



Prevention of Neurocognitive impairment

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Potential causes/risk factors of cognitive decline in persons living with HIV

1. Direct HIV damage in CNS (HIV-associated NCI)
2. Previously established irreversible tissue damage by HIV or other causes (legacy effect)
3. Aging
4. Psychiatric disorders
5. Drugs, alcohol abuse
6. Metabolic problems
7. Cerebro-vascular disease
8. Alzheimer's and other neurodegenerative diseases
9. Drug toxicity (ART, other drugs) ?

Potential causes/risk factors of cognitive decline in persons living with HIV

- | | |
|---|------------------------------|
| 1. Direct HIV damage in CNS (HIV-associated NCI) | |
| 2. Drugs, alcohol abuse | PREVENTABLE |
| 3. Drug toxicity (ART, other drugs) ? | |
| 4. Metabolic problems | |
| 5. Cerebro-vascular disease | PARTIALLY PREVENTABLE |
| 6. Psychiatric disorders | |
| 7. Alzheimer's and other neurodegenerative diseases | |
| 8. Previously established irreversible tissue damage by HIV or other causes (legacy effect) | NON PREVENTABLE |
| 9. Aging | |

Potential causes/risk factors of cognitive decline in persons living with HIV

1. **Direct HIV damage in CNS (HIV-associated NCI)**

2. Drugs, alcohol

PREVENTABLE

3. Drug toxicity (ART, other drugs) ?

4. Metabolic problems

5. **Cerebro-vascular disease**

**PARTIALLY
PREVENTABLE**

6. Psychiatric disorders

7. Alzheimer's and other neurodegenerative diseases

8. Previously established irreversible tissue damage
by HIV or other causes (legacy effect)

**NON
PREVENTABLE**

9. **Aging**

Prevention of HIV replication and damage in CNS (HIV-associated NCI)

All cART regimens control HIV-associated NCI by suppressing HIV replication in the CNS (consequently to VL control in blood)

vs.

'Neuro-active' ART (with enhanced CNS penetration/efficacy) is needed to suppress HIV replication in the CNS

NCI and ART neuropenetrations

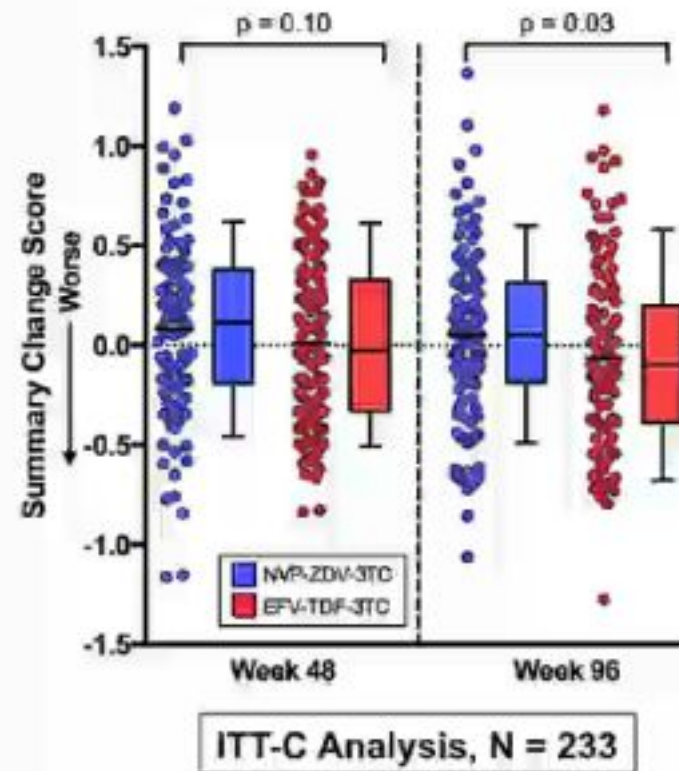
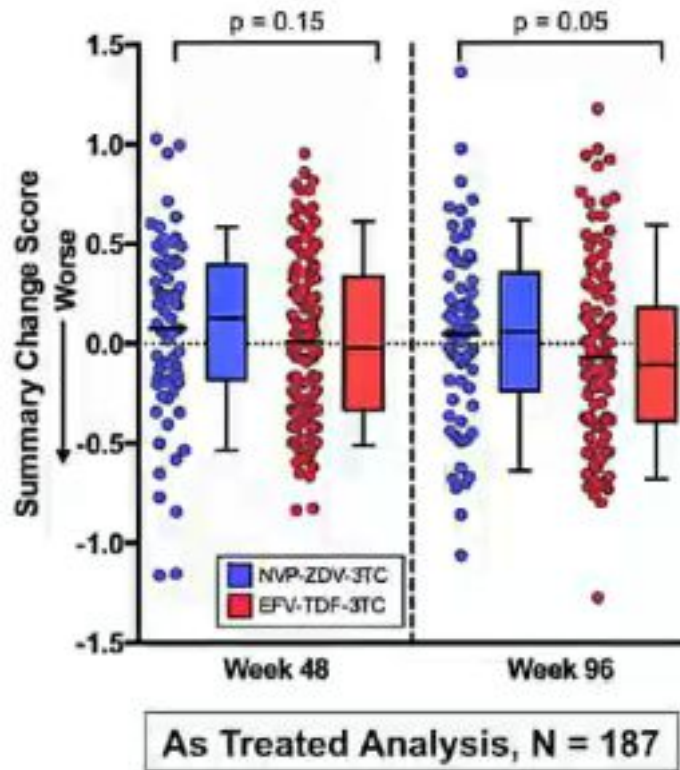
	Cysique	Tozzi	Smurzynski	Marra	Winston	Arendt	Garvey	Rourke	Ciccarelli	Robertson	Kahouadji	Ellis
Study	UCSD CIT	INMI	ALLRT	ACTG 736	ALTAIR	Dusseldorf NA Cohort	Imperial College, UK	OHTN Cohort Study	UCSC	ACTG 5199	INSERM	HNRP/UCSD
Sample Size	37	185	2,636	26	30	3,883	101	545	101	860	54	49
CPE: CSF VL	Lower VL	No CSF	No CSF	Lower VL	No CSF	Lower VL	No CSF	No CSF	No CSF	No CSF	No CSF	No effect
Number of NP Tests	6	15	3	4	CogState	2	2	4	18	6	4	14
CPE: NP Tests	Better	Better	Better (only by >3 drugs)	Poorer	Poorer	Better	No effects	Not conclusive	Better	No effect	Poorer	No effect
Prospective	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Controlled	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes
Norms for NP Change	Yes	No	No	No	No	No	No	No	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; Smurzynski et al, AIDS 2011;25:357-365; Marra et al, AIDS 2009, 23(11):1359-66; Winston A, et al. Clin Infect Dis 2010;50:920-929; Arendt, et al. 18th CROI, Boston (MA, 2011. Poster #425; Garvey et al. HIV Clin Trials, 2011;12(6):333-338; Rourke SB, et al. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, 2011; Ciccarelli N, et al. Antiviral Ther, 2013; Robertson et al. Clin Infect Dis 2012;55(6):868-76; Kahouadji Y, et al. HIV Medicine 2012;14:311-315; Ellis et al. 20th CROI, Atlanta (GA), 2013; Abst#20.

(Courtesy of S. Letendre, 201

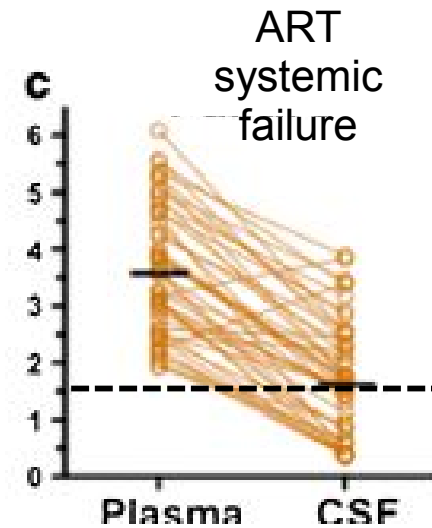
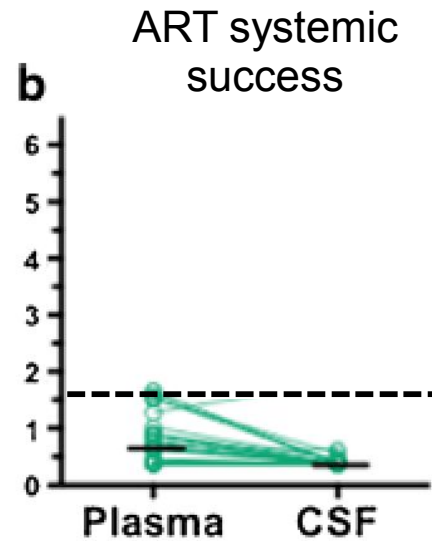
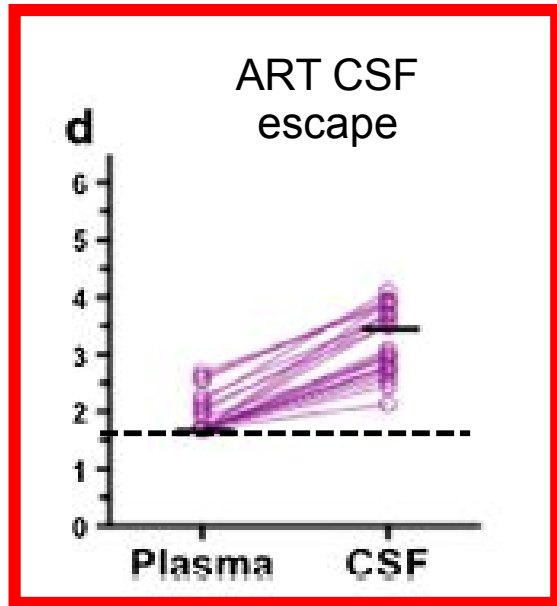
Randomized Clinical Trial of Antiretroviral Therapy for Prevention of HAND in naïve pts (Beijing, China)

NVP+AZT+3TC vs. **EFV+TDF+3TC**



- 1036 pts, no NCI
- 97-100% M, median CD4 235-222/ μ L, median logVL 4.2 c/mL
- 8 test battery

CSF viral escape



Ferretti F et al. Curr HIV/AIDS Rep 2015

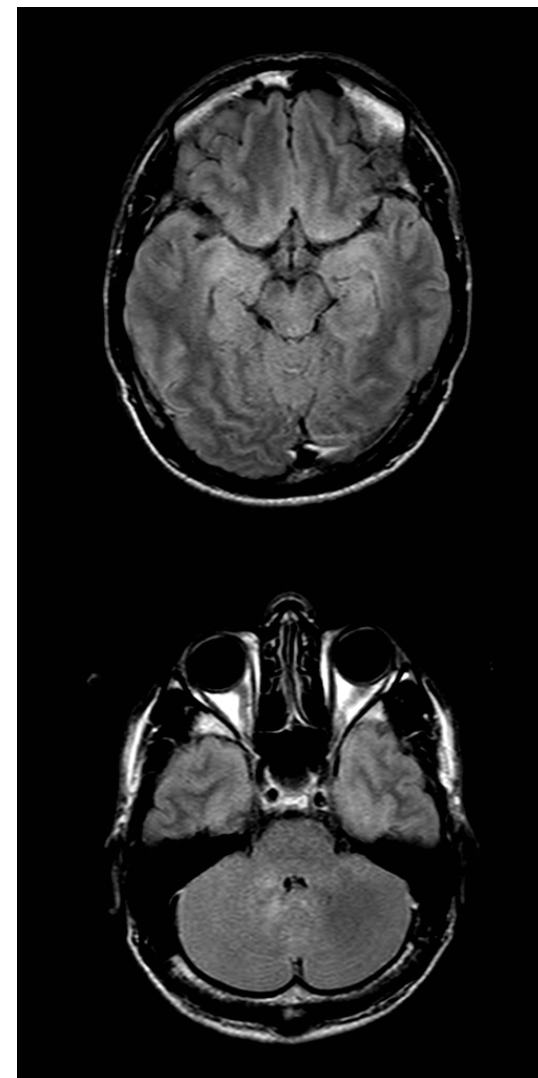
- On ART > 6/9 months
- CSF VL > LLD (if plasma VL suppressed) or CSF VL > plasma VL (if plasma VL >50)
- Symptomatic or asymptomatic

Neuro-symptomatic CSF viral escape (meningoencephalitis)

- M, 26
- **2010**: Headache, disarthria, ataxia (days)
- History of systemic OIs
- CD4 nadir: 9
- 2009: Starts ART (AZT,3TC,LPV/r)
- Change to **TDF,FTC,ATV**

- CD4 290
- **Plasma HIV 98 c/mL**
- **CSF HIV 5200 c/mL**
- **CSF cells: 200/ μ L**

No CSF mutations to NRTIs and PIs



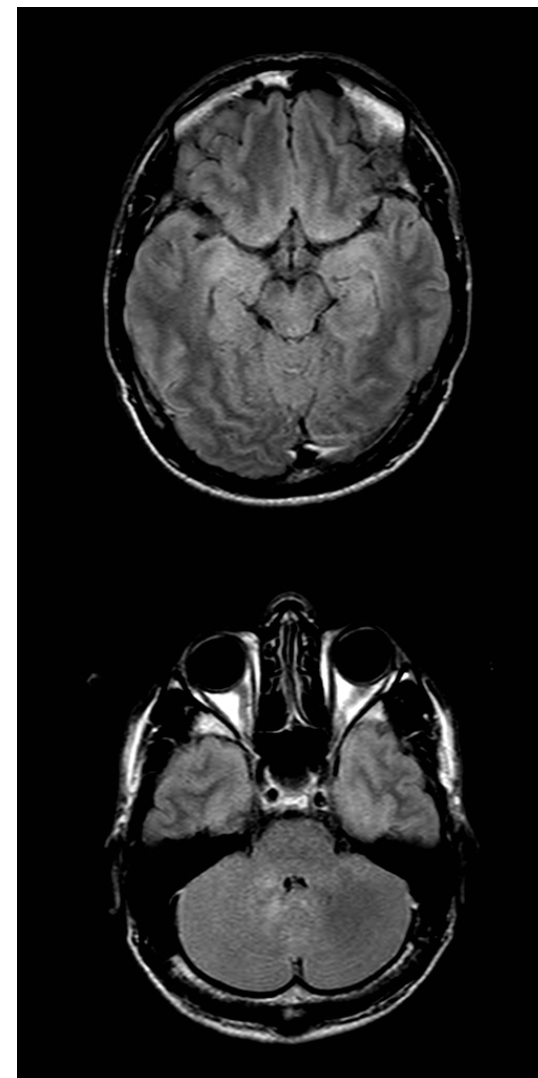
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→ **Resolution by cART optimization for
neuropenetration (AZT, 3TC, DRV/r bid)**



CD4 cells and VL values in patients with neuro-symptomatic CSF escape

Variable	Median (IQR)	Range
Blood CD4 (cells/ μ L)	520 (308–592)	107–660
Nadir blood CD4 (cells/ μ L)	55 (12–145)	2–250
CSF WBC (cells/ μ L) ^a	22 (10–55)	0–200
Plasma HIV (\log_{10} copies/mL)	1.69 (1.69–2.68)	1.69–2.68
CSF HIV (\log_{10} copies/mL)	3.01 (2.76–3.72)	2.13–4.11
CSF:plasma difference (\log_{10} copies/mL)	1.25 (1.06–1.44)	0.44–2.23

Possible risk factors for symptomatic CSF escape

- Presence and size of brain 'reservoir' (low nadir CD4 cells, previous HIV-E, previous CSF-escape)
- ARV drug resistance
- Inadequate ART adherence
- Inadequate efficacy of individual drugs/regimens
 - CNS 'penetration'
 - Efficacy in macrophages/microglial cells

Prevention of CSF escape

- Presence and size of brain 'reservoir' (low nadir CD4 cells, previous HIV-E, previous CSF-escape)
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In persons at risk:

→Clinical monitoring for CSF escape

→ART with enhanced CNS penetration/efficacy?

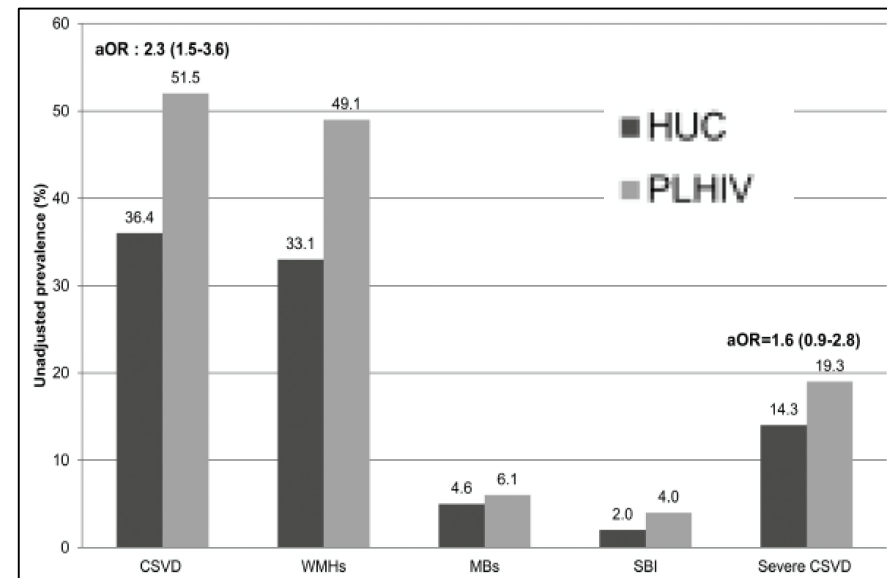
Cerebral small vessel disease (CSVD) in HIV-infected cART-controlled patients

ANRS EP51 MICROBREAK (NCT02082574) cross-sectional study (June 2013 - May 2016)

- CSVD prevalence by MRI in treated HIV, >50 years with controlled VL for >12 months vs. HIV negative controls

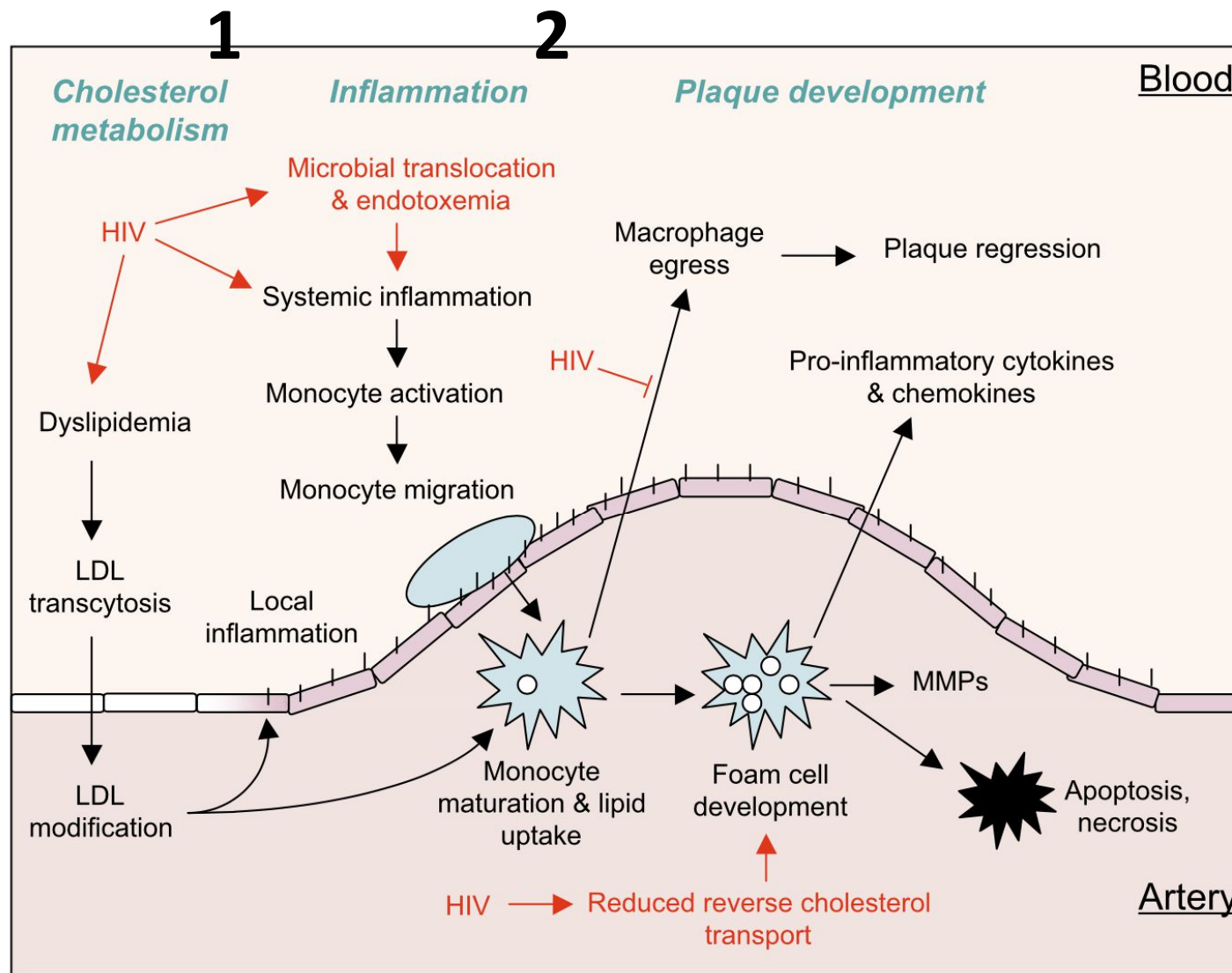
- **456 HIV+ and 154 HIV-neg**

- CSVD prevalence:
 - HIV-pos: **51.5%**
 - HIV-neg: 36.4%
 - OR 2.3 (95% CI: 1.5–3.6)

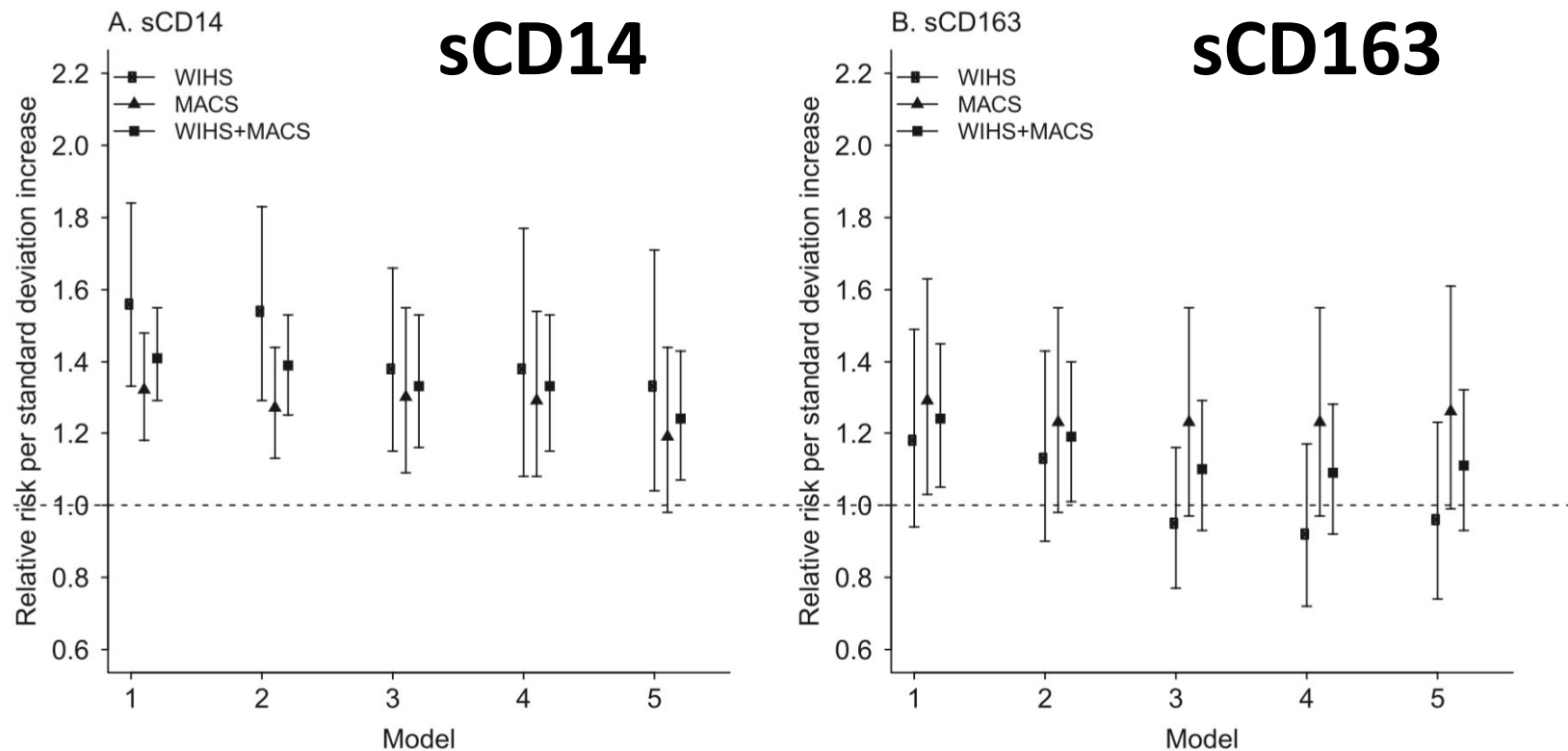


- Independent predictors of risk in HIV+:
 - Older age
 - Hypertension
 - Lower CD4 nadir

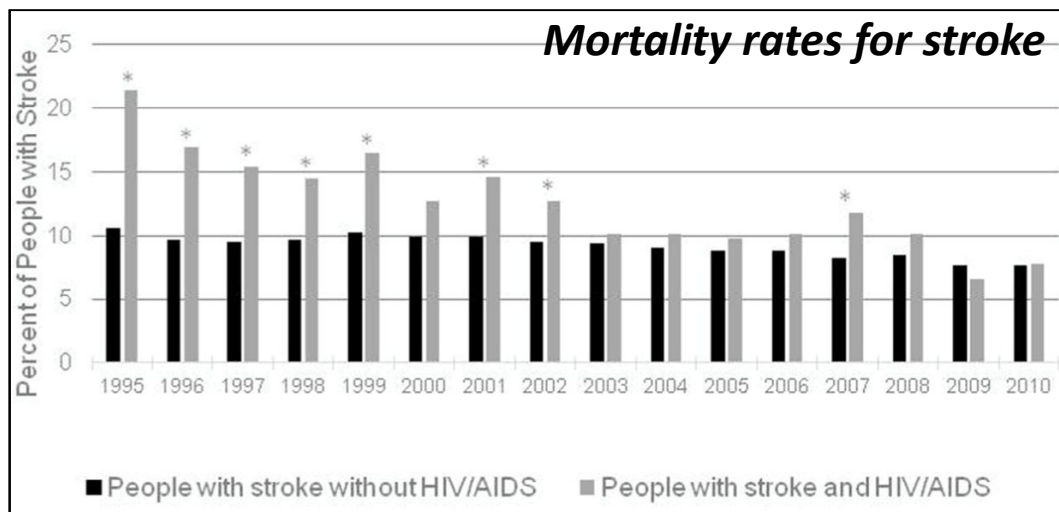
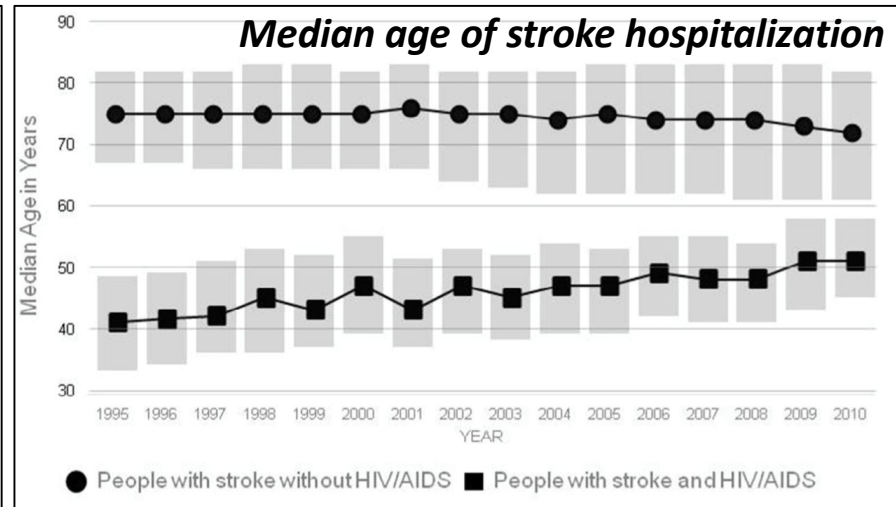
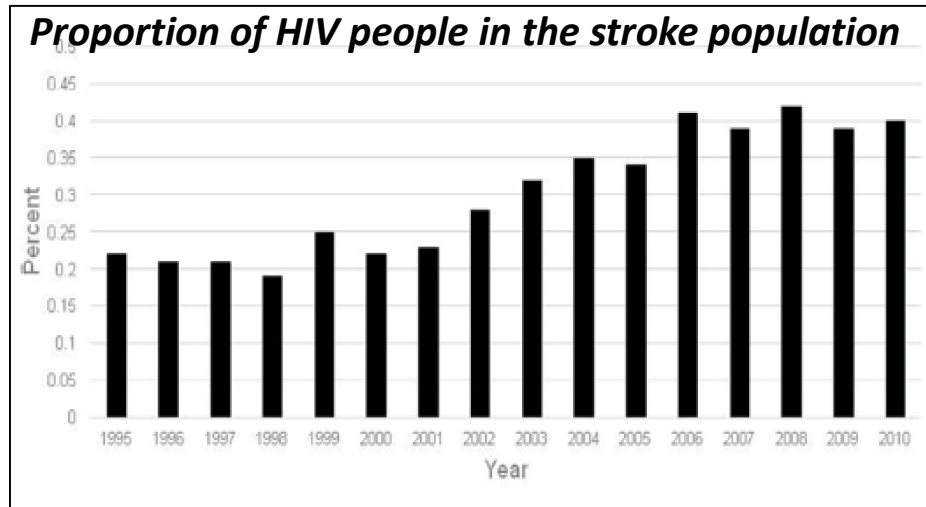
Cardiovascular and cerebrovascular disease: Potential mechanisms of heightened atherogenesis in HIV



Association of Macrophage Inflammation Biomarkers with Progression of Subclinical Carotid Artery atherosclerosis in HIV-infected patients



Epidemiology of cerebrovascular disease in a post-cART era



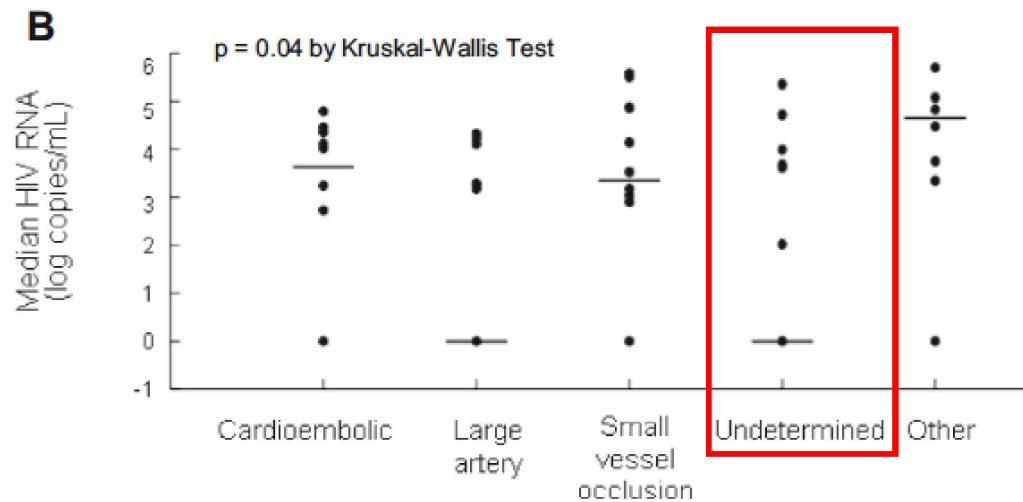
Data from the Nationwide Inpatient Sample from 1995 to 2010.

Patients with ischemic stroke and AIDS identified using ICD-9 codes.

1,874,067 hospitalizations for ischemic stroke over 16 years

Greater Risk of Stroke of Undetermined Etiology in a Contemporary HIV Cohort Compared to non-HIV

	HIV-infected individuals, n = 60 No. (%)*	HIV-uninfected individuals, n = 60 No. (%)*
Ischemic stroke subtype		
Large artery	14 (23)	13 (22)
Small vessel	12 (20)	20 (33)
Cardioembolic	12 (20)	24 (40)
→ Undetermined etiology	14 (23)	2 (3)
Other etiology	8 (13)	1 (2)



Stroke risk factors that are not within your control

- Age
- Sex
- Race
- Family history
- Prior stroke, TIA or heart attack

Stroke risk factors that you can control, treat and improve

- High blood pressure
- Smoke
- Diabetes
- Diet
- Physical activity
- Obesity
- High blood cholesterol
- Carotid artery disease
- Peripheral artery disease
- Atrial fibrillation
- Other heart disease
- Sickle cell disease

Understanding stroke risk, American Heart Association

http://www.strokeassociation.org/STROKEORG/AboutStroke/Underst...dingRisk/Understanding-Stroke-Risk_UCM_308539_SubHomePage.jsp

Additional factors that may be linked to higher stroke risk

- Geographic location
- Socio-economic factors
- Alcohol abuse
- Drug abuse
- Sleep habits

Conclusions

Prevention
is an important component
towards control of
neurocognitive impairment
in HIV-infected persons