

The Mind Matters: Current Evidence on HIV, and the Brain

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HIV DISEASE

Neuromedical

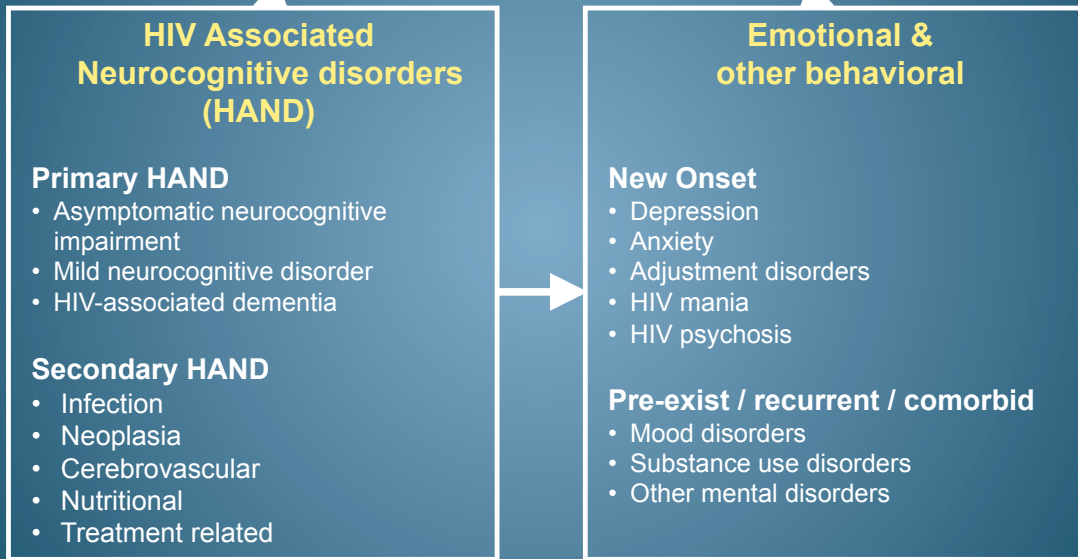
Neurobehavioral



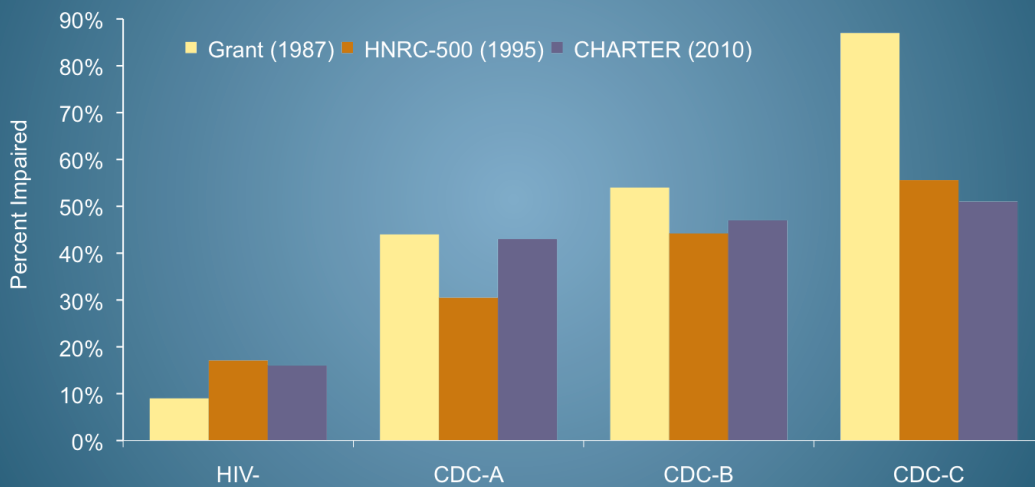
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HIV Neurobehavioral Disturbances



Combination antivirals prolong survival but NeuroAIDS remains prevalent

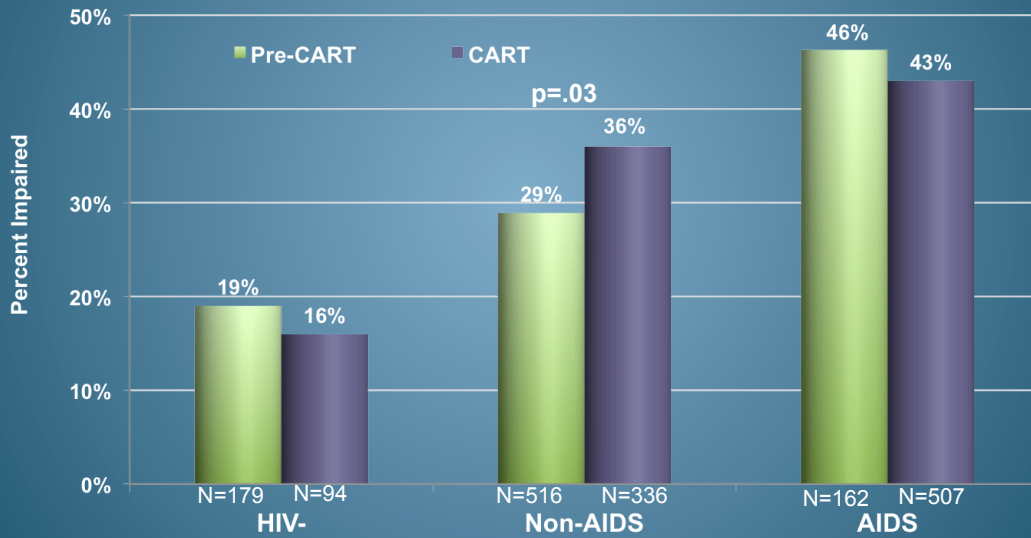


Grant I, et al. Ann Intern Med 1987; 107(6):828-36
 Heaton RK, et al. J Int Neuropsychol Soc 1995;1(3):231-51
 Heaton RK, et al. (2010). Neurology, 75, 2087-2096



HAND in Pre-CART and CART Eras by AIDS Status

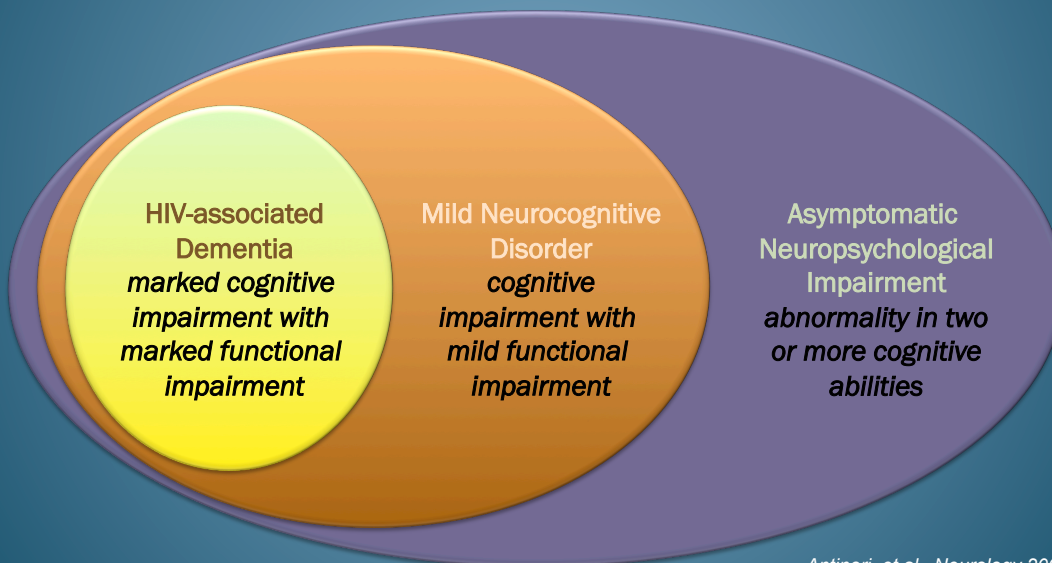
Heaton, et al, (2011) *Journal of Neurovirology*, 17(1), 3-16.



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HIV Associated Neurocognitive Disorders (HAND): Frascati Criteria



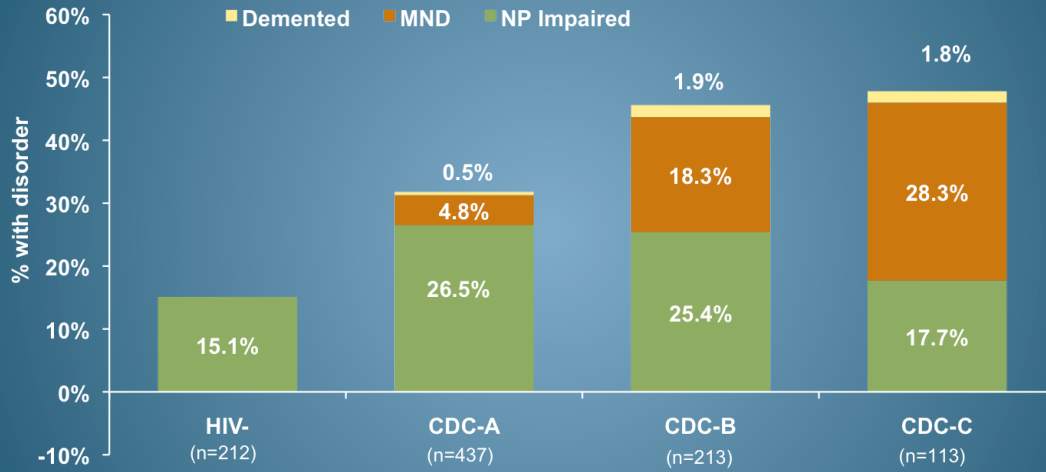
Antinori, et al., *Neurology* 2007



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Prevalence of HAND by stage of HIV disease



NP = neuropsychologically impaired;
MND = mild neurocognitive disease

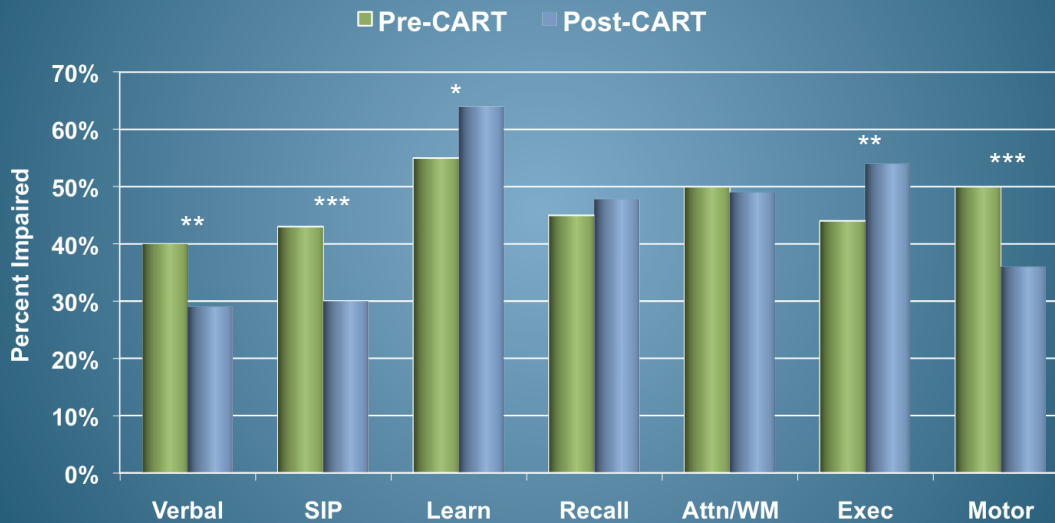
Heaton RK, et al. J Int Neuropsychol Soc 1995;1(3):231-51



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NC Impairment by Domain in HIV+ Samples from Pre-CART and Post-CART Eras (NCI only)



* p<.05; ** p<.01; ***p<.001

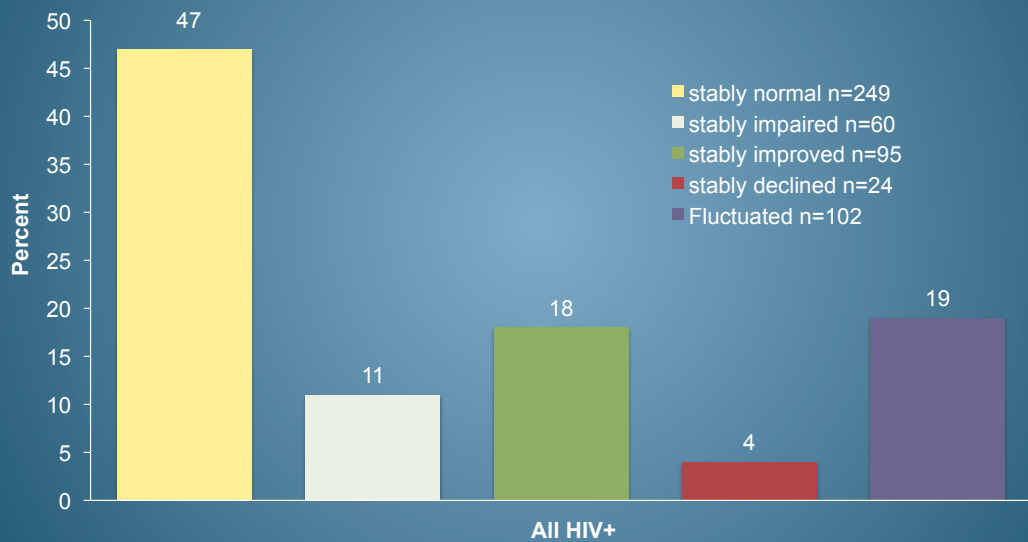
Heaton, et al. (2011) *Journal of Neurovirology*, 17(1), 3-16.



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Neuropsychological course for HIV neurocognitive states



N = 534; HNRC

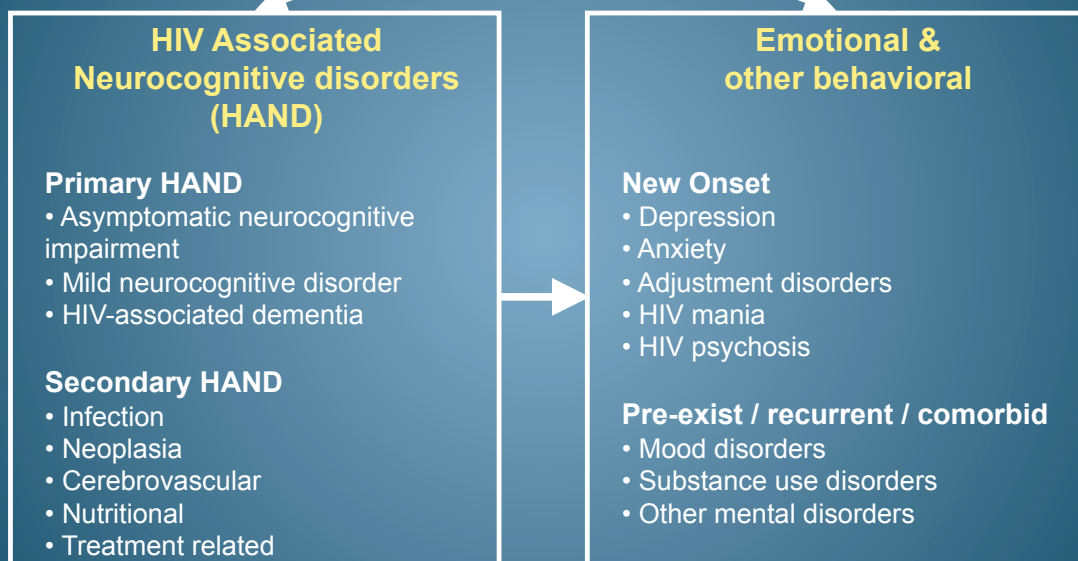
Antinori A, et al. Neurology 2007;69:1789-99



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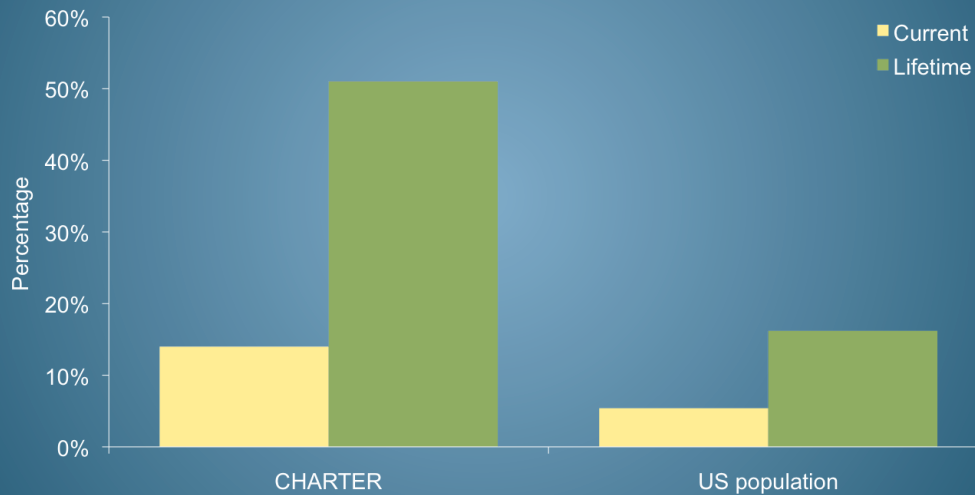
HIV neurobehavioral disturbances



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Prevalence of major depressive disorder in people with HIV



N = 1555

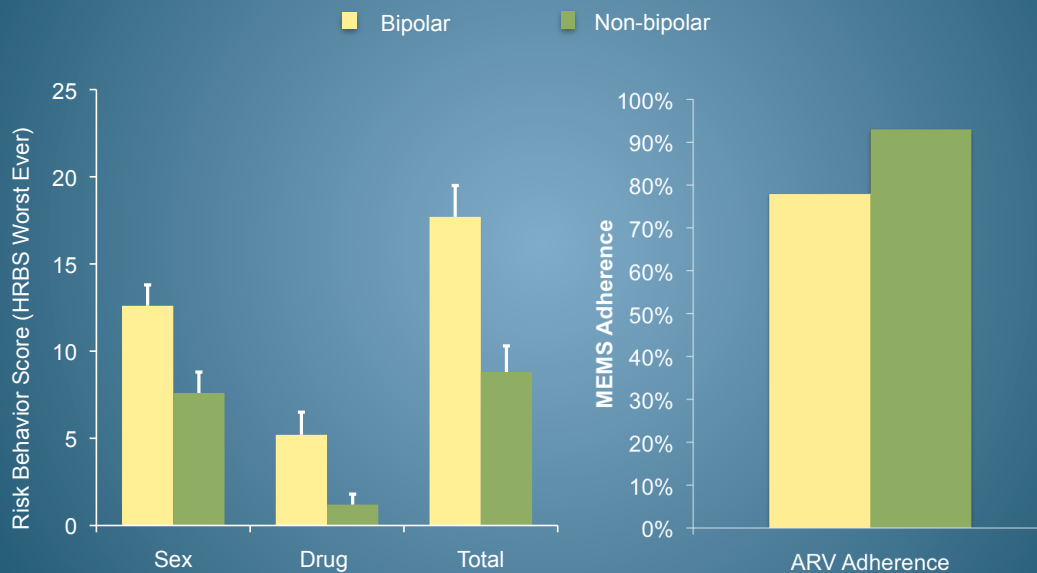
CHARTER study. Unpublished data



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More HIV risk behaviors and poorer ARV adherence in bipolar HIV infected persons



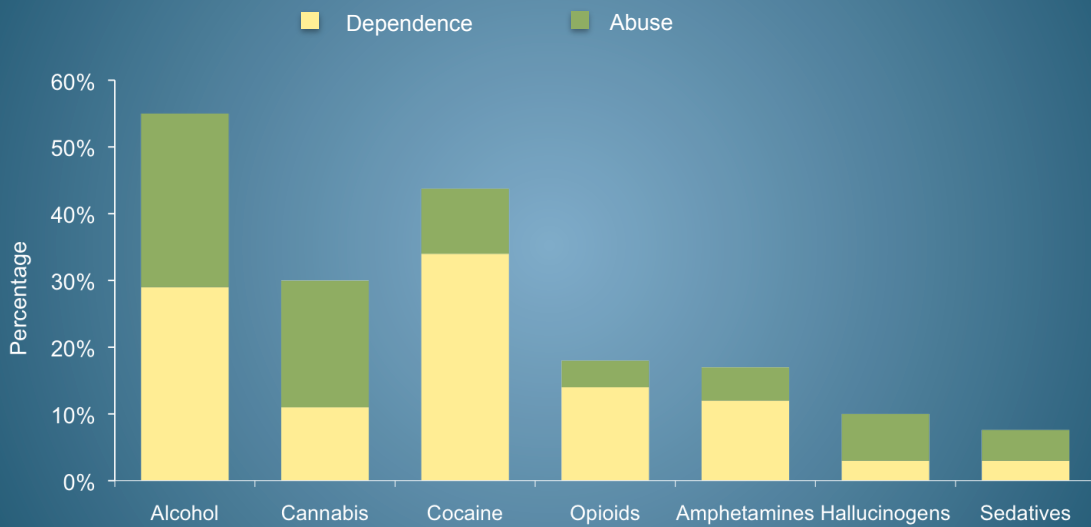
David Moore, et al., HNR Group. Unpublished data



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70% of HIV+ CHARTER participants have substance disorders



N = 1555

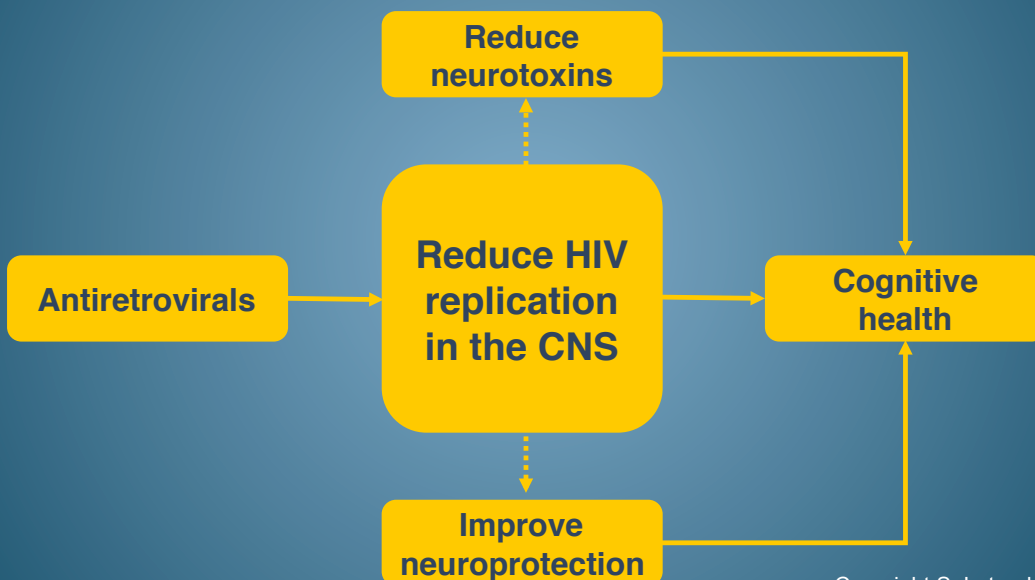
CHARTER study. Unpublished data



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Management of HAND requires consideration of multiple mechanisms



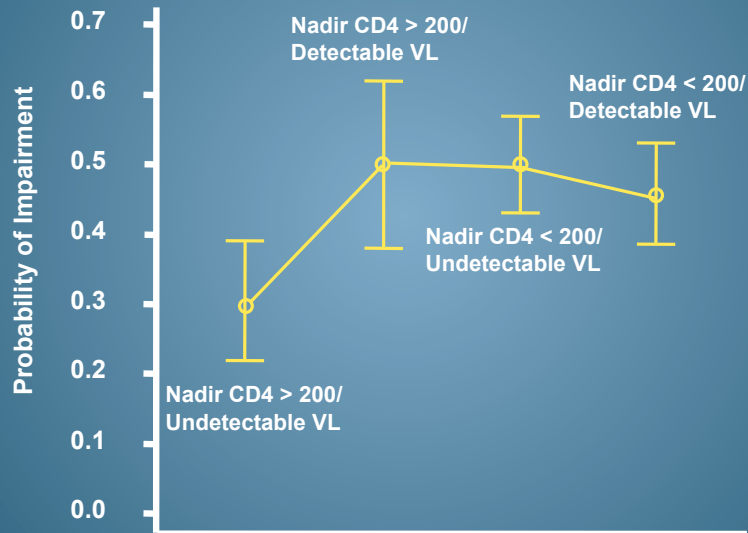
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Lower neurocognitive impairment risk when immunosuppression is avoided and virologic control is good



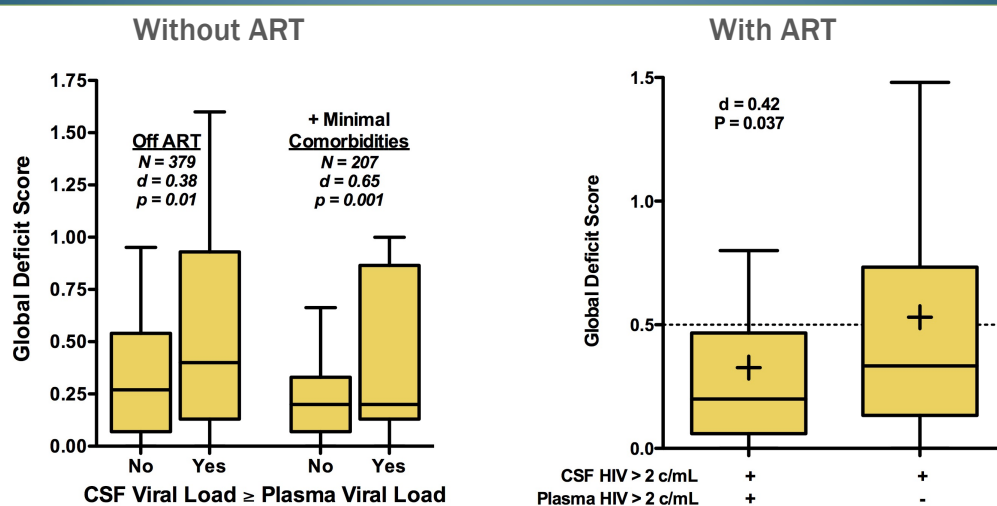
Heaton RK, et al. (2010). *Neurology*, 75, 2087-2096



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



Letendre et al, 17th CROI 2010, Abstract 172

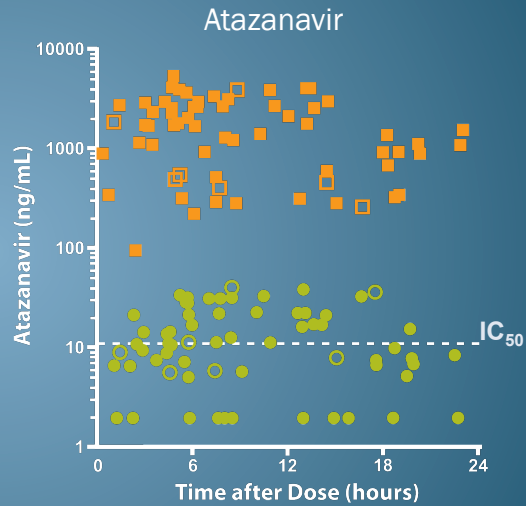
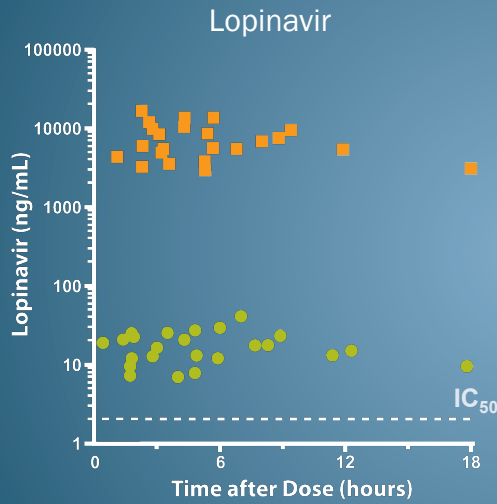
Letendre et al, 16th CROI 2009, Abstract 484b



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“Neuroeffective” ARV depends BOTH on CNS penetration AND antiviral potency



Capparelli EV, et al. AIDS 2005;19:949–95
Best BM, et al. AIDS 2009;23:83–7



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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		

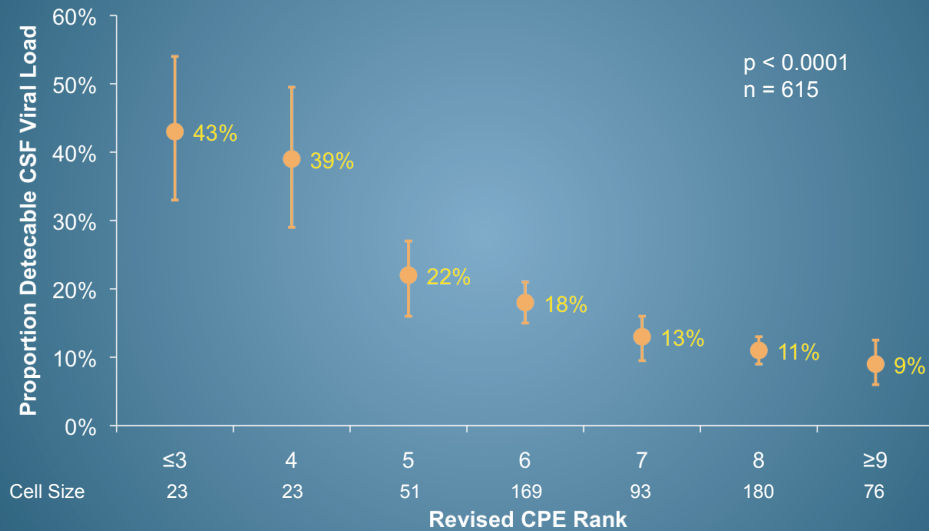
Letendre SL, et al. 17th CROI 2010, Abstract 172



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Estimation of penetration-effectiveness in CNS Better Penetration = Lower CSF viral loads



Letendre SL, et al. 17th CROI 2010, Abstract 172

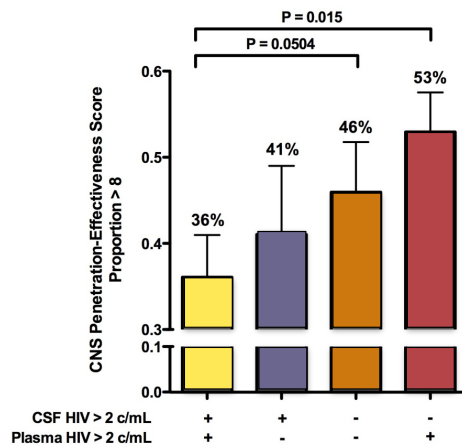


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High CPE regimens related to greater likelihood of undetectable HIV in CSF vs plasma

ART Penetration vs. Low-Level HIV



Undetectable viral loads in the CSF (HIV < 2c/mL) were noted in 46% - 53% of those receiving regimens with higher CPE (>8) scores, compared to 36% - 41% of those on lower rated CPE regimens

Letendre SL, et al. 17th CROI 2010, Abstract 172

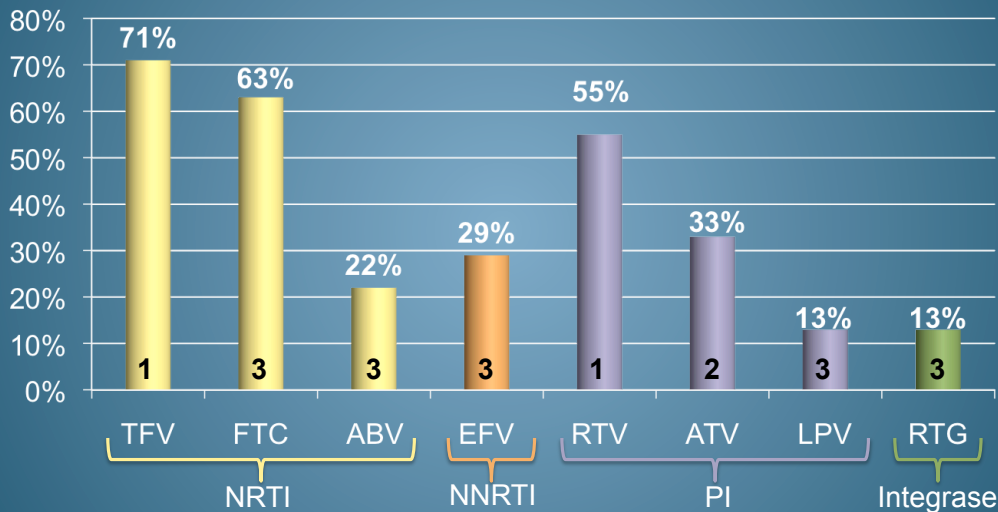


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Individual ART from CHARTER Study (10% or more taking)

CHARTER, unpublished data



Most common combo regimens: Atripla (EFV/FTC/TFV) 22%

Boosted Atazanavir (ATV/RTV) and Truvada (FTC/TFV) 18%



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CPE, CSF suppression, and NP change

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

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

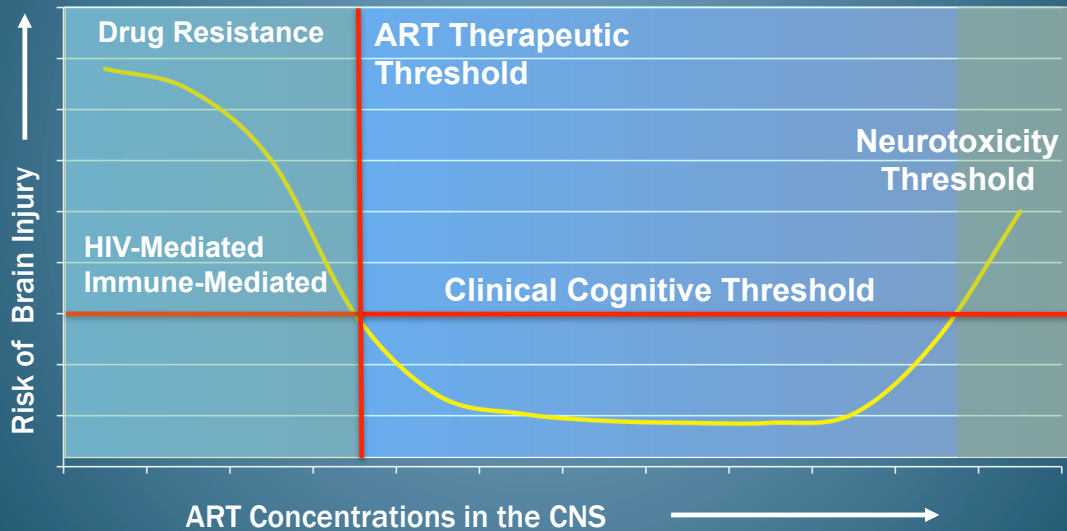


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Conceptual therapeutic window in the nervous system

Model courtesy of S. Letendre, Copyright S. Letendre



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HNRP Recommendations

- **Question** patients about cognitive symptoms and activities of daily living at routine visits and before initiating ART
 - » **Brief testing** improves the ability to correctly identify HAND
 - » **Screen for and treat other conditions** that could account for nervous system complaints (e.g. co-infections, substance use, mood disorders, vascular disease, metabolic disorders)
 - » Consider lumbar puncture and neuroimaging
- **Consider using ART with higher CPE** since accumulating data support that it better reduces HIV in CSF and leads to neurocognitive improvements
- **Continue to monitor** effectively treated patients
 - » Cognitive impairment might persist or even occur for the first time in treated individuals: drug resistance and/or drug neurotoxicity?

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Approach to antiretroviral therapy

HAND – off ART

- Initiation of ART with a more neuroeffective regimen?
 - » Most strongly supported scenario
 - » Consistent findings from observational studies

HAND – on ART

- Switching or intensifying to a more neuroeffective regimen?
 - Concept supported by existing data
 - Must consider risk of failure and toxicity when changing therapy
 - No clinical trial is yet being performed

No Hand

- Initiation of ART with a more neuroeffective regimen?
 - » Indirectly supported by existing data
 - » No clinical trial being performed
 - » Treating all patients with CNS optimized ART may not be necessary

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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) ng ART

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



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EACS Recommendations for Treatment if Neurocognitive Impairment Detected

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

Interventions if neurocognitive impairment detected:

- » If patient is not on ART:
 - Consider initiation of ART in which at least 2 drugs penetrate CNS
 - 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
 - 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



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- ...Drug Abuse
- ...Neurological Disorders and Stroke

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