

HIV in the Brain

MANAGING COMORBIDITIES
IN PATIENTS WITH HIV

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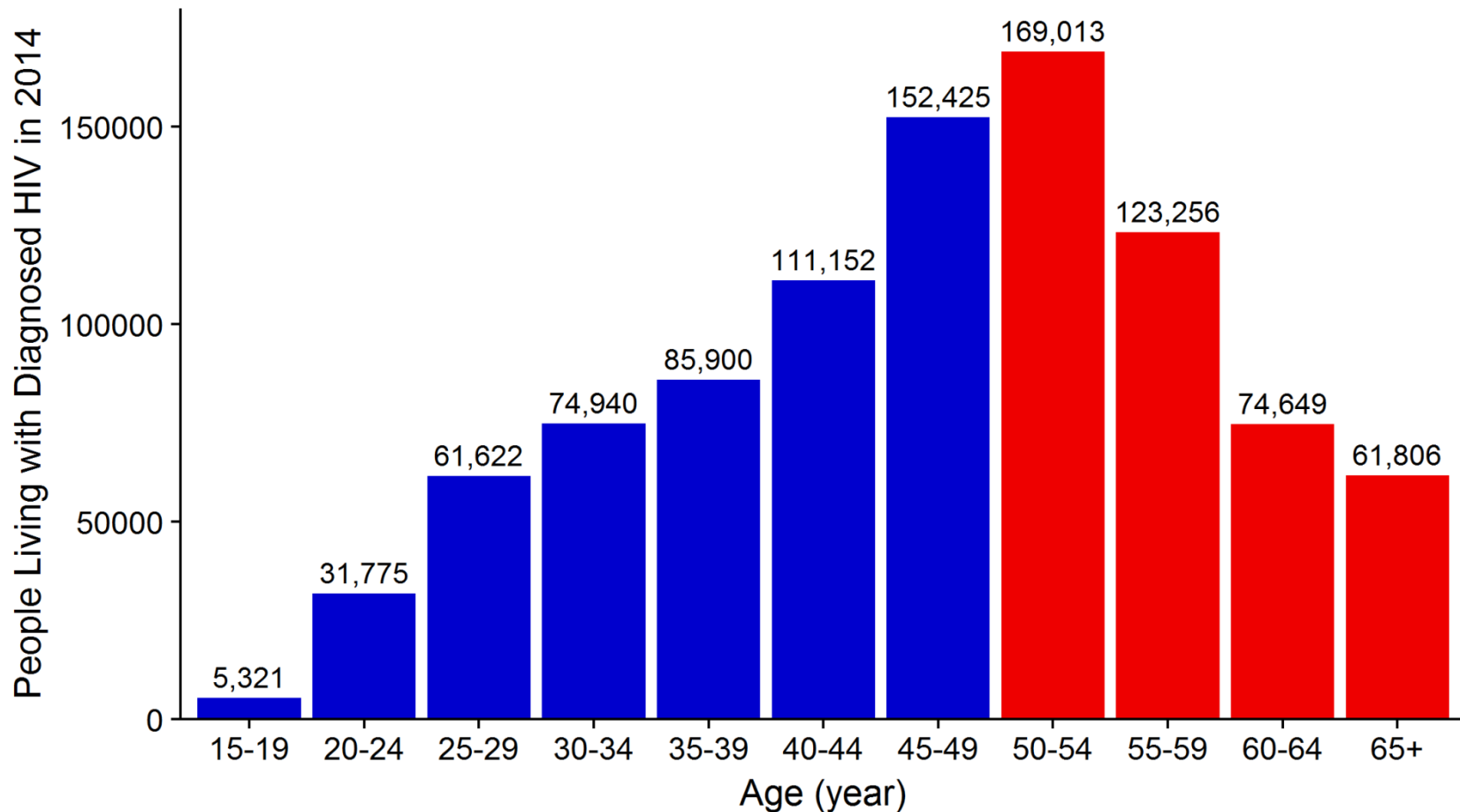
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Immunology and Virology

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Disclosure

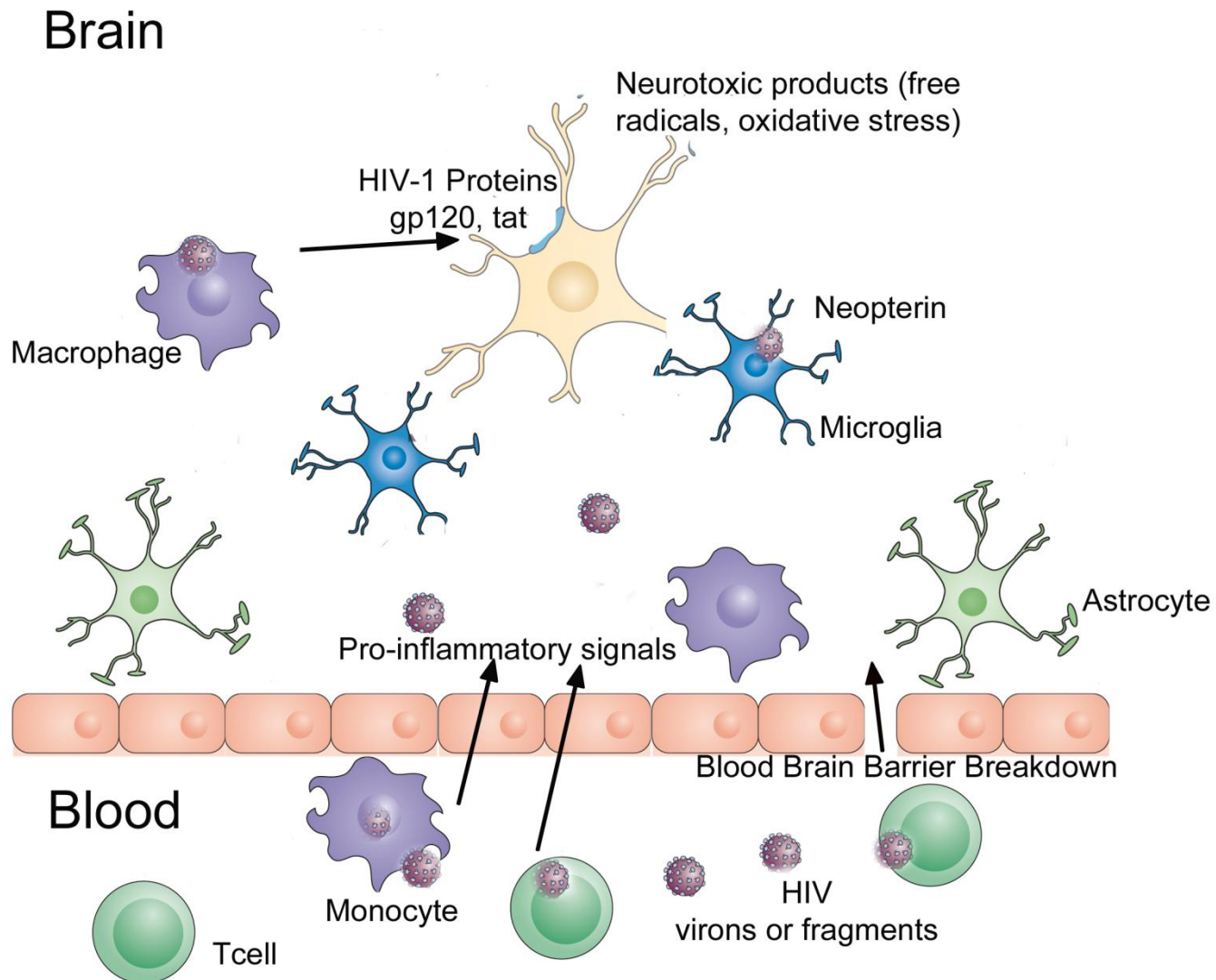
- No financial disclosures

The Majority of People Living with HIV Infection In the US Are Over Age 50 Years

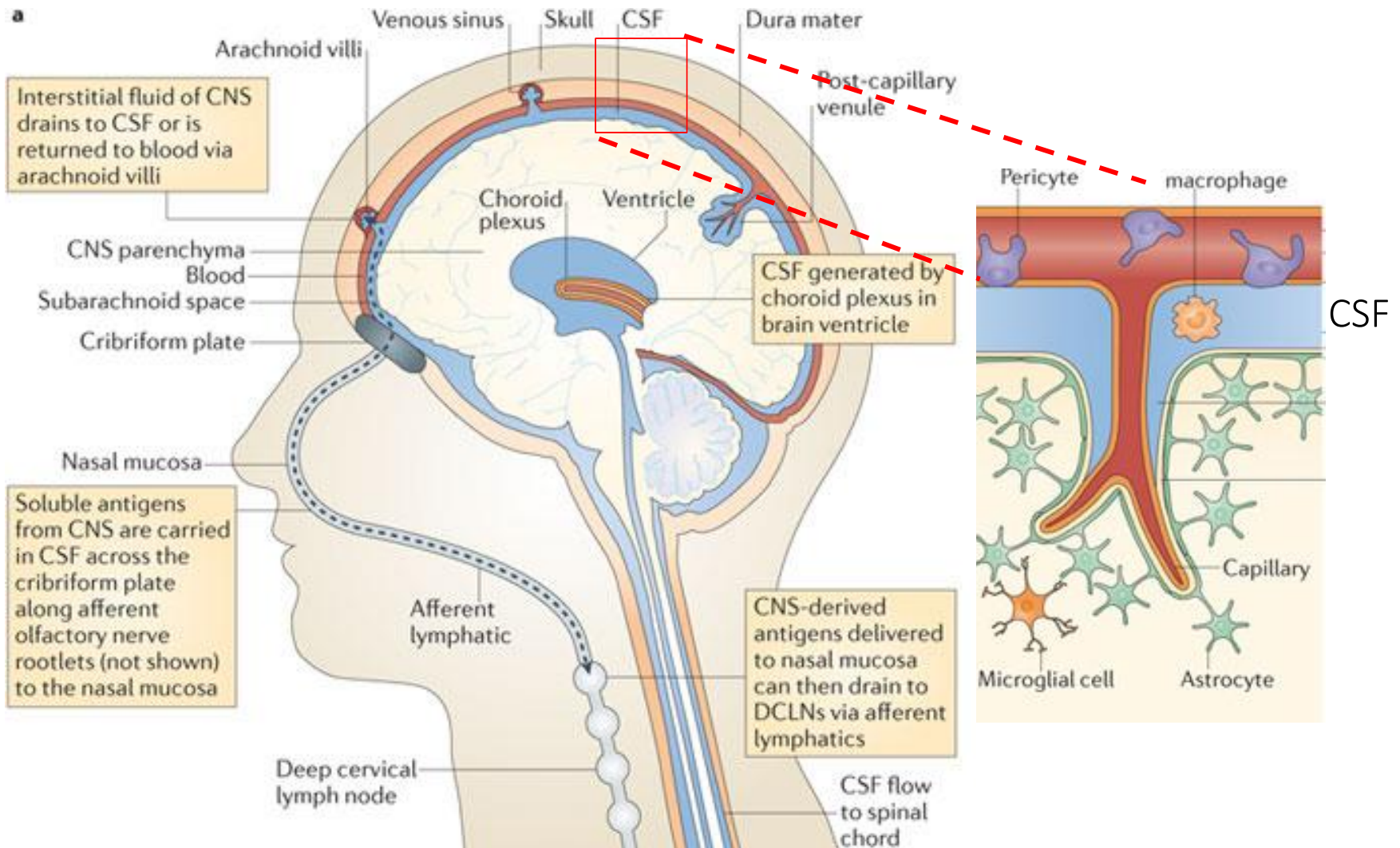


Source: Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, Sexual Transmitted Diseases and Tuberculosis Prevention, Centers for Disease Control and Prevention.

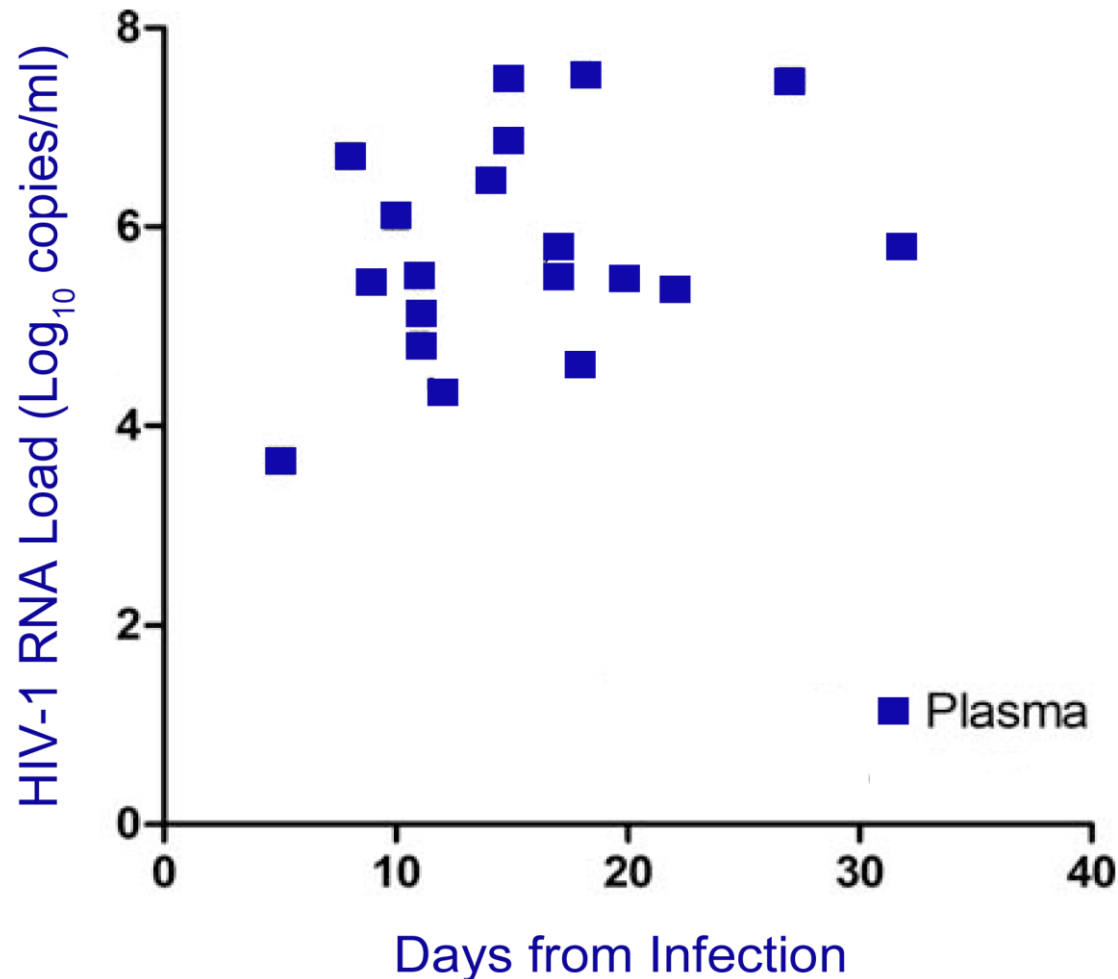
HIV Infection Entry Into CNS Prior to ARV



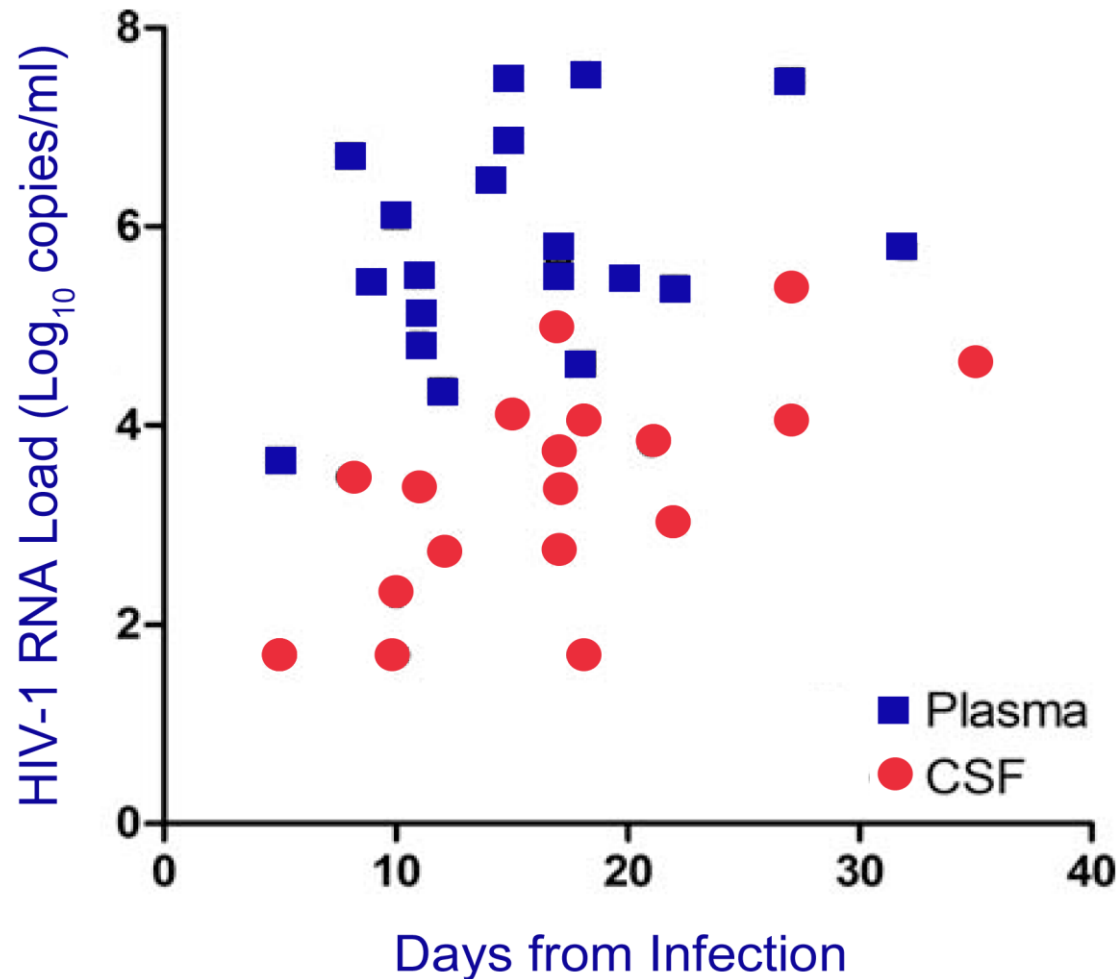
Multiple Anatomical Compartments Exist for CNS HIV Infection



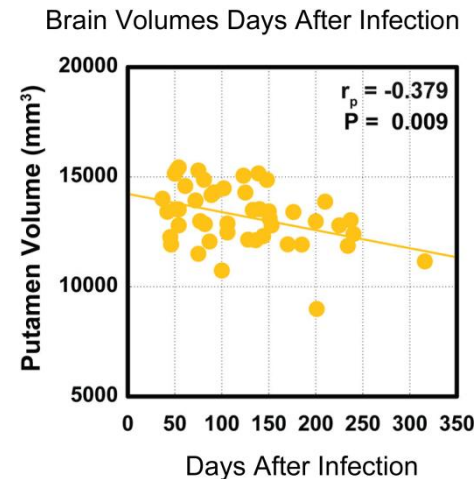
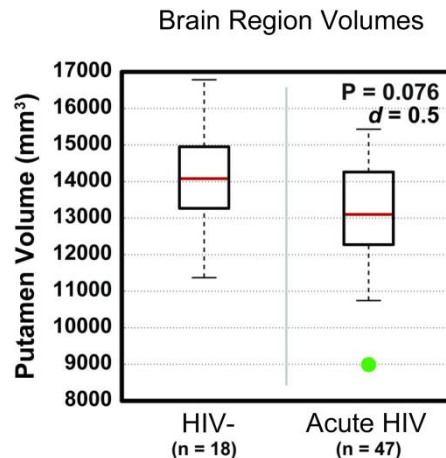
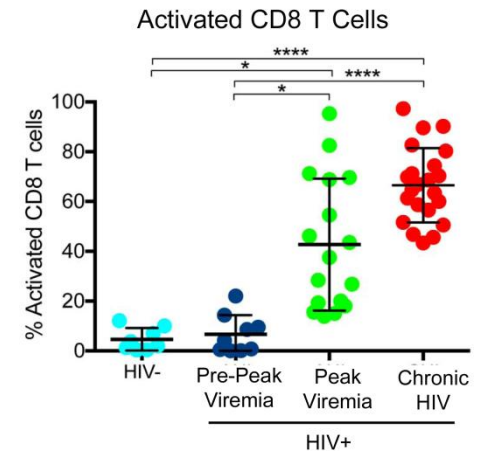
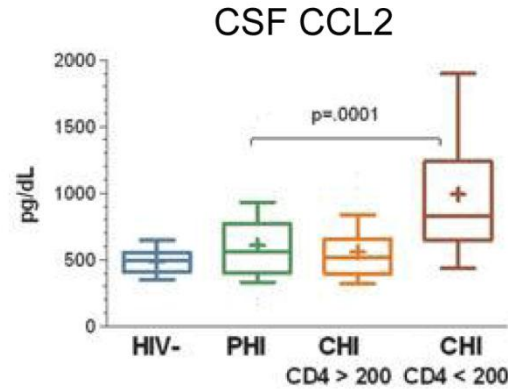
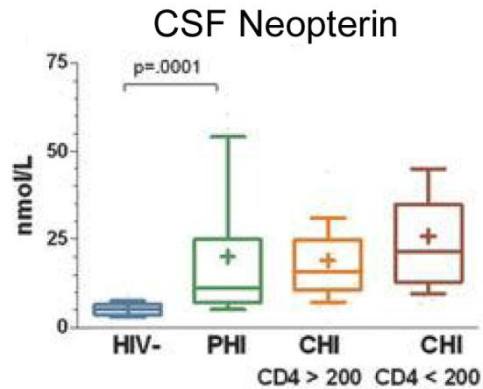
HIV Enters the Central Nervous System Early in Acute Infection



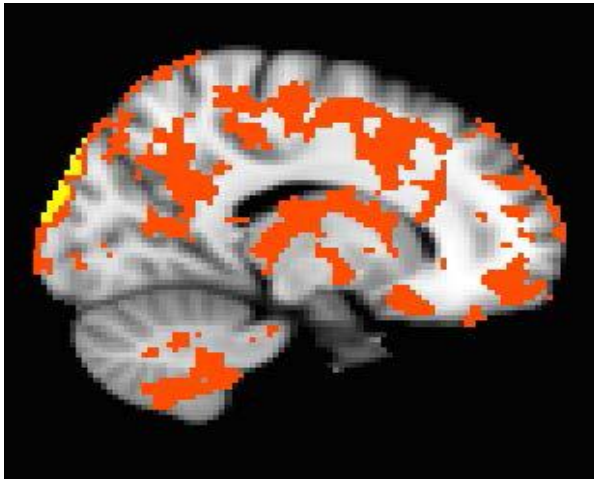
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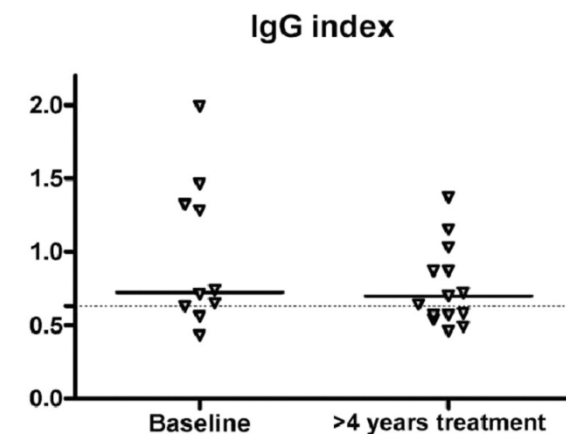
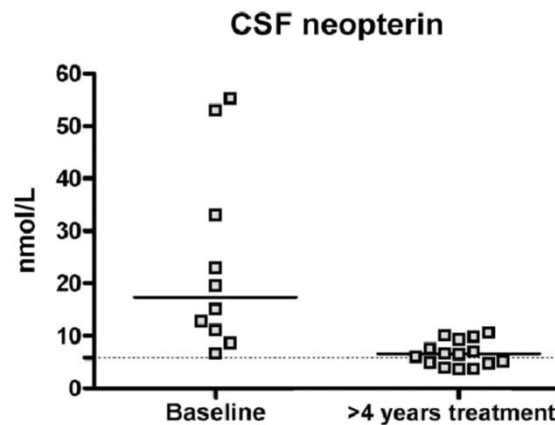
Neuroinflammation and Neuroanatomical Changes Occur in Acute HIV Infection



Neuroinflammation Persists in Chronic HIV Infection Despite ARV

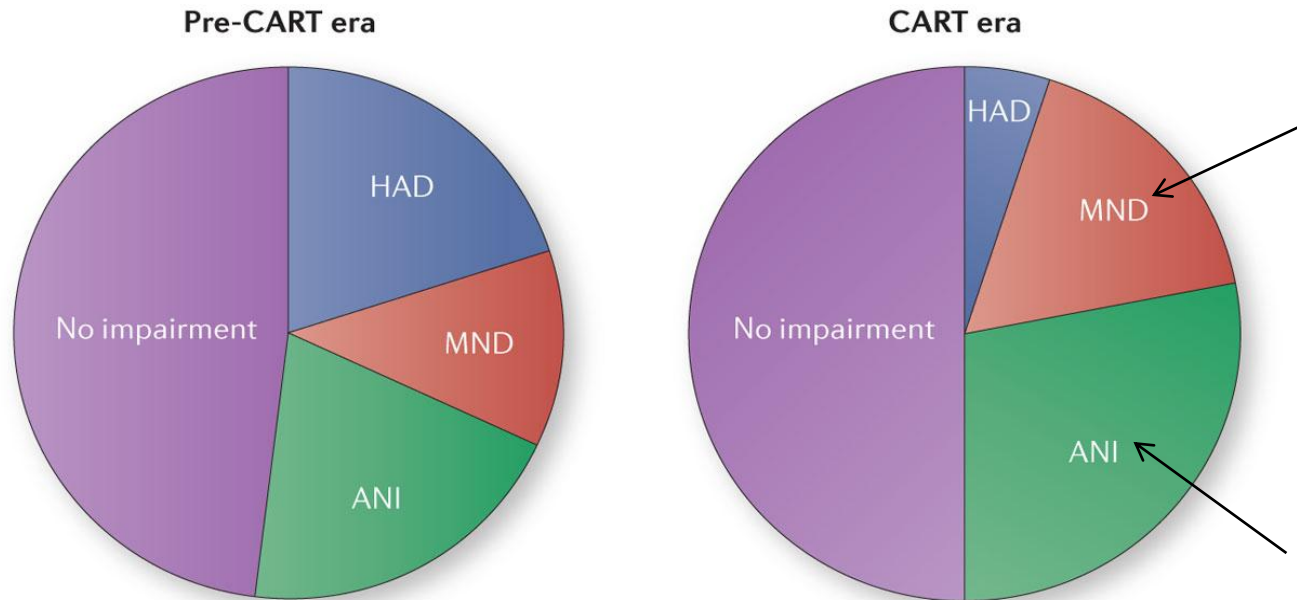


Positron emission tomography (PET): Abnormal brain uptake of ligand targeting activated microglia vs. HIV-controls (mean age 40 yrs; ARV 4 years)



CSF: Elevated Neopterin levels and abnormal intrathecal humoral responses in CSF despite ARV (mean age 51 years; ARV 4.8yrs)

Landscape of Cognitive Impairment in HIV Infection has Changed Dramatically with ARV



HAD: HIV associated dementia
MND: Mild neurocognitive disorder
ANI: Asymptomatic neurocognitive impairment

Therapeutic paradox: ARV has reduced prevalence of most severe manifestation of HAND (dementia) but not less severe manifestations.

HAND may continue to affect daily functions, quality of life, ART adherence

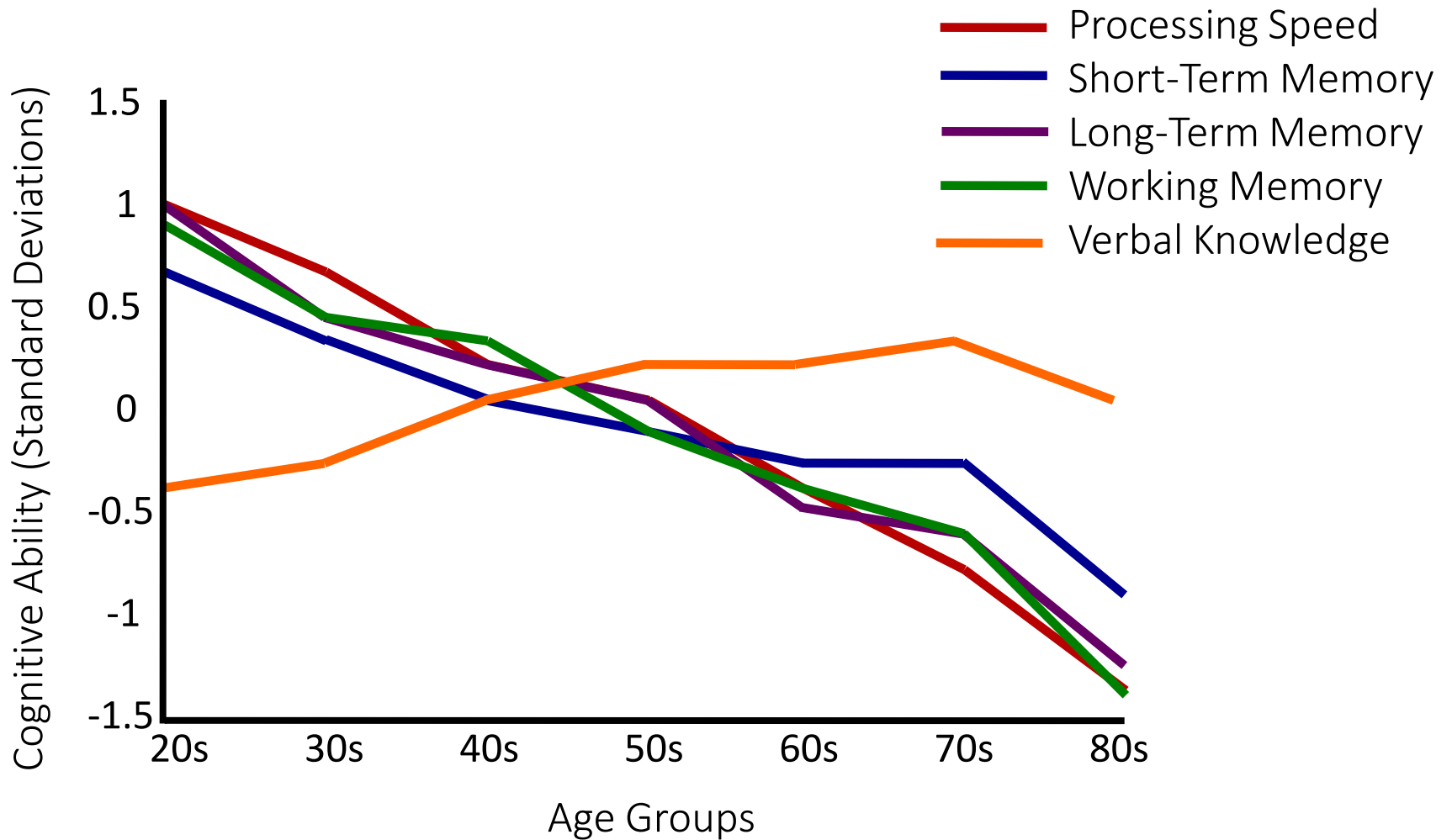
Adapted from Saylor et al, *Nature Reviews Neurology*, 12(4), pp.234-248; McArthur et al, *Aids*, 24(9), pp.1367-1370;

Heaton et al, *Journal of neurovirology*, 17(1), pp.3-16.; Heaton et al, *Clinical Infectious Diseases*, 60(3), pp.473-480.

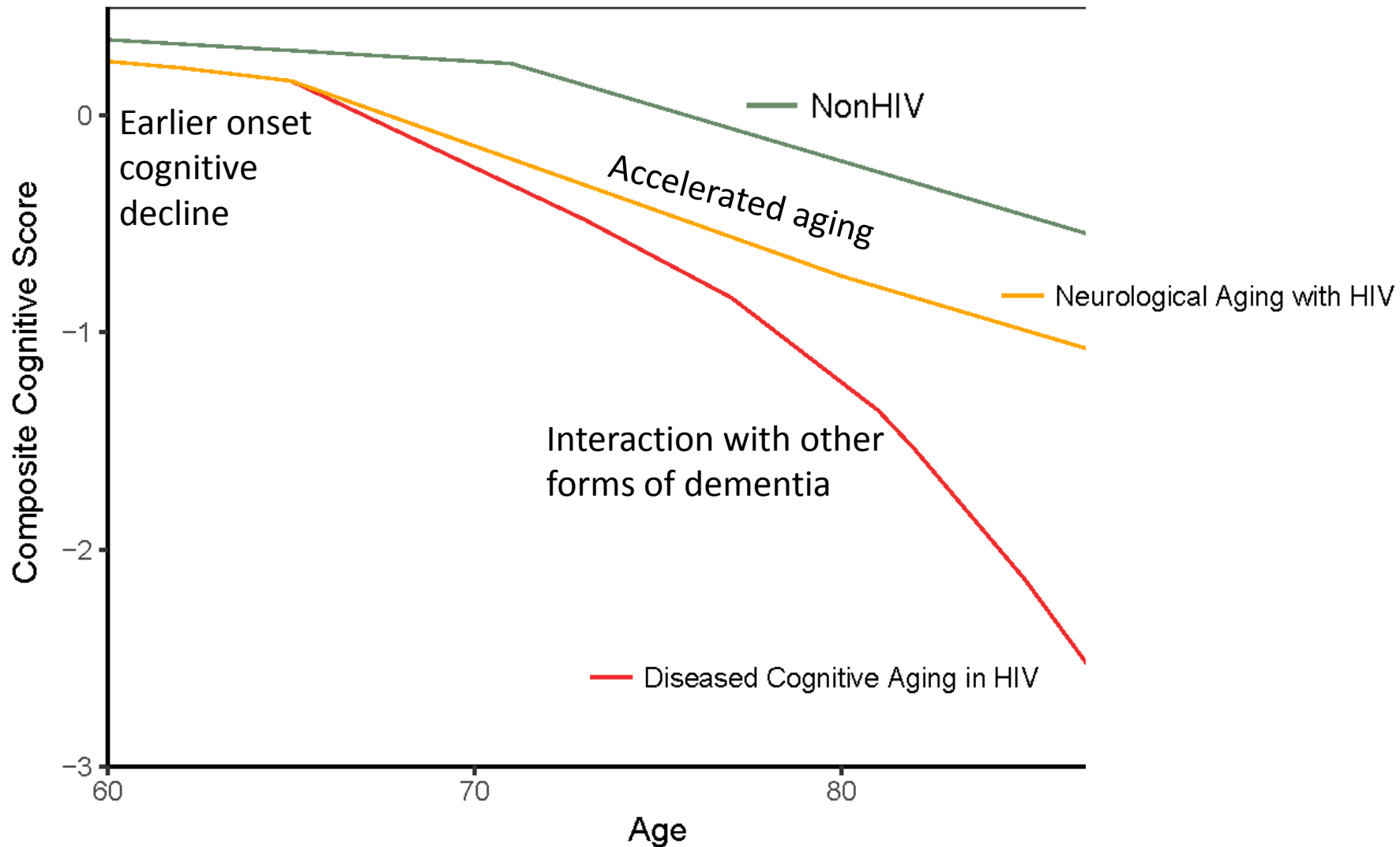
Clinical Spectrum of HIV-Associated Neurocognitive Disorders (HAND)

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

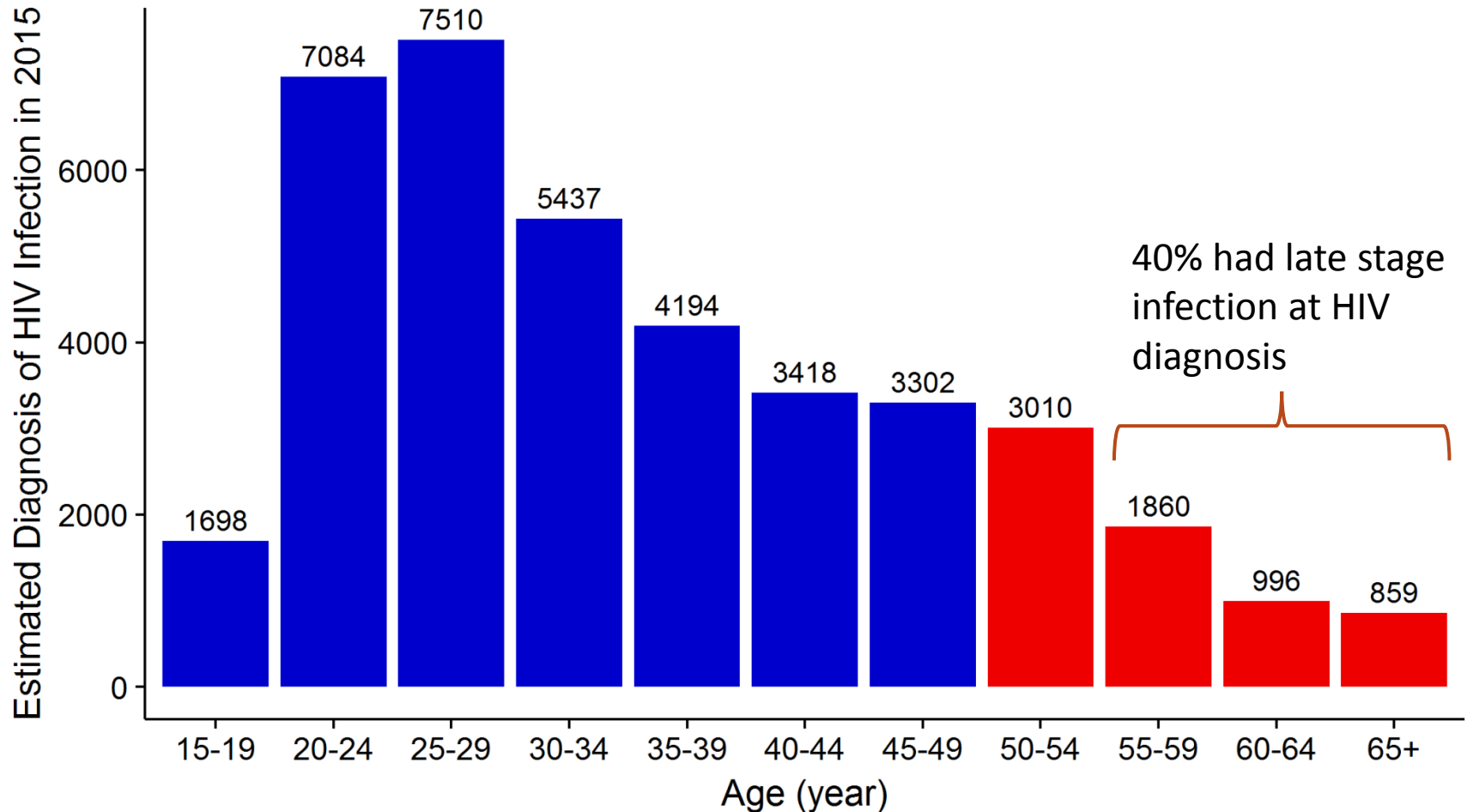
Cognitive Functioning Across the Lifespan In The General Population



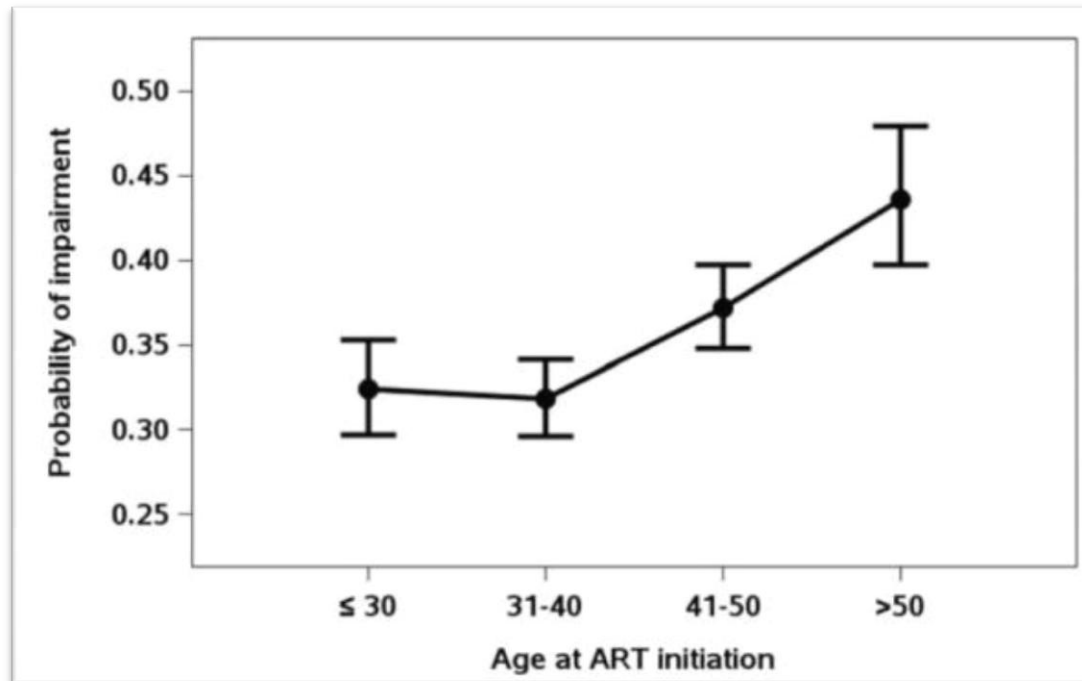
Key Questions Regarding the Relationship of HIV Infection and Age to Cognitive Function



The Challenge: New Diagnoses Among Older People Living with HIV Infection Is Population At Risk

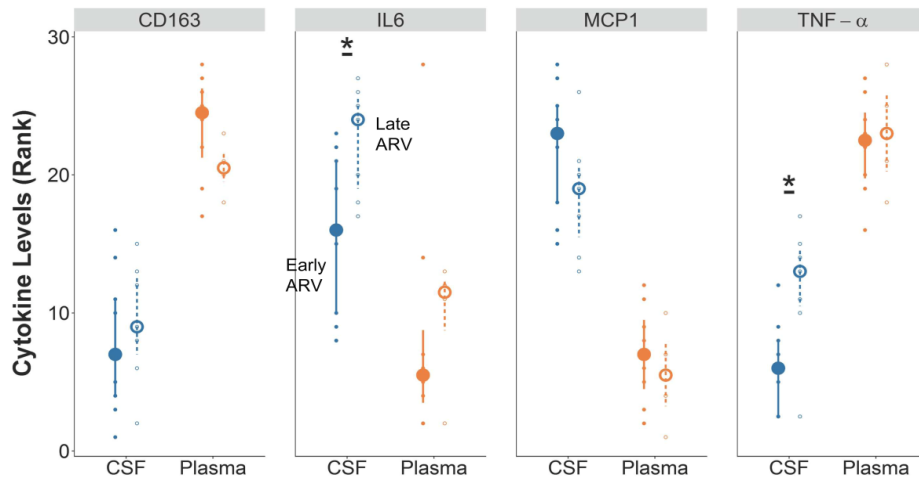


Older People Living with HIV Infection Is Population At Risk for Cognitive Impairment

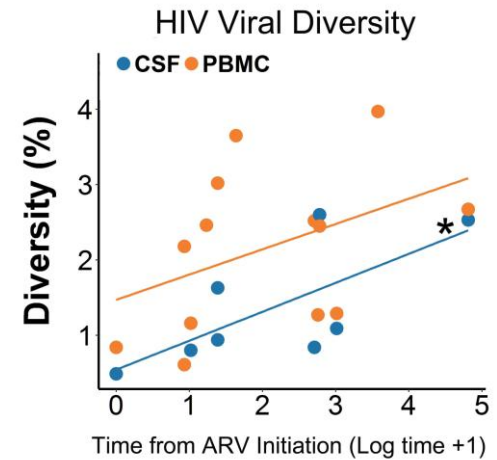


Neurocognitive Testing: The odds of neurocognitive impairment increased by 20% every decade of life in virologically suppressed PLWH who were ART adherent at 97% of visits over 2 years (median age 38 yrs).

Early ARV Treatment

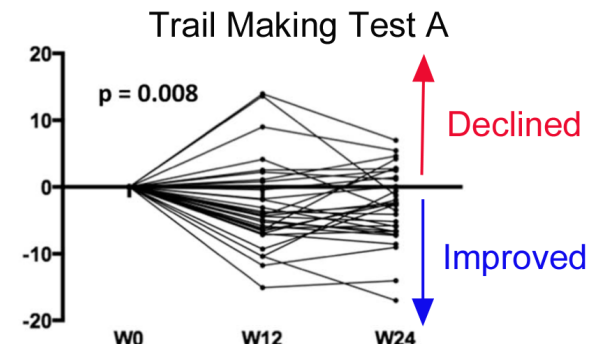
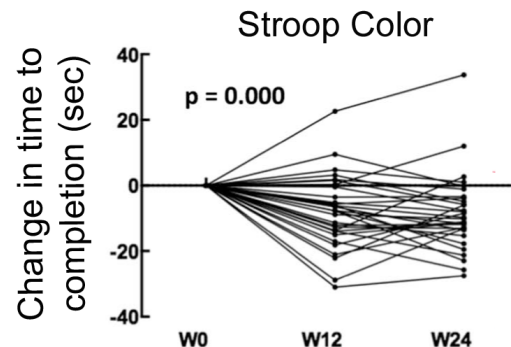


CSF: Early ART resulted in lower IL-6 and TNF-a levels but did not differ for other soluble inflammatory markers (early ART [<4 mo EDI] vs late ARV [>14 mo EDI])



CSF: Predicted higher percentage of viral diversity with longer time to ARV in CSF but not PBMCs

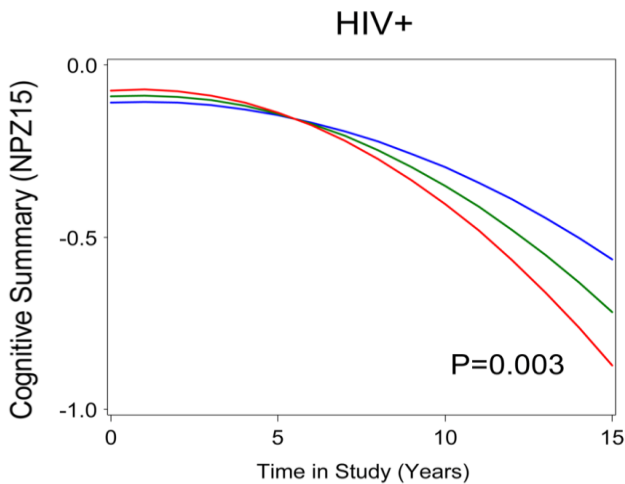
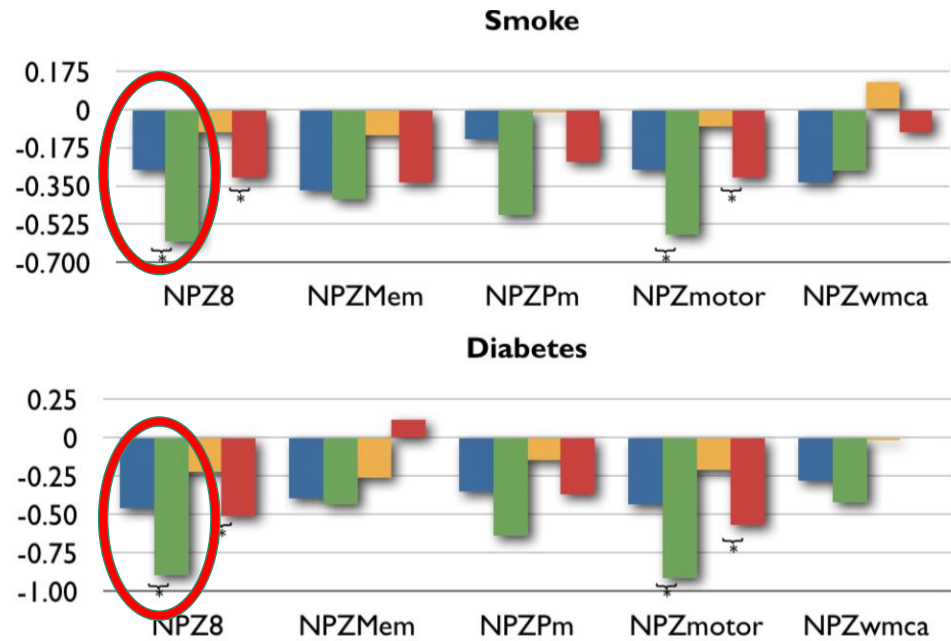
Neurocognitive Testing: Early ART resulted in subtle improvement in some cognitive test. Those with impaired baseline cognitive function had higher CSF HIV viral load and did not reverse with early ART (Mean age 28, EDI 19 days, CD4 411)



Prevention of Metabolic and Cardiovascular Disease

Neurocognitive Studies: Among older (>50 years old) HIV+ adults compared to HIV- controls, tobacco use and diabetes was associated with worse cognitive scores (mean age 55 years).

- HIV+/CVD Risk-
- HIV+/CVD Risk+
- HIV-/CVD Risk-
- HIV-/CVD Risk+



- Total Cholesterol**
- 190 mg/dl (Desirable)
 - 220 mg/dl (Borderline)
 - 250 mg/dl (High)

Neurocognitive Studies: In longitudinal studies elevated total cholesterol predicted increased rate of cognitive decline among HIV+ adults (median age 51 years)

ARV drugs have variable distribution into the CNS and may contribute to neuropathology

CNS Penetration Effectiveness Score (CPE)

	4 (high)	3 (above average)	2 (average)	1 (below average)
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir	Nelfinavir
		Fosamprenavir-r	Atazanavir-r	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir-r		Saquinavir-r
				Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors	<i>Dolutegravir</i> *	Raltegravir	<i>Elvitegravir</i>	

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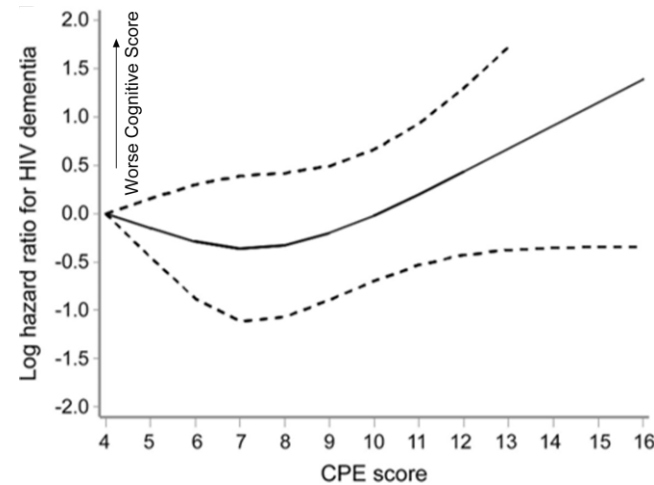
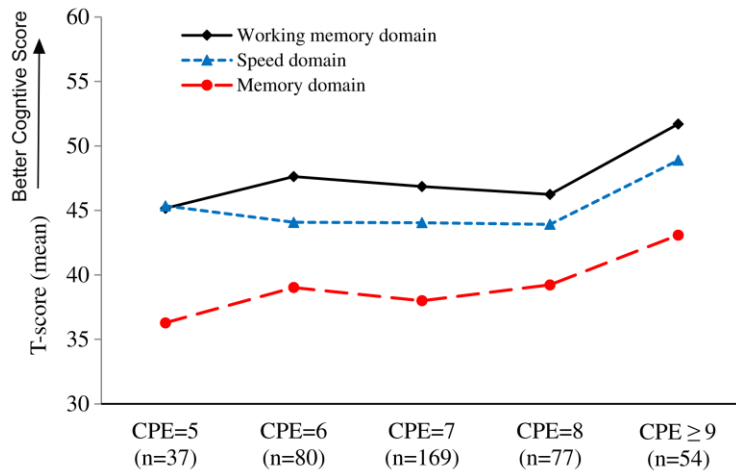
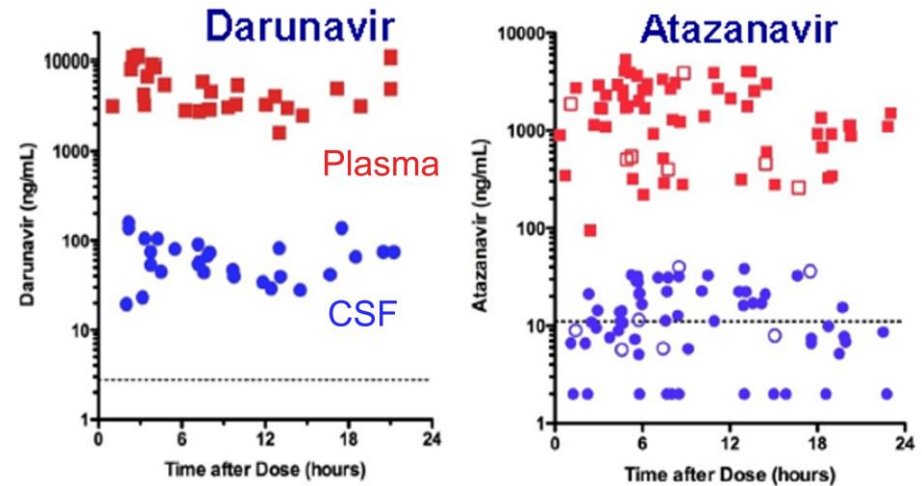
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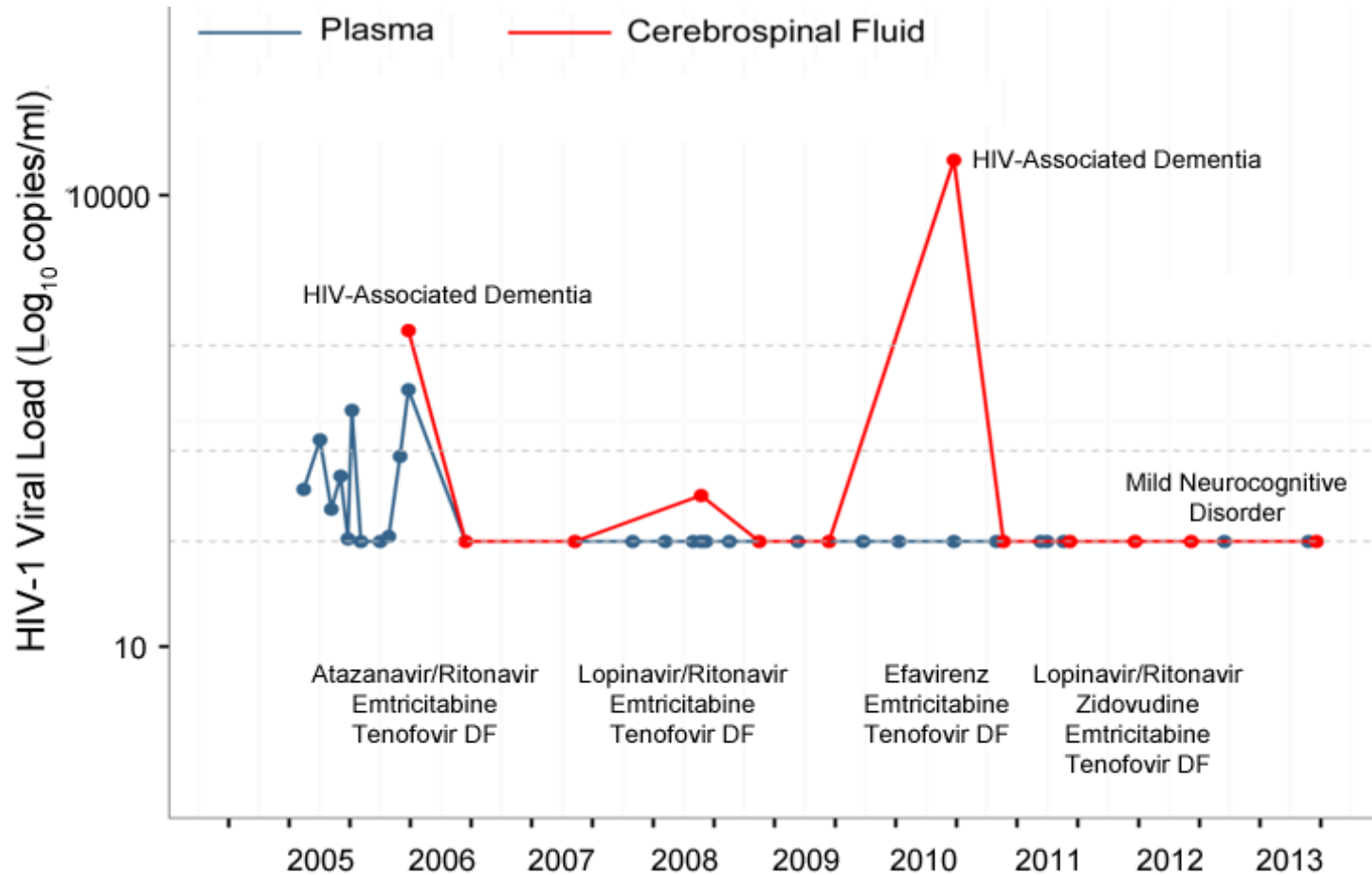
The relationship between CNS penetration scores and neurological outcomes remain unclear

CSF: Median CSF concentrations of PIs are up to 100 fold lower than plasma concentrations even with ritonavir boosting. For Atazanavir, CSF concentrations may not consistently exceed wide-type IC_{50} .

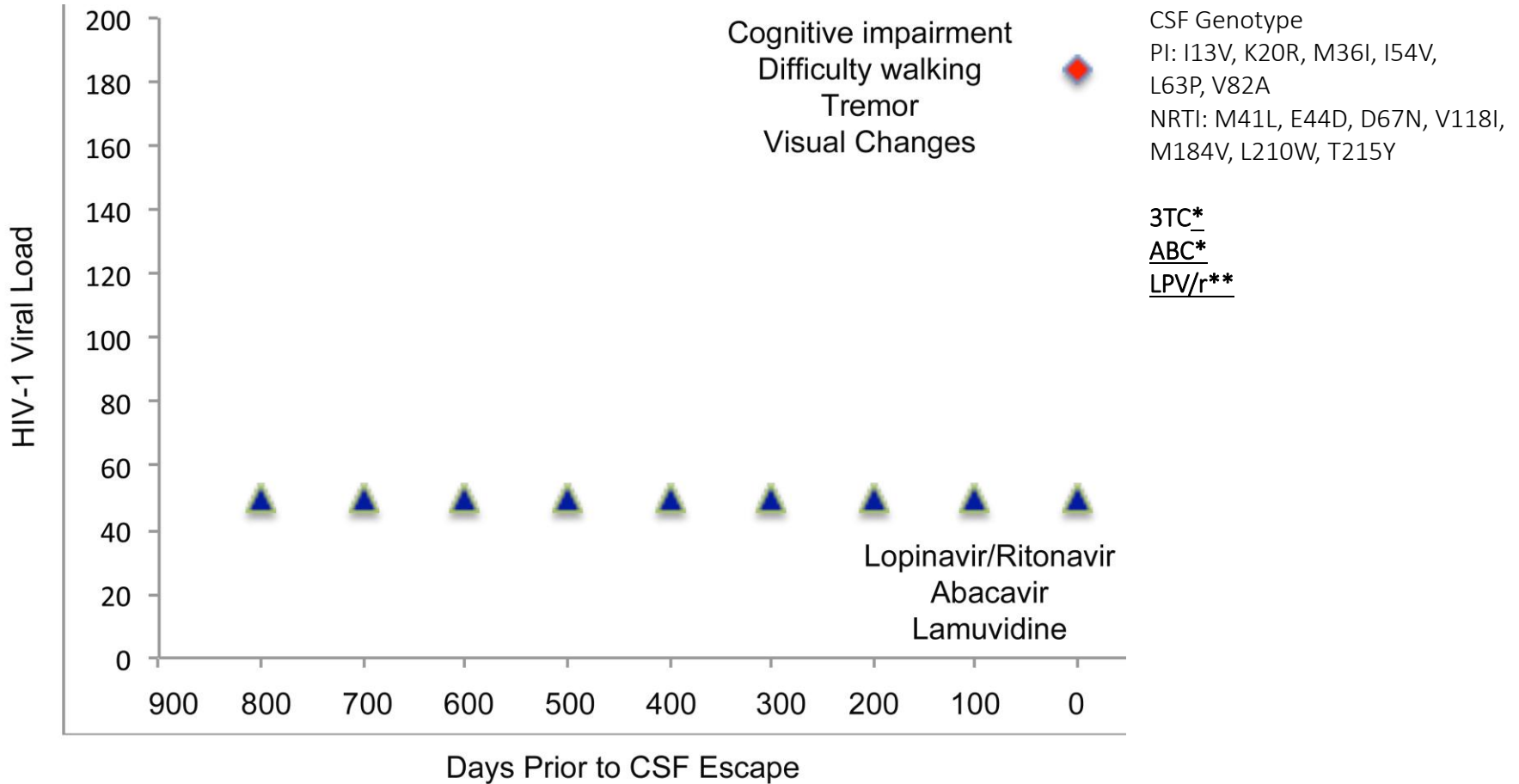


Neurocognitive Testing: Some studies have shown that individuals with high CPE scores (≥ 9) had better cognitive scores and decreased odds of impairment (left). In contrast, other studies have shown that higher CPE scores are associated with increased risk of HIV dementia (right)

Persistent CNS HIV on ARV with Plasma Viral Suppression: CSF 'Escape'



Symptomatic CNS HIV on ARV with Plasma Viral Suppression: CSF 'Escape'



Current First-Line Antiretroviral Regimens and Neurological Considerations

**Tenofovir
-FTC**

or

**Abacavir-
3TC**

+

**Darunavir/
ritonavir**

Raltegravir

**Elvitegravir/
cobi**

Dolutegravir

- **Good CSF concentration**
- **Disadvantage: Less well tolerated than other agents**

- **Good CSF concentration**
- **Disadvantage: twice daily (other agents are once daily)**

- **No CSF pharmacokinetic data**

- **Good CSF concentration**
- **Once daily**
- **Well tolerated**

- **No CSF abacavir pharmacokinetic data with daily dosing**

Slide adapted from Dr. Scott Letendre

Take Home Points

- HIV enters the central nervous system early
 - CNS has multiple anatomical compartments
 - CSF is one representative biofluid
- Neuroinflammation is established early in HIV infection and persists in chronic infection despite ART
- Neurological Cognitive Impairment is Common Among HIV infected Individuals on ART and Increases with Age
- Metabolic and Cardiovascular Disease Risk Factors are Targets to Impact Cognitive Function
- ART does not equally penetrate all tissue compartments
 - CSF resistance may be considered in patients with new neurological symptoms