not all people with HIV will develop NCI

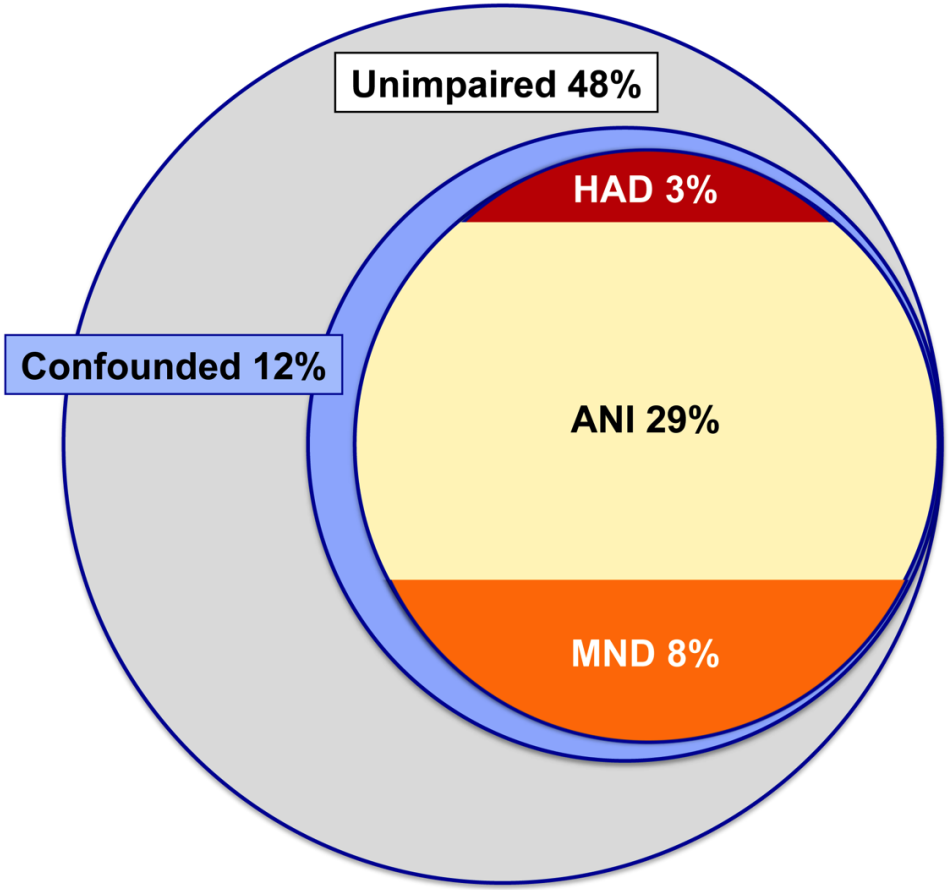


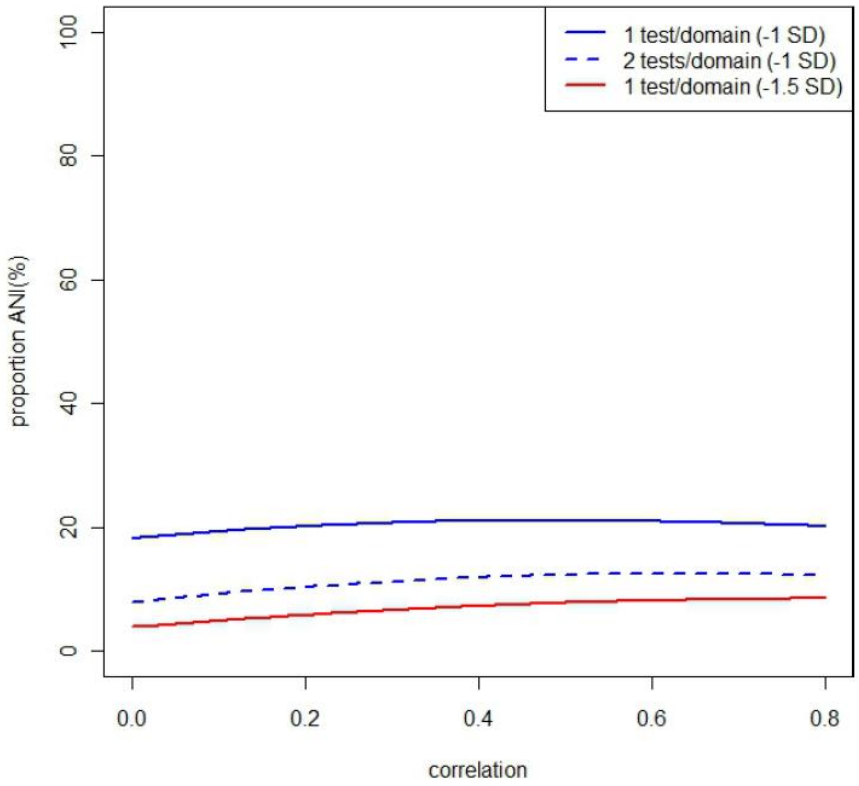
CHARTER Baseline Data

Do the Benefits of Screening for Neurocognitive Impairment in People with HIV Outweigh the Risks?

- Argument: You should not screen for MND because you might find ANI
  - This is akin to saying, “Don’t investigate chest pain because sometimes it’s not due to coronary disease”
- Argument: Telling people that they have ANI is dangerous and unethical
  - This is akin to saying, “Telling people that their chest pain is due to esophageal spasm is dangerous and unethical”

Neurocognitive Impairment is Common in Most But Not All Reported Cohorts





Heaton, et al. Neurology 2010, 75:2087-96

Gisslén, et al. BMC ID 2011, 11:356

Goals of Mind Exchange program

- Identify and address the most important clinical questions relating to the management of HAND
- Use robust methods to reach expert consensus on current best practice in screening, diagnosis, monitoring, treatment and prevention of HAND
- Facilitate maximum exchange of the outputs of the programme, to ensure that best practice in managing CNS issues related to HIV, specifically HAND, is understood and implemented in the HIV community
- Identify areas that may require additional research

Oxford Centre for Evidence Based Medicine

Level of evidence (March 2009)

Level 1A	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	1a SR (with homogeneity*)of RCTs SR (withhomogeneity*) of inception cohort studies; CDR† validated in different populations SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres SR (with homogeneity*) of prospective cohort studies SR (with homogeneity*) of Level 1 economic studies
Level 1B	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual RCT (with narrow Confidence Interval‡) Individual inception cohort study with > 80% follow-up; CDR† validated in single population Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre Prospective cohort study with good follow-up**** Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level	Therapy/Prevention, Aetiology/Harm Prognosis	Individual cohort study (including low quality RCT; e.g., <80% follow-up) Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or
Level 5	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"
Level 3A	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of case-control studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b And better studies
Level 3B	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual Case-Control Study Non-consecutive study; or without consistently applied reference standards Non-consecutive cohort study, or very limited population Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses Incorporating clinically sensible variations.
Level 4	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Case-series (and poor quality cohort and case control studies§§) Case-series (and poor quality prognostic cohort studies***) Case-control study, poor or nonindependent reference standard Case-series or superseded reference standards Analysis with no sensitivity analysis
Level 5	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

HNRP HIV NEUROBEHAVIORAL RESEARCH PROGRAM

http://www.cebm.net/index.aspx?o=1025

Grades of recommendation

Grade	Definition
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

University of Oxford (UK) Centre for Evidence Based Medicine
Further details available from http://www.cebm.net/index.aspx?o=1025

When should CSF analysis be performed in the management of HAND?

-Paola Cinque & Jacques Gasnault

- CSF analysis should be performed in **patients who have neurological symptoms or signs**, ideally at the first presentation (CEBM 2a; GOR B)
- **In untreated patients**, CSF analysis *would be better* performed just **before initiation of ART**. **In treated patients**, CSF analysis *would be better* performed just **before a change in ART** (CEBM 2b; GOR C)
- Since almost all patients will have clearance of HIV RNA in CSF during ART, there is **no general indication to repeat CSF analysis during follow-up** (CEBM 2b; GOR B)
  - Possible exceptions include patients whose ART was changed for CSF viral escape or who do not neurologically improve

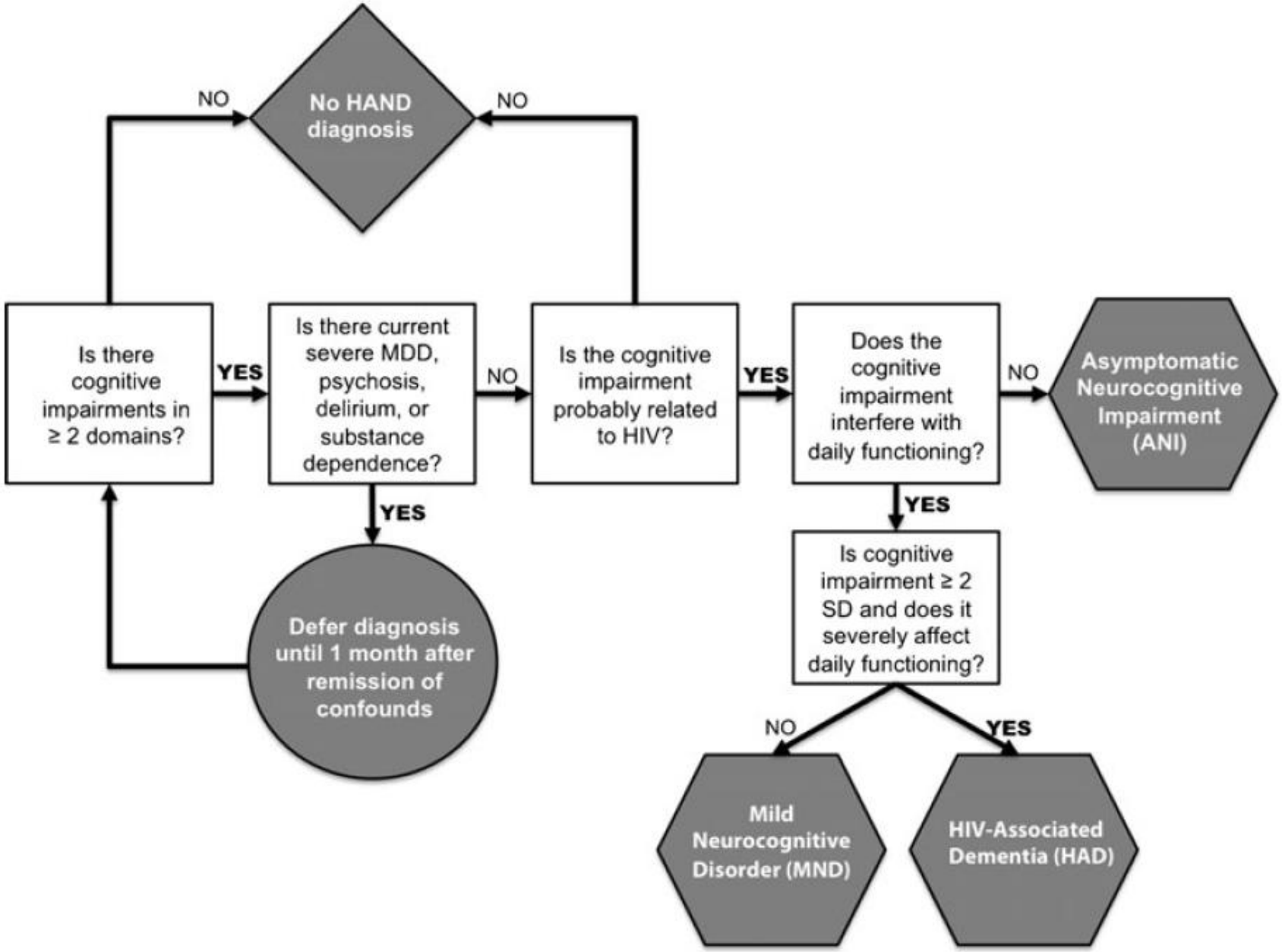
Clinical Infectious Diseases Submission Submitted June 2012

What interventions should be considered in treated patients with persistent or worsening HAND and CSF viral load <50 copies/mL?

-Daniel Podzamczer & Christian Eggers

- **Consider other causes** of NCI, such as non-infectious types of dementia (e.g., vascular dementia), major depressive disorder, current drug use, and infections (CEMB 5; GOR D)
  - Diagnostic measures may include brain MRI, lumbar puncture and psychiatric evaluation
- Identify whether HIV RNA are detectable or undetectable
- **If HIV RNA is detectable in plasma** but not CSF, **adapt the regimen** according to resistance profiles and possibly the CPE score (CEBM 2b; GOR C)
- **If HIV RNA is undetectable in plasma and CSF**, the same considerations apply but the evidence is less strong (CEBM 2c; GOR C)

Clinical Infectious Diseases Submission Submitted June 2012


No HAND diagnosis
NO
NO
Is there cognitive impairments in ≥ 2 domains?
YES
Is there current severe MDD, psychosis, delirium, or substance dependence?
NO
Is the cognitive impairment probably related to HIV?
YES
Does the cognitive impairment interfere with daily functioning?
NO
Asymptomatic Neurocognitive Impairment (ANI)
YES
YES
Defer diagnosis until 1 month after remission of confounds
Is cognitive impairment ≥ 2 SD and does it severely affect daily functioning?
NO
YES
Mild Neurocognitive Disorder (MND)
HIV-Associated Dementia (HAD)

What is the nature of the legacy effect?

- Neuroadaptation
- Dysregulated immune and glial responses

Interim Summary

- **ART characteristics are associated with surrogate markers of HIV disease in the CNS**
  - HIV RNA levels in CSF
  - Biomarkers of immune/glial activation in CSF
- **Associations are present in people taking suppressive ART**
- **ART characteristics are also associated with CSF viral escape**
  - The clinical significance of CVE is unknown

How Can We Correctly Translate These Findings to Clinical Practice?

1. **ART portfolio and practice continues to grow and diversify**
   - More potent and less toxic drugs are increasingly used
   - CNS benefits of HIV suppression and immune recovery alone are likely substantial
   - How does toxicity outside the CNS affect the CNS?
2. **Treatment guidelines change more quickly than the field can perform CNS clinical trials**
   - Patients are starting ART at higher CD4+ T-cell counts
3. **Surrogate biomarkers are critically important in making clinical trials of ART cost-effective**
   - Unmet need in CNS clinical trials

Interim Summary

- **Analyses with larger sample sizes and more thorough assessments typically found beneficial associations between estimated drug distribution and neurocognitive functioning**
- **Improving estimated drug distribution into the CNS might be most beneficial in impaired patients who are already taking suppressive ART**
  - InMIND clinical trial in the ACTG (A5324)
- **Factors other than drug distribution may influence the relationship with neurocognitive functioning**
  - CPE values are based largely on CSF drug concentrations, which may not reflect concentrations in brain tissue