8° WORKSHOP NAZIONALE CISAI

PERUGIA, 30 - 31 MARZO 2017
HOTEL GIÒ - CENTRO CONGRESSI
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

Eventi cerebro-vascolari: davvero una nuova frontiera?

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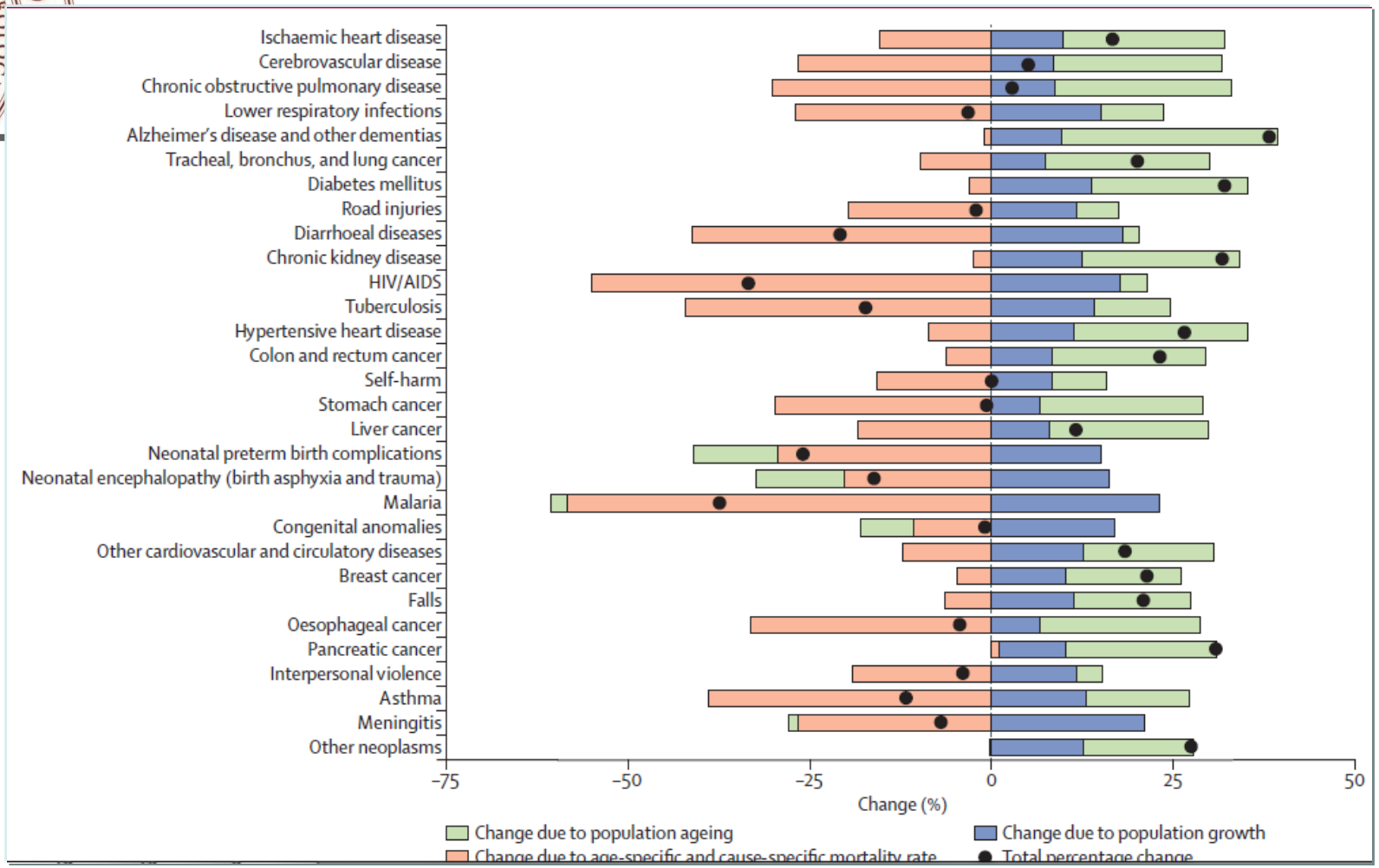
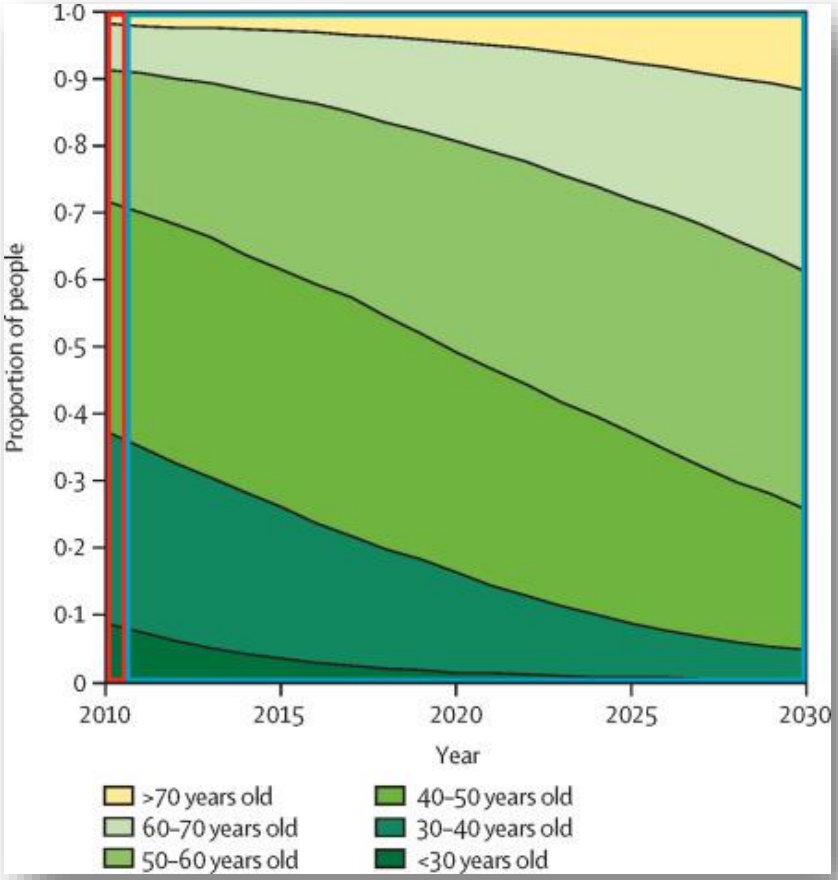
Changes in leading 30 causes of death, 2005 to 2015

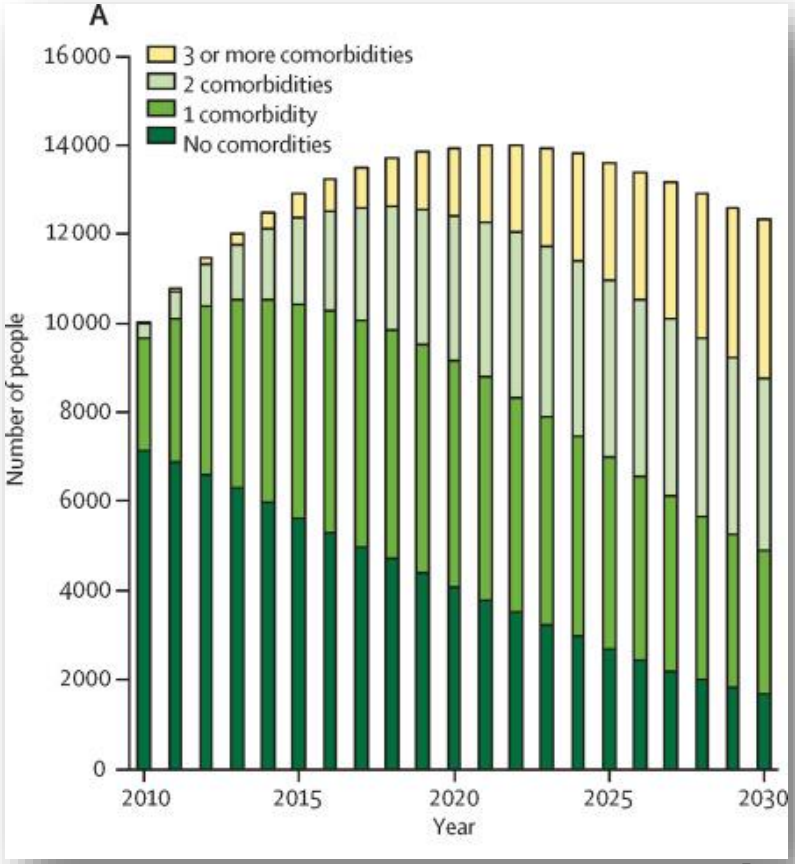


(Lancet 2016)

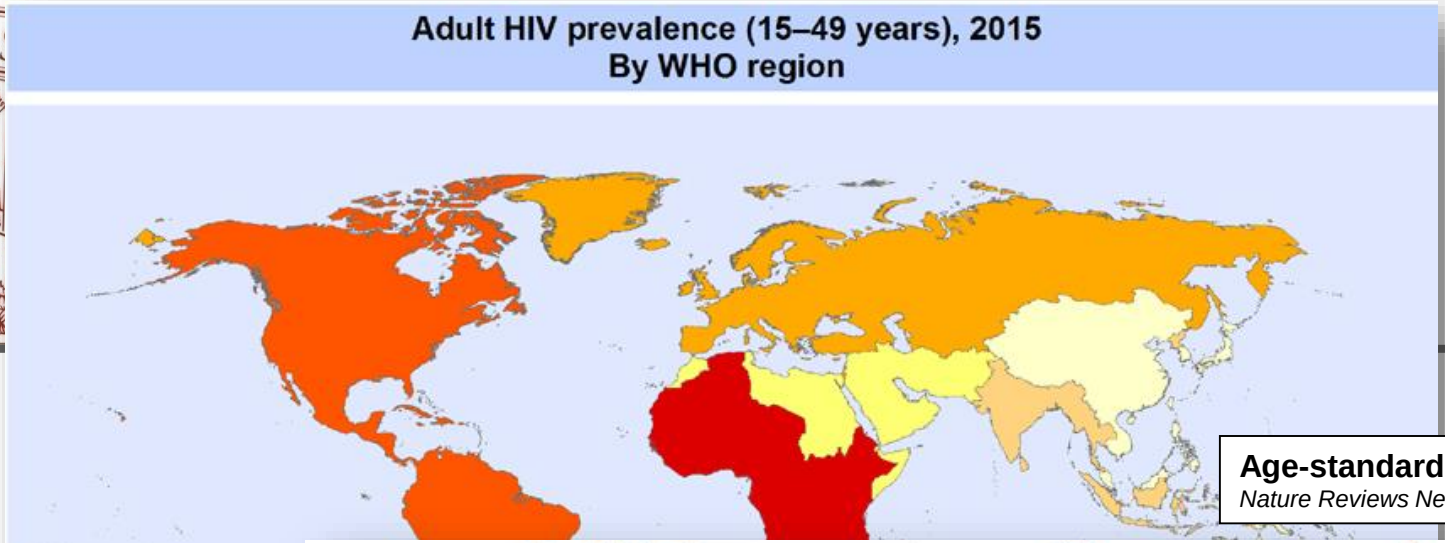
Future challenges for clinical care of an ageing population infected with HIV: a modelling study

Mikaela Smit, Kees Brinkman, Suzanne Geerlings, Colette Smit, Kalyani Thyagarajan, Ard van Sighem, Frank de Wolf, Timothy B Hallett, on behalf of the ATHENA observational cohort

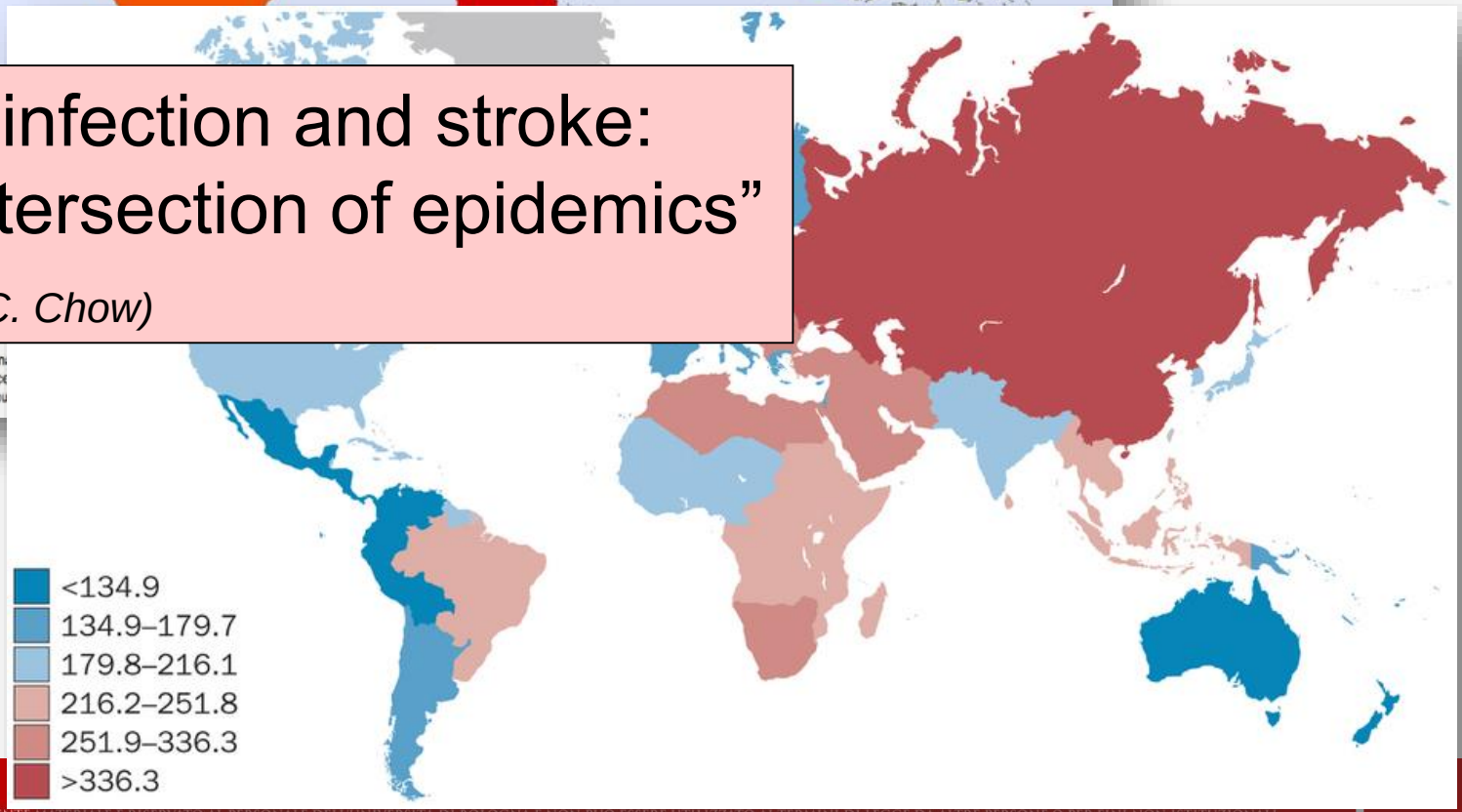




(Lancet Infect Dis 2015)



Age-standardized stroke incidence
Nature Reviews Neurology 2014



"HIV infection and stroke: an intersection of epidemics"

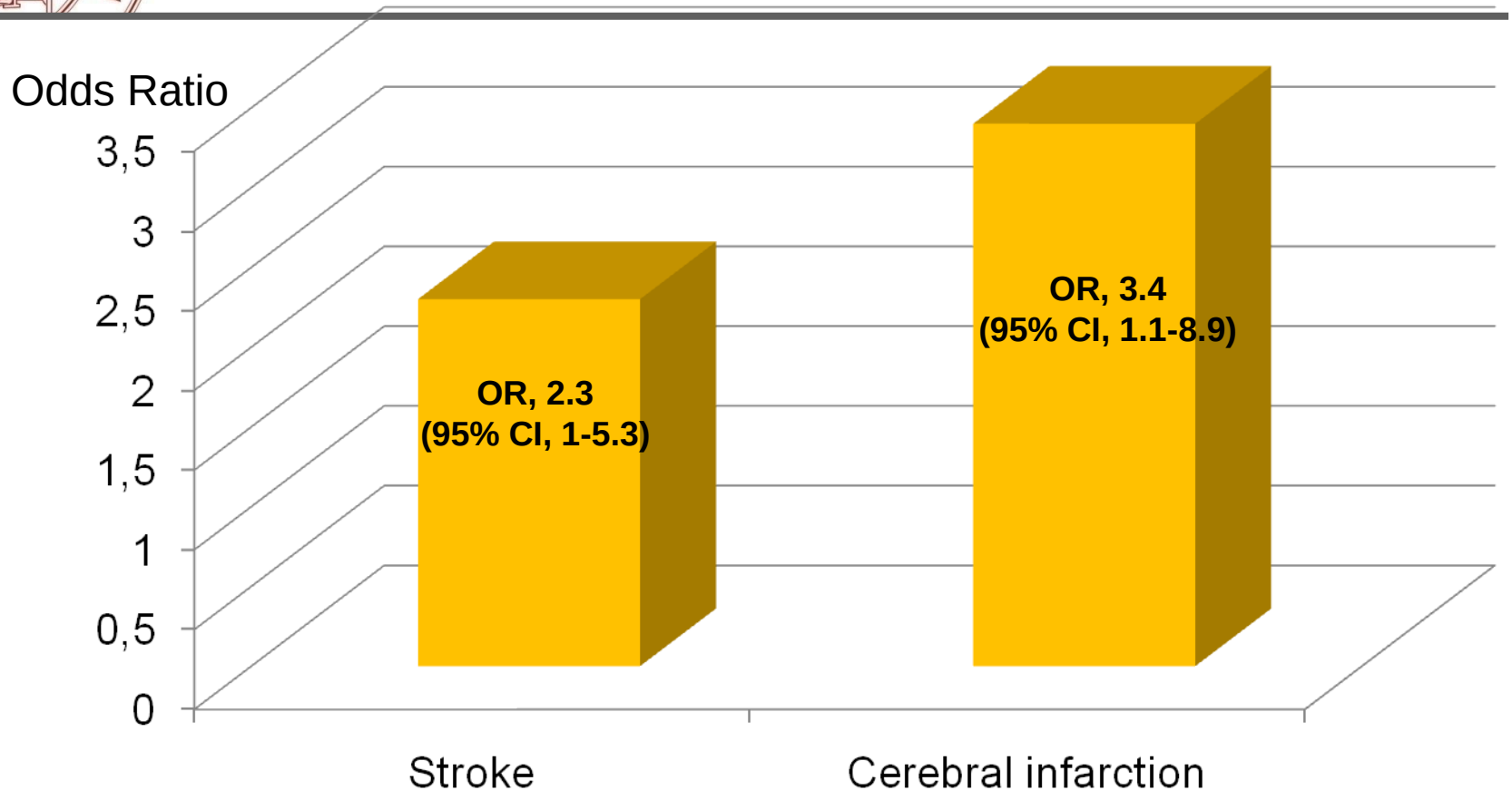
(Felicia C. Chow)

HIV infection and cerebrovascular diseases: critical issues

- Epidemiology of stroke in HIV infection
- Proposed mechanisms underlying elevated stroke risk in HIV infection
- cART impact on stroke risk
- Cerebrovascular disease and neucognitive disorders
- Prevention strategies

Risk of cerebrovascular diseases among HIV-infected patients in the pre-cART era

(Case-control study; 1990-1994)



(Qureshi AI et al., Arch Neurol 1997)

History of AIDS in HIV-Infected Patients Is Associated With Higher In-Hospital Mortality Following Admission for Acute Myocardial Infarction and Stroke

- U.S. National Inpatient Sample (NIS)
- 18,369,785 AMI/stroke hospitalizations
- 2002-2012

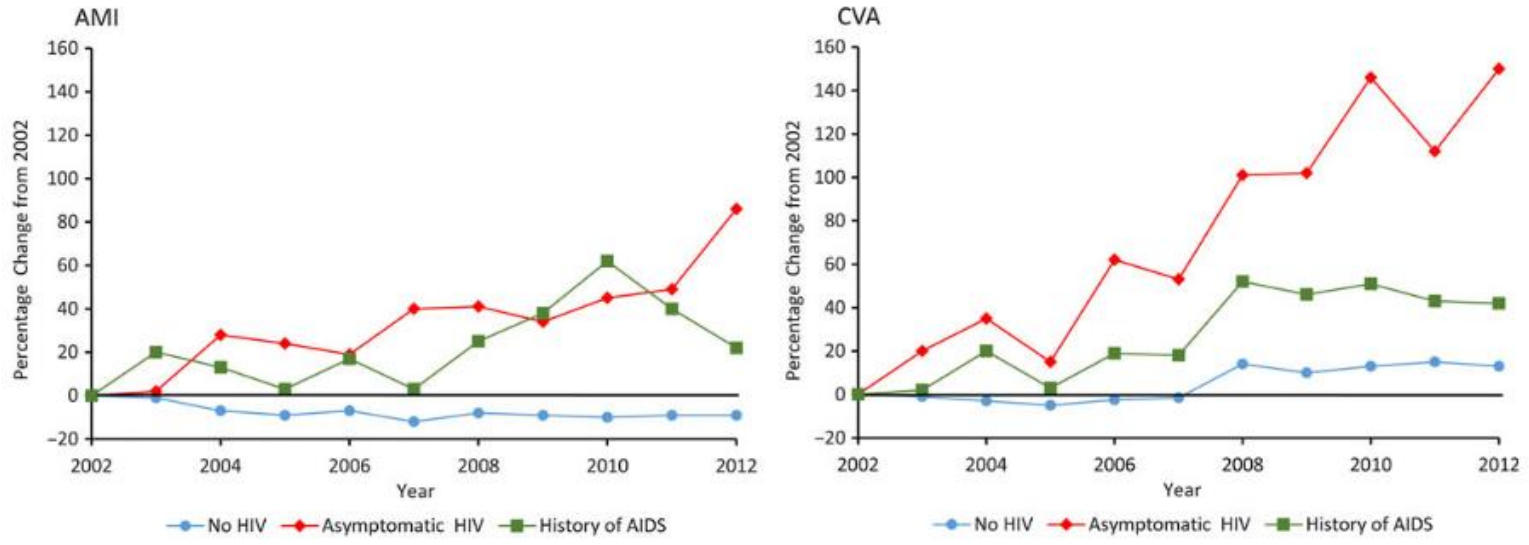


Figure 1. Trends in hospitalizations for acute myocardial infarction and cerebrovascular accident, by human immunodeficiency virus (HIV) claim code, Nationwide Inpatient Sample, 2002–2012. Abbreviations: AMI, acute myocardial infarction; CVA, cerebrovascular accident.

(Okeke NL et al., J Infect Dis 2016)

Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study

Table 4. Uni- and Multivariable Hazard Ratios for Clinical Events From 1 January 2008 Until 31 December 2010, Stratified by Age

	Univariable analyses			Multivariable analyses		
Events	50–64 HR (95% CI)[a]	≥65 HR (95% CI)[a]	*P* value	50–64 HR (95% CI)[a]	≥65 HR (95% CI)[a]	*P* value[d]
Non-AIDS comorbidities						
Bacterial pneumonia	1.69 (1.27–2.26)	1.25 (0.673–2.32)	.002	1.89 (1.40–2.55)	2.04 (1.08–3.88)	<.001
Cerebral infarction	3.59 (1.72–7.52)	10.9 (4.70–25.2)	<.001	3.96 (1.86–8.42)	17.7 (7.06–44.5)	<.001
Coronary angioplasty	5.60 (3.30–9.50)	7.86 (3.84–16.1)	<.001	4.72 (2.76–8.10)	7.43 (3.51–15.7)	<.001
Myocardial infarction	7.05 (3.74–13.3)	5.99 (2.27–15.7)	<.001	5.95 (3.12–11.3)	5.89 (2.17–16.0)	<.001
Procedure on other arteries	3.92 (1.83–8.36)	3.53 (0.987–12.7)	.001	4.29 (1.97–9.36)	5.04 (1.34–19.1)	<.001
Pulmonary embolism	1.90 (0.660–5.48)	3.25 (0.691–15.3)	.272	1.87 (0.632–5.52)	3.93 (0.760–20.4)	.251
Deep vein thrombosis	1.26 (0.590–2.68)	1.29 (0.302–5.52)	.815	1.29 (0.594–2.80)	2.06 (0.453–9.40)	.608
Fracture, adequate trauma	2.37 (1.63–3.46)	3.52 (1.99–6.23)	<.001	2.28 (1.55–3.36)	4.71 (2.57–8.63)	<.001
Fracture, inadequate trauma	4.01 (1.95–8.25)	6.46 (2.42–17.2)	<.001	3.93 (1.88–8.24)	10.5 (3.58–30.5)	<.001
Osteoporosis	3.09 (1.78–5.36)	5.65 (2.69–11.9)	<.001	3.60 (2.04–6.34)	9.13 (4.10–20.3)	<.001
Avascular necrosis of bone	0.838 (0.305–2.30)	1.72 (0.393–7.51)	.720	0.767 (0.274–2.15)	2.32 (0.489–11.0)	.493
Diabetes mellitus	2.23 (1.34–3.70)	4.09 (2.01–8.31)	<.001	2.23 (1.33–3.76)	3.75 (1.80–7.85)	<.001
Pancreatitis	2.94 (1.36–6.36)	2.15 (0.481–9.61)	.023	3.27 (1.48–7.24)	3.85 (0.799–18.5)	.01
Liver-associated event[b]	1.64 (0.959–2.80)	0.379 (0.519–2.77)	.082	1.29 (0.748–2.23)	0.494 (0.066–3.72)	.440
Kidney-associated event[c]	1.40 (0.647–3.04)	2.16 (0.637–7.34)	.426	1.41 (0.638–3.14)	2.84 (0.781–10.3)	.303
Non-AIDS malignancy	3.98 (2.64–6.02)	7.11 (4.13–12.3)	<.001	3.73 (2.45–5.69)	6.88 (3.89–12.2)	<.001

(Hasse B et al., Clin Infect Dis 2011)

Increased incidence of stroke in the cART era

- Improved survival and aging of the HIV-positive people
- High prevalence of comorbidities
- High prevalence of traditional risk factors (mostly dyslipidemia, smoking and substance abuse)
- HIV-associated vasculopathy
- cART-induced vascular damage
- Cerebral vasculitis from concomitant infections (syphilis, CMV, tuberculosis)

Types of ischemic strokes among HIV-infected individuals across the United States

- CNICS U.S. Multisite Clinical Cohort
- 20973 HIV-infected patients
- 312 strokes

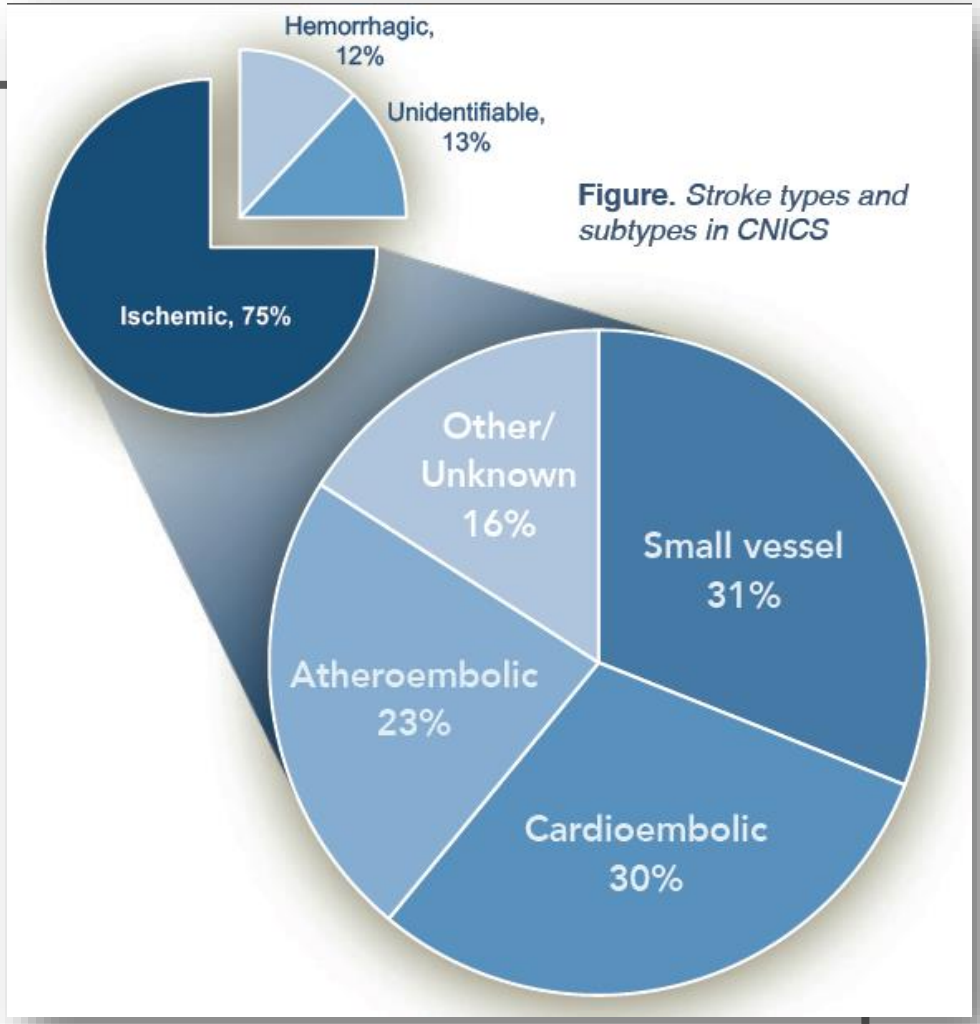


Figure. *Stroke types and subtypes in CNICS*

(Crane HM et al., Abstract 347, CROI 2017)

HIV status and the risk of ischemic stroke among men

- Veterans Aging Cohort Study-Virtual Cohort
- 76835 male patients, 2003-2009
- Median follow-up: 5.9 years

Table 4 Association between HIV infection and ischemic stroke[a]

	HR[b] (95% CI)	p Value
HIV infection	1.17 (1.01-1.36)	0.04
Age[c]	1.86 (1.72-2.01)	<0.01
Race/ethnicity[d]		
African American	1.33 (1.14-1.54)	<0.01
Hispanic	1.18 (0.91-1.53)	0.22
Other	0.96 (0.68-1.36)	0.83
Hypertension[e]		
Treated	1.76 (1.41-2.2)	<0.01
Untreated	2.41 (2.08-2.8)	<0.01
Diabetes	1.58 (1.36-1.83)	<0.01
Dyslipidemia	1.06 (0.91-1.23)	0.44
HMG-CoA reductase inhibitor use (yes/no)	0.91 (0.74-1.13)	0.39
Smoking status[d]		
Current smoker	1.56 (1.32-1.85)	<0.01
Past smoker	0.83 (0.65-1.07)	0.15
Hepatitis C infection	1.27 (1.09-1.48)	<0.01
Estimated GFR,[d] mL/min/1.73 m^2		
31-59	1.45 (1.15-1.83)	<0.01
<30	2.58 (1.7-3.92)	<0.01

Table 5 Association of HIV-specific biomarkers and ischemic stroke

HIV status	Stroke risk, HR (95% CI)[a]	p Value
Model 1		
HIV–	1 (referent)	
HIV+; CD4 ≥500	0.99 (0.78-1.25)	0.91
HIV+; CD4 200-499	1.06 (0.86-1.32)	0.57
HIV+; CD4 <200	1.66 (1.30-2.12)	<0.01
Model 2		
HIV–	1 (referent)	
HIV+; HIV-1 RNA <500	0.97 (0.80-1.19)	0.78
HIV+; HIV-1 RNA ≥500	1.36 (1.15-1.63)	<0.01
Model 3		
HIV–	1 (referent)	
HIV+; HIV-1 RNA <500; on HAART	0.89 (0.7-1.12)	0.3
HIV+; HIV-1 RNA ≥500; on HAART	1.38 (1.07-1.80)	0.02
HIV+; not on HAART	1.30 (1.09-1.56)	<0.01

(Sico JJ et al., Neurology 2015)

Immunosuppression and uncontrolled viremia associated with greater cerebrovascular risk

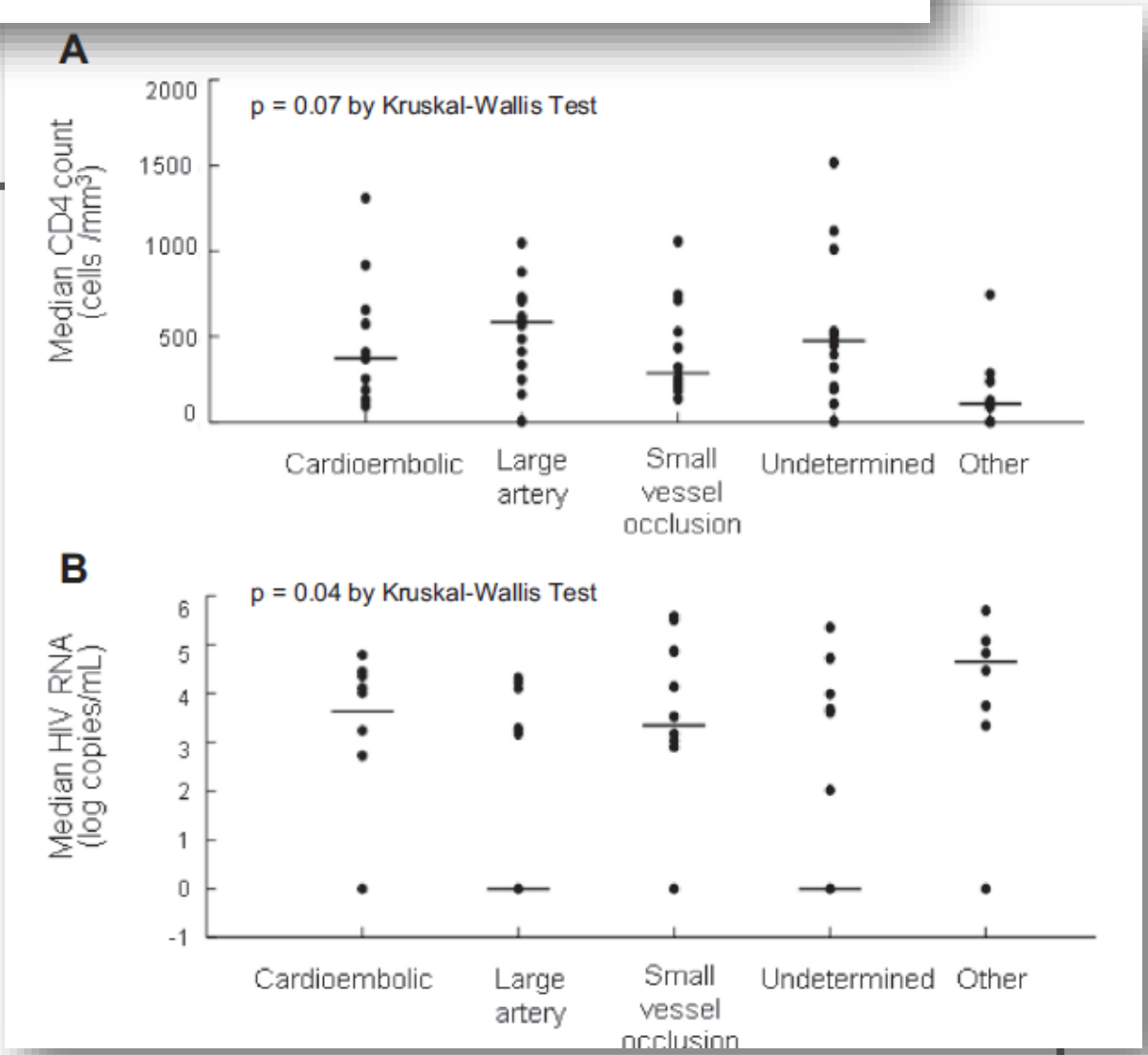
Association between CD4 count or viral load and stroke risk

Study	Predictor	Outcome	HR (95% CI)	P value
Danish HIV cohort (n=5031)	CD4 ≤200	Cerebrovascular events	2.26 (1.05-4.86)	NA
Partners HIV cohort (n=2255)	Detectable VL	Ischemic stroke	2.22 (1.23-4.00)	0.008
Partners HIV cohort (n=2278)	CD4 ≤200	Intracerebral hemorrhage	4.61 (2.09-10.17)	<0.001
North Carolina cohort (n=2515)	CD4 ≤200 Detectable VL	Cerebrovascular events	3.36 (1.92-5.88) 2.83 (1.64-4.87)	<0.01 <0.01

Rasmussen AIDS 2011, Chow JAIDS 2012, Chow Neurology 2014, Vinikoor AIDS Res Hum Retroviruses 2013, Chow CROI 2016

Greater Risk of Stroke of Undetermined Etiology in a Contemporary HIV-Infected Cohort Compared with Uninfected Individuals

- Case control study
- 60 HIV-positive and 60 HIV-negative patients with first-ever ischemic stroke
- 2000-2012



(Chow FC et al., J Stroke Cerebrovasc Dis 2017)

HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults

- Case-control study
- Malawi
- 222 adults with acute stroke and 503 population controls
- Median age: 60-57 years
- HIV prevalence: 31% in cases, 19% in controls

Table 3 Multivariate analysis for modifiable risk factors in younger and older stroke patients

	Prevalence		Younger (≤45 years) stroke[a]			Prevalence		Older (>45 years) stroke[b]		
	Cases (n = 61), n (%)	Controls (n = 151), n (%)	Multivariate,[c] OR	95% CI; p value	PAF,[d] (95% CI)	Cases (n = 16), n (%)	Controls (n = 352), n (%)	Multivariate,[c] OR	95% CI; p value	PAF,[d] (95% CI)
HIV-positive	41 (67)	41 (31)	5.57	2.43 to 12.8; <0.001	42 (20 to 58)	28 (18)	48 (14)	2.10	1.10 to 4.01; 0.024	6 (0.3 to 10)
HIV treatment status										
HIV-negative	20 (33)	104 (69)	1			131 (81)	304 (86)	1		
Untreated	24 (39)	29 (19)	5.04	1.99 to 12.8; 0.001		14 (9)	18 (5)	2.93	1.18 to 7.27; 0.020	
Had ART for <6 months	12 (20)	4 (3)	22.8	4.91 to 106; <0.001		4 (2)	3 (1)	15.9	2.03 to 124; 0.008	
Had ART for ≥6 months	5 (8)	13 (9)	3.27	0.88 to 12.1; 0.077		9 (6)	25 (7)	1.31	0.52 to 3.28; 0.591	
Hypertension	21 (34)	46 (31)	1.92	0.84 to 4.36; 0.119	11 (−4 to 24)	144 (89)	227 (64)	8.57	4.31 to 17.0; <0.001	68 (52 to 79)
Other vascular risk factors										
Diabetes	1 (2)	1 (1)	4.83	0.23 to 100; 0.308	1 (−2 to 4)	18 (11)	10 (2)	2.79	1.17 to 6.65; 0.021	4 (1 to 7)
Hypercholesterolemia	4 (7)	3 (2)	4.66	0.71 to 30.8; 0.110	3 (−1 to 7)	14 (9)	25 (7)	1.32	0.62 to 2.80; 0.465	1 (−3 to 4)
Recent infection	14 (23)	11 (7)	2.87	0.98 to 8.42; 0.054	9 (−1 to 17)	11 (7)	26 (7)	1.36	0.97 to 1.91; 0.077	2 (0.2 to 5)
Current smoker	8 (13)	16 (11)	0.73	0.18 to 2.87; 0.655	−2 (−11 to 6)	33 (21)	47 (13)	2.65	1.40 to 5.03; 0.003	8 (3 to 13)

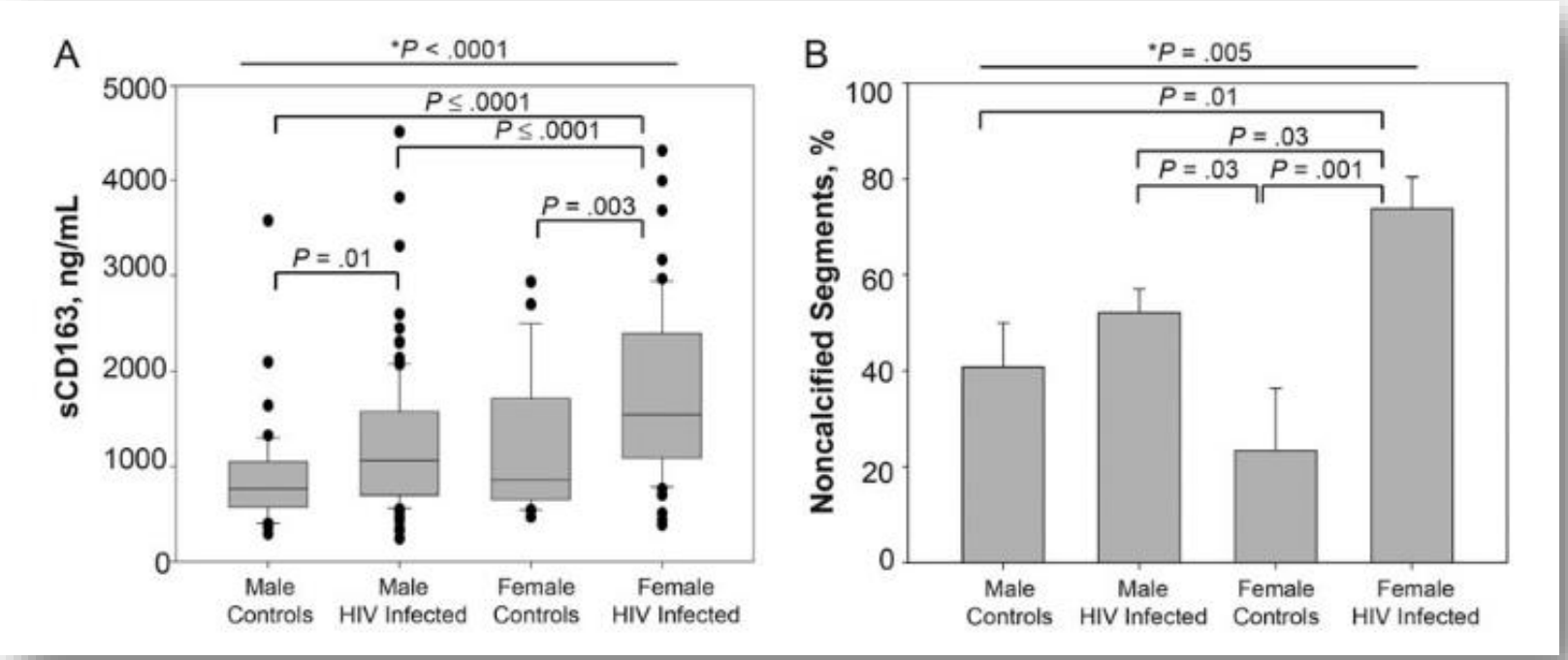
(Benjamin LA et al., Neurology 2016)

Elevated ischemic stroke risk in PLWH primarily driven by women

Chow et al. JAIDS 2012, Chow et al. CROI 2016

Noncalcified Coronary Atherosclerotic Plaque and Immune Activation in HIV-Infected Women

- Case-control study
- 90 women and 143 men (mean age, 47 years)
- HIV-positive group: HIV RNA<50 cp/mL in the 87% of cases
- Coronary CT angiography and immune activation markers



(Fitch KV et al., J Infect Dis 2013)

Reduced ovarian reserve relates to monocyte activation and subclinical coronary atherosclerotic plaque in women with HIV

- Cross-sectional study
- 49 HIV-positive and 25 HIV-negative women
- Coronary CT angiography and immune activation markers

	Premenopausal		Postmenopausal
MENSTRUAL HISTORY	Menses within the past 12 months		No menses within the past 12 months
AMH LEVELS	Detectable AMH; variable by age	Undetectable AMH	Undetectable AMH
	Group 1: Premenopausal with measurable AMH	Group 2: Premenopausal with reduced ovarian reserve	Group 3: Postmenopausal

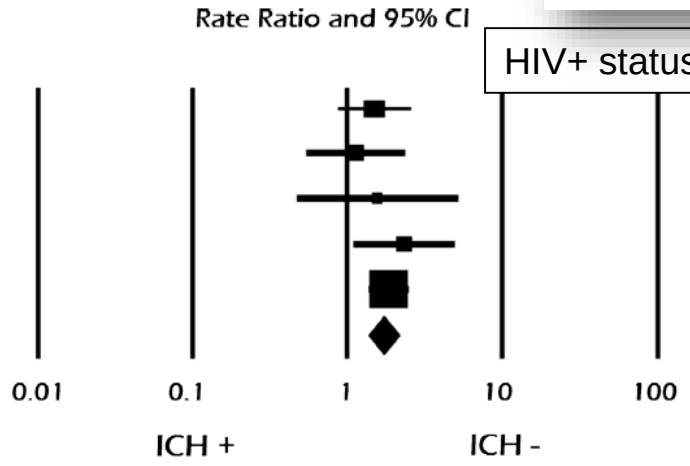
HIV-positive women

	Premenopausal with measurable AMH (group 1) ($N=17$)	Premenopausal with reduced ovarian reserve (group 2) ($N=7$)	Postmenopausal (group 3) ($N=25$)	*P* values
Demographics and traditional CV risk parameters				
Race/Ethnicity				0.62
White	23% (4/17)	43% (3/7)	24% (6/25)	
Black/African-American	65% (11/17)	57% (4/7)	56% (14/25)	
Hispanic	12% (2/17)	0% (0/7)	8% (2/25)	
Other	0% (0/17)	0% (0/7)	12% (3/25)	
Age (years)	40 (36, 45)	47 (47, 49)	52 (48, 57)	**<0.0001**
Current statin use	12% (2/17)	0% (0/7)	8% (2/25)	0.48
Current HTN	12% (2/17)	0% (0/7)	16% (4/25)	0.34
Current diabetes mellitus	6% (1/17)	0% (0/7)	20% (5/25)	0.15
Current smoking	47% (8/17)	71% (5/7)	40% (10/25)	0.33
Total cholesterol (mmol/l)	4.9±1.1	4.2±0.8	5.1±1.2	0.21
LDL cholesterol (mmol/l)	2.9±1.0	2.2±0.5	2.8±1.0	0.27
HDL cholesterol (mmol/l)	1.4±0.4	1.6±0.7	1.6±0.5	0.51
Triglycerides (mmol/l)	0.9 (0.8, 1.6)	1.1 (0.7, 1.1)	1.0 (0.8, 1.4)	0.83
BMI (kg/m^2)	29±5	27±5	27±5	0.41
Framingham point score	8±5	11±4	12±4	**0.009**
ASCVD risk score (%)[a]	0.8 (0.5, 1.8)	1.2 (0.9, 3.2)	1.8 (0.9, 4.4)	0.11
HCV co-infection	6% (1/17)	43% (3/7)	44% (11/25)	**0.01**
HIV-specific parameters				
Years since HIV	13±4	14±3	16±7	0.39
Currently on ART	100% (17/17)	86% (6/7)	100% (25/25)	0.13
Duration ART (years)	8±4	6±5	8±5	0.61
Current protease inhibitor	47% (8/17)	71% (5/7)	64% (16/25)	0.43
Duration protease inhibitor (years)	2 (0, 9)	2 (0, 11)	3 (1, 8)	0.84
Current NRTI	94% (16/17)	71% (5/7)	92% (23/25)	0.31
Duration NRTI (years)	7±4	4±5	7±5	0.33
Current NNRTI	35% (6/17)	14% (1/7)	8% (2/25)	0.08
Duration NNRTI (years)	2 (0, 4)	0 (0, 2)	0 (0, 0)	**0.01**
CD4$^+$ cell count (cell/μl)	535 (415, 723)	602 (416, 706)	513 (389, 737)	0.99
Nadir CD4$^+$ (cells/μl)	140 (63, 250)	249 (29, 350)	180 (50, 200)	0.47
Log viral load (copies/ml)	4.0±0.8	5.0±1.9	3.9±0.3	**0.03**
Viral load undetectable	81% (13/16)	71% (5/7)	87% (20/23)	0.64
Hormonal parameters				
Estradiol (pmol/l)	345 (128, 606)	40 (22, 70)	33 (22, 88)	**<0.0001**
FSH (mIU/ml)	7 (6, 11)	57 (50, 71)	64 (43, 78)	**<0.0001**
AMH <0.023 ng/ml	0% (0/17)	100% (7/7)	100% (25/25)	**<0.0001**
Immune parameters				
Log sCD163 (ng/ml)	3.1±0.2	3.3±0.2	3.3±0.2	**0.002**
Log sCD14 (ng/ml)	3.4±0.3	3.0±0.6	3.2±0.4	0.13
Log MCP-1 (pg/ml)	2.2±0.2	2.4±0.2	2.4±0.2	**0.02**
Log CXCL10 (pg/ml)	2.2±0.3	2.3±0.3	2.5±0.4	0.13
Cardiac CT parameters				
Any plaque	6% (1/17)	67% (4/6)	48% (10/21)	**0.002**
# Plaque segments	0 (0, 0)	2.0 (0, 4.5)	0 (0, 3.5)	**0.005**
	0.1±0.2	2.3±2.4	2.0±3.0	
Any noncalcified plaque	6% (1/17)	67% (4/6)	43% (9/21)	**0.004**
# Noncalcified plaque segments	0 (0, 0)	1.5 (0, 2.3)	0 (0, 2.5)	**0.009**
	0.1±0.2	2.3±2.3	2.2±3.0	
% of plaque segments which are noncalcified	100 (100, 100)	58 (50, 92)	75 (58, 100)	0.41

(Looby SE et al., AIDS 2016)

Risk of intracerebral hemorrhage in HIV/AIDS: a systematic review and meta-analysis

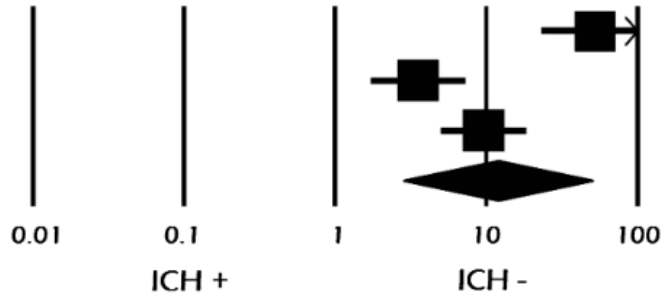
HIV+ status alone



	STATISTICS FOR INDIVIDUAL STUDIES					ICH /TOTAL	
STUDY	RATE RATIO	LOWER LIMIT	UPPER LIMIT	Z-VALUE	P	HIV+	HIV-
Justice et al, 2008	1.48	0.88	2.55	1.49	0.137	23/98,979	33/212,585
Rasmussen et al, 2011*	1.14	0.55	2.35	0.34	0.73	8/36,161	80/410,666
Rasmussen et al, 2011	1.57	0.48	5.17	0.74	0.46	3/4,225	27/59,582
Durand et al, 2013	2.33	1.11	4.9	2.24	0.025	11/25,440	19/102,560
Chow et al, 2014	1.85	1.39	2.46	4.25	<0.0001	58/25,379	262/212,38
	1.73	1.39	2.16	4.85	<0.0001		

- 5 eligible studies
- 1985-2010
- 310,426 person-years evaluated
- Pooled crude incidence ratio for ICH in HIV/AIDS: 3.40 (95% CI 1.44-8.04, p=0.005)

AIDS status alone



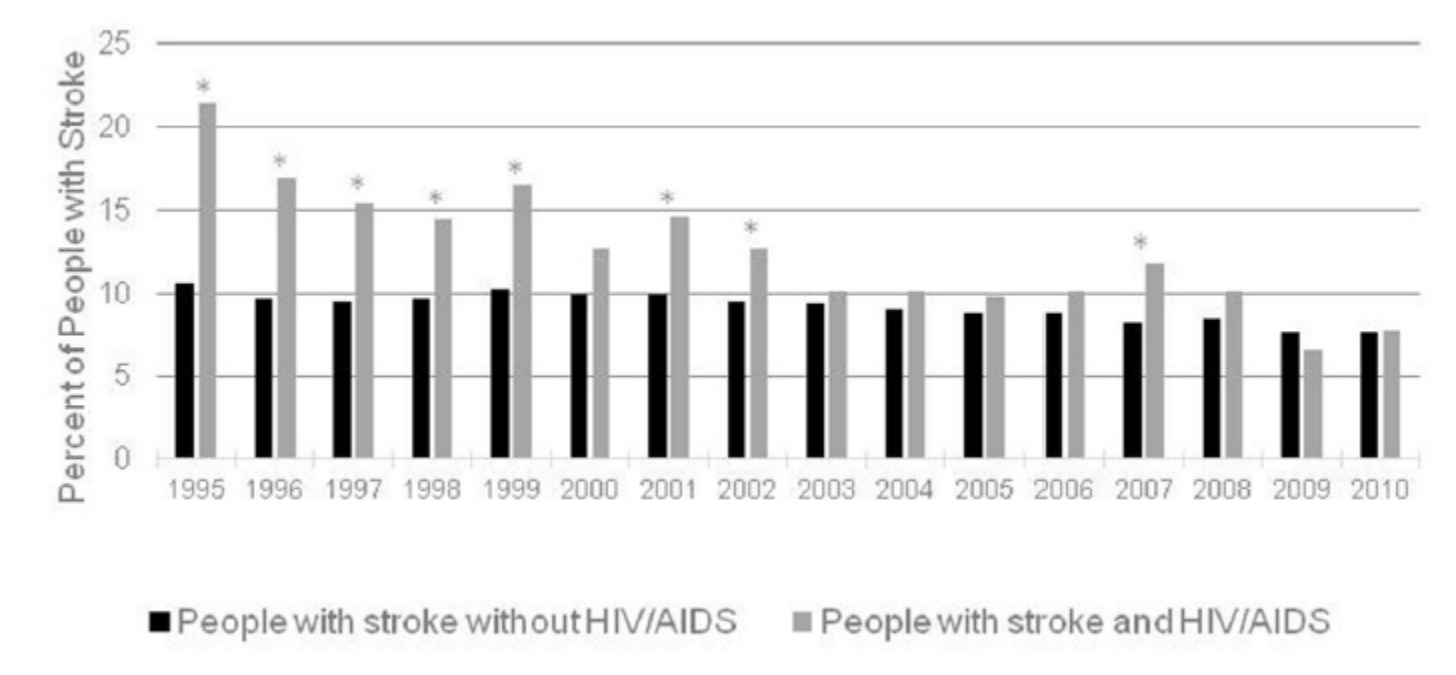
	STATISTICS FOR INDIVIDUAL STUDIES					ICH /TOTAL	
STUDY	RATE RATIO	LOWER LIMIT	UPPER LIMIT	Z-VALUE	P	AIDS+	AIDS-
Cole et al, 2004	52.76	23.36	119.15	9.54	<0.0001	6/2,829	165/4,104,734
Justice et al, 2008	3.54	1.74	7.19	3.5	<0.0001	10/212,589	33/212,589
Durand et al, 2013	9.61	5.1	18.15	6.98	<0.0001	19/10,670	19/102,560
	11.99	2.84	50.54	3.38	0.001		

(Behrouz R et al., J Neurovirol 2016)

Epidemiology of Acquired Immune Deficiency Syndrome and Cerebrovascular Disease in a Post Antiretroviral Era

- U.S. National Inpatient Sample (NIS)
- 1,874,067 stroke hospitalizations
- 1995-2010

Mortality rates for stroke



(Kucab P et al., J Stroke Cerebrovasc Dis 2017)

History of AIDS in HIV-Infected Patients Is Associated With Higher In-Hospital Mortality Following Admission for Acute Myocardial Infarction and Stroke

- U.S. National Inpatient Sample (NIS)
- 18,369,785 AMI/stroke hospitalizations
- 2002-2012

Stroke-associated hospitalizations

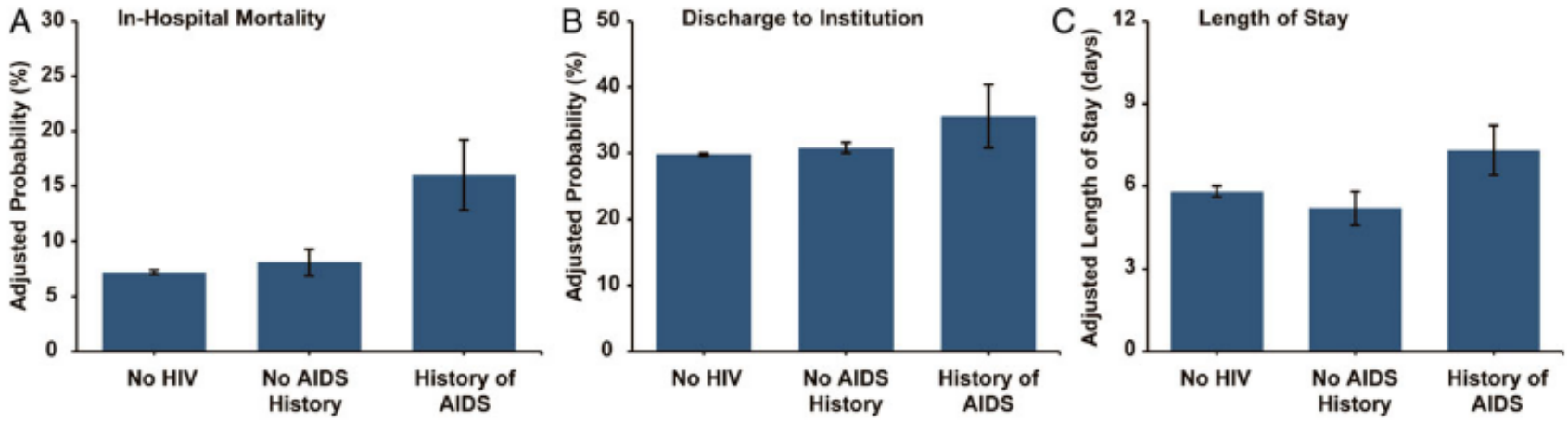
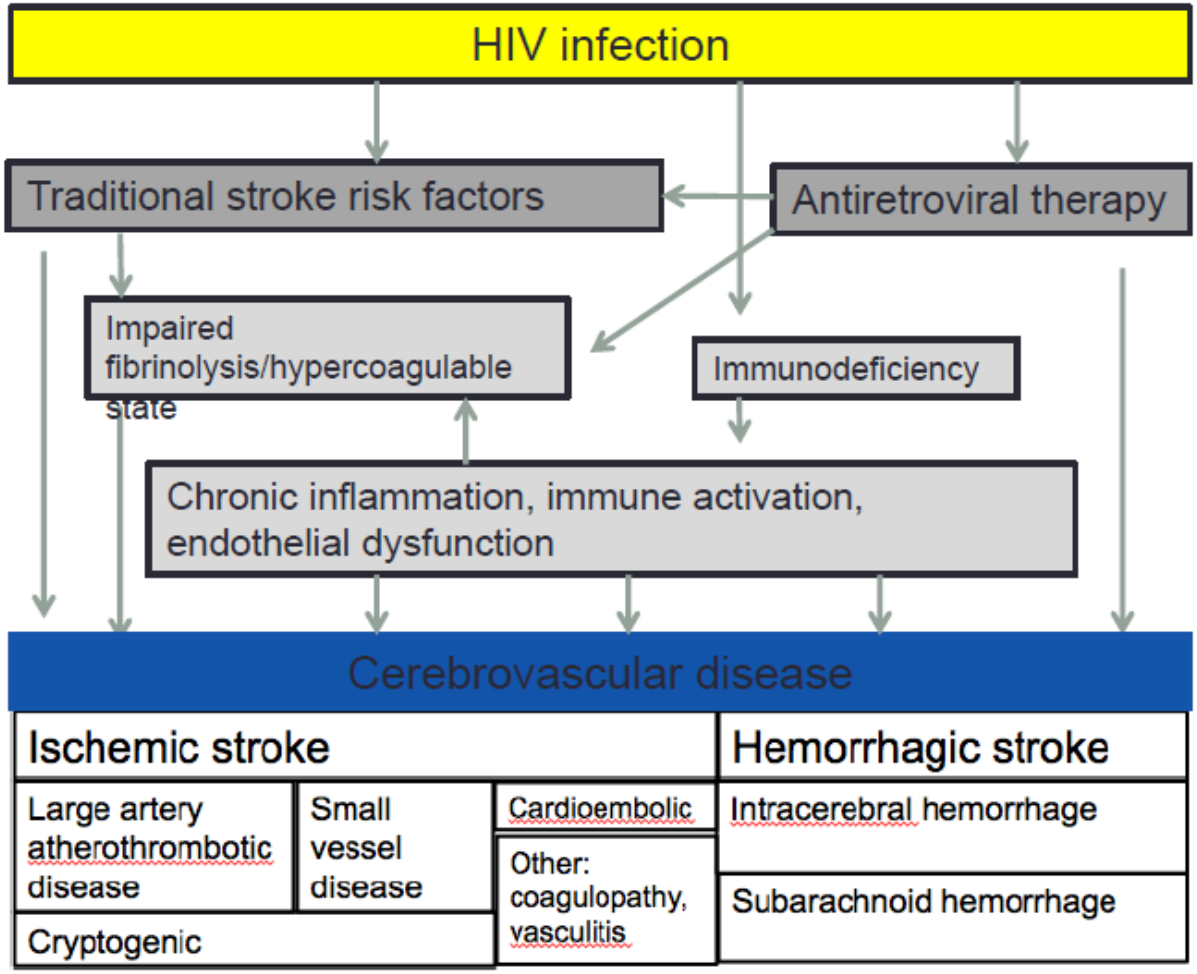


Figure 3. Adjusted values for major outcome metrics for stroke-associated hospitalizations, by human immunodeficiency virus (HIV) diagnosis code, Nationwide Inpatient Sample, 2002–2012. All point estimates were adjusted for age, sex, race/ethnicity, insurance status, hospital size, hospital with academic affiliation, urban versus rural hospital, hospital region, tobacco use, substance abuse, and comorbid medical conditions.

(Okeke NL et al., J Infect Dis 2016)

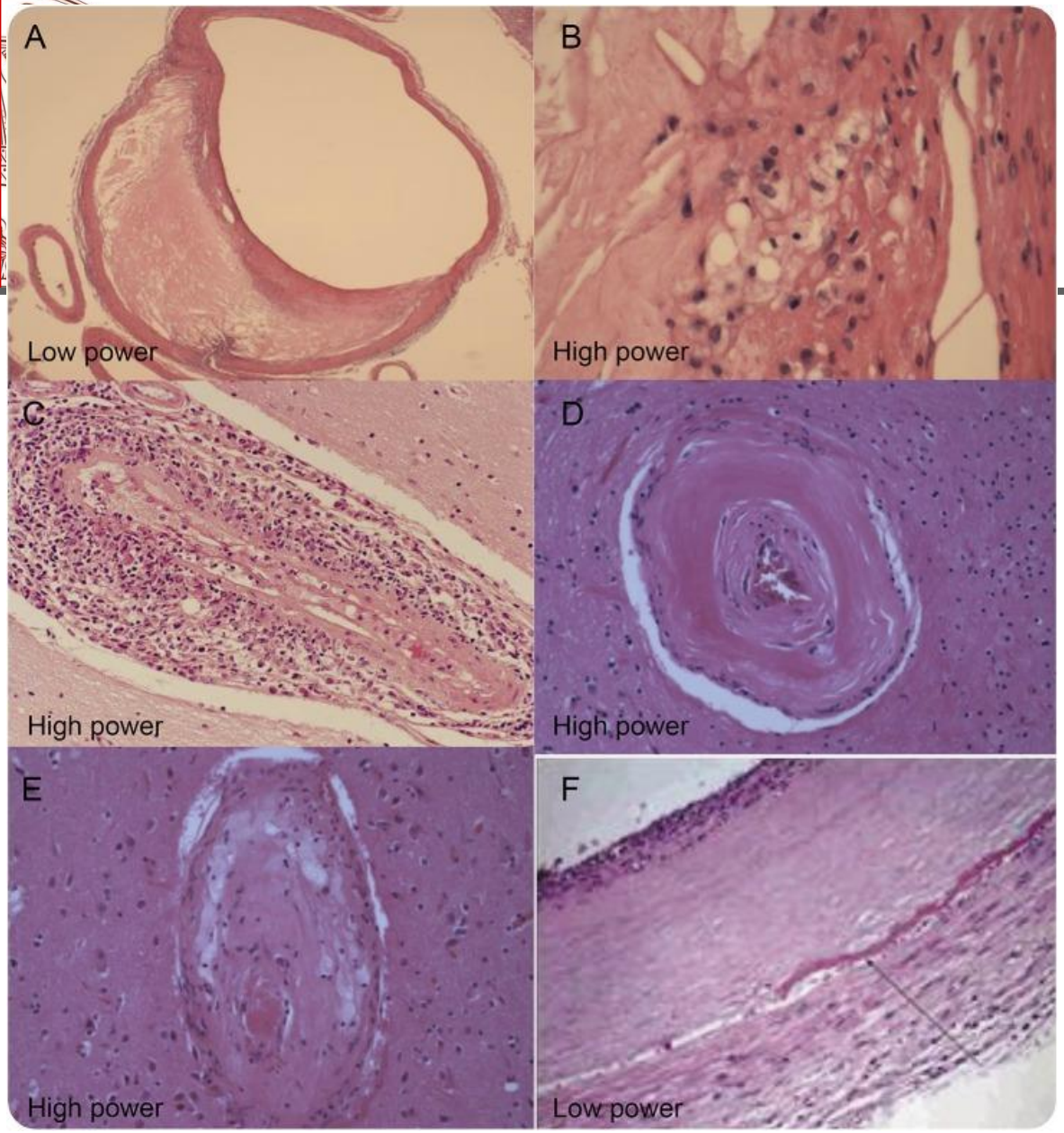
Mechanisms of increased vascular risk in HIV



- Higher rates of traditional vascular risk factors including smoking and substance abuse
- Antiretroviral therapy (ART)
- Chronic inflammation and activation of the immune system and endothelium

El Sadr NEJM 2006, Hsue AIDS 2009, Lichtenstein CID 2010, Triant JAIDS 2010, Kaplan JID 2011, Friis-Moller NEJM 2007, Worm JID 2010, Grinspoon NEJM 2005

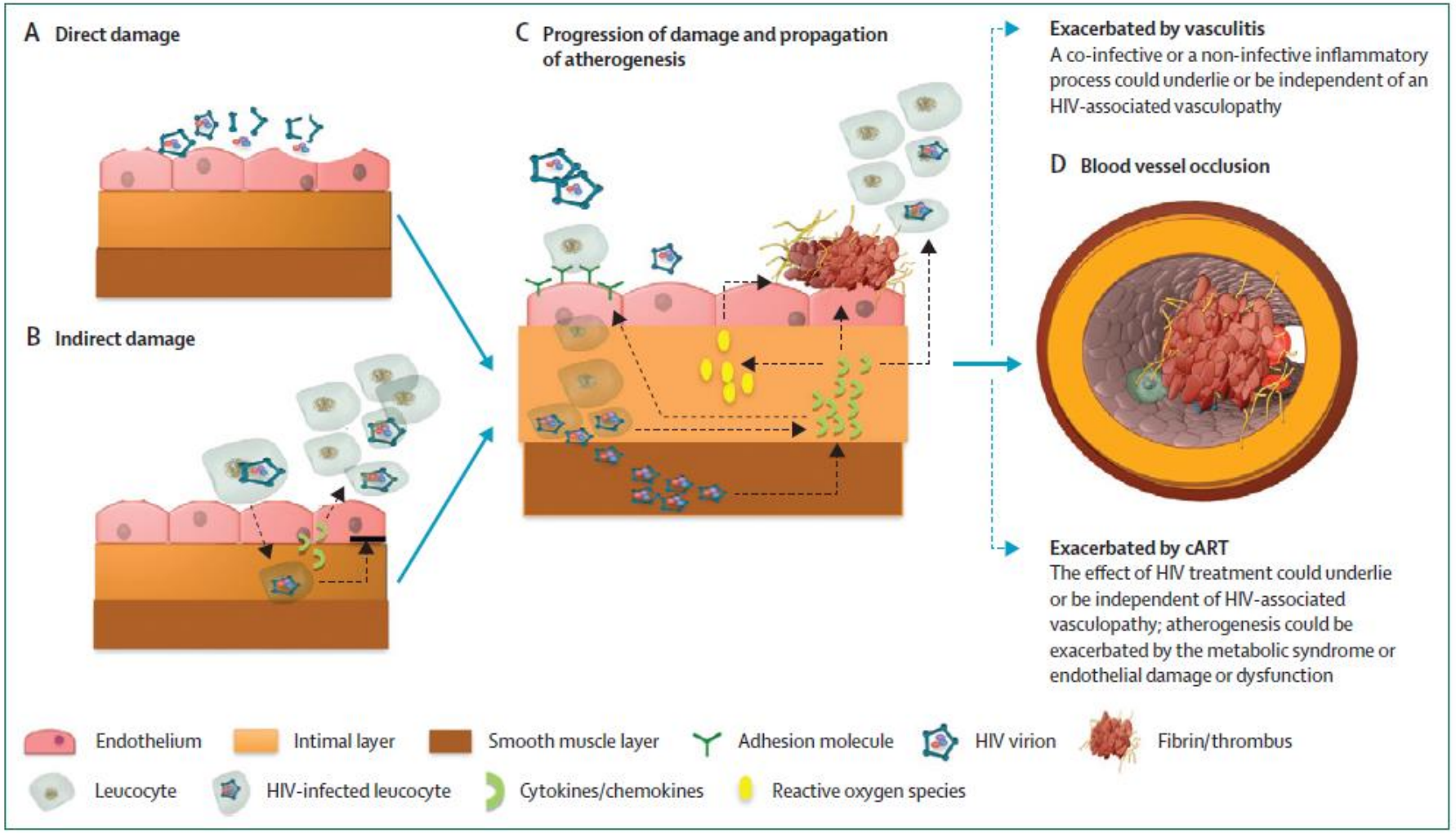
HIV-associated vasculopathy



A,B- atherosclerotic vasculopathy
C- HIV-associated vasculitis
D- small vessel disease: arteriolosclerosis
E- small vessel disease: lipohyalinosis
F- non-atherosclerotic vasculopathy

(Benjamin LA et al., Neurol Neuroimmunol Neuroinflamm 2016)

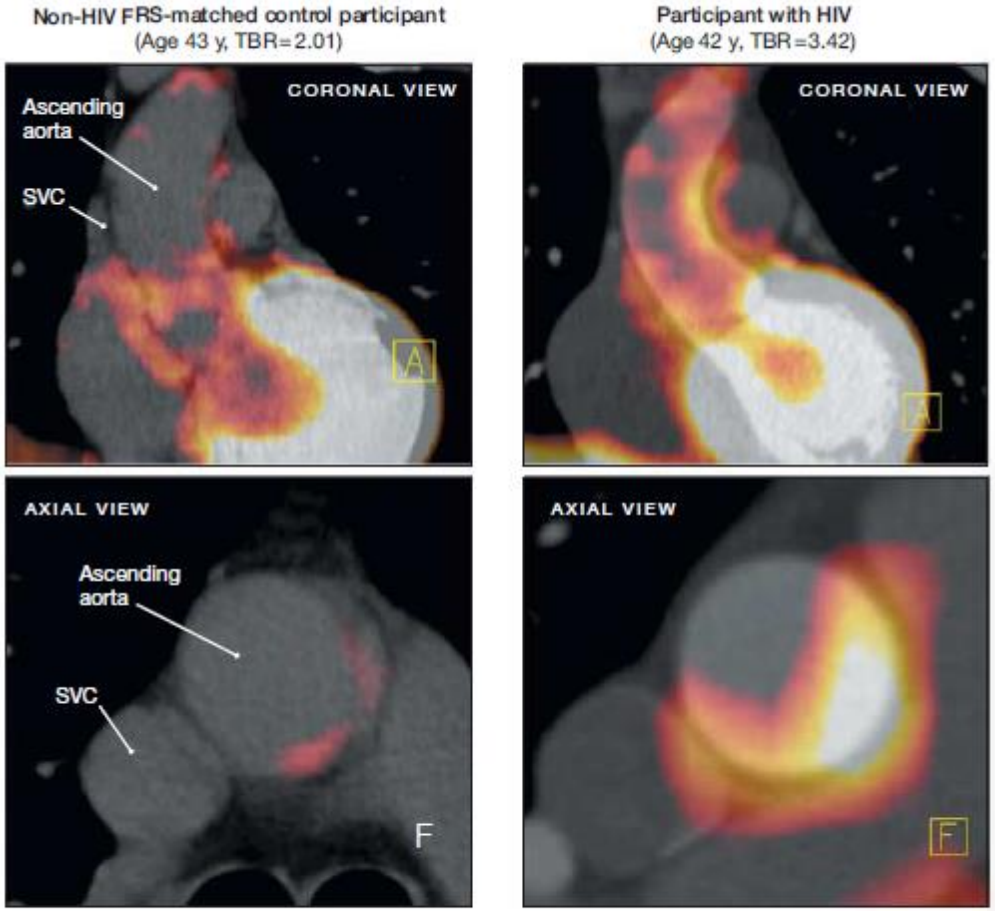
HIV-associated vasculopathy



(Benjamin LA et al., Lancet Neurol 2012)

Arterial Inflammation in Patients With HIV

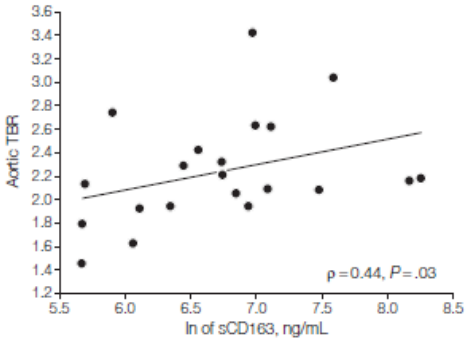
Figure 2. Representative ^{18}F-FDG-PET/CT Imaging of the Aorta



^{18}F-FDG-PET indicates ^{18}fluorine-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; FRS, Framingham risk score; HIV, human immunodeficiency virus; SVC, superior vena cava; TBR, target-to-background ratio. There is increased aortic PET-FDG uptake (red coloration) in a participant infected with HIV compared with a non-HIV FRS-matched control participant. Neither participant had known heart disease. For each participant, the FRS was low with a score of 2 and calcium was not present on the cardiac CT scan. Neither participant was receiving a statin. A indicates anterior-posterior orientation and F, foot-head orientation.

- Cross-sectional study
- 81 patients
- HIV+ patients on cART and with HIV RNA<48 cp/mL; mean CD4 count 641 cells/mmc
- Cardiac ^{18}F-FDG-PET and coronary CT scan
- Serum inflammatory markers

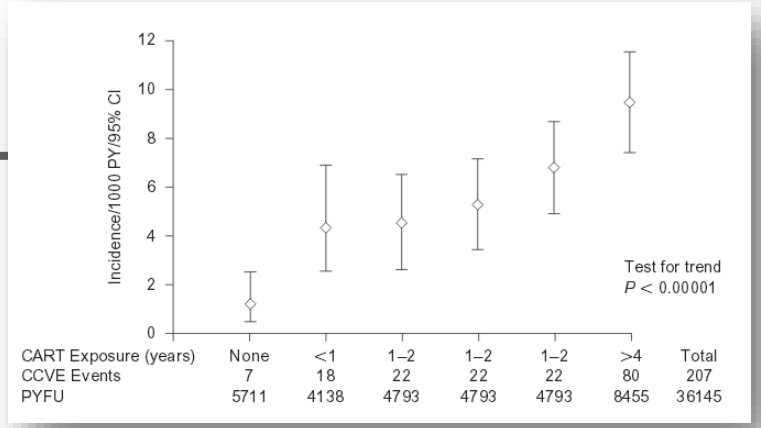
Figure 3. Linear Regression of Aortic Target-to-Background Ratio (TBR) vs ln of sCD163 in 21 Patients With HIV With Undetectable Viral Load



HIV indicates human immunodeficiency virus; ln, natural logarithm; sCD163, soluble CD163. Solid line represents the linear regression fit across all 21 patients (aortic TBR=0.8+0.22×ln sCD163). A sCD163 level of more than 800 ng/mL corresponds with a ln of more than 6.7 and an aortic TBR of more than 2.3.

(Subramanian S et al., JAMA 2012)

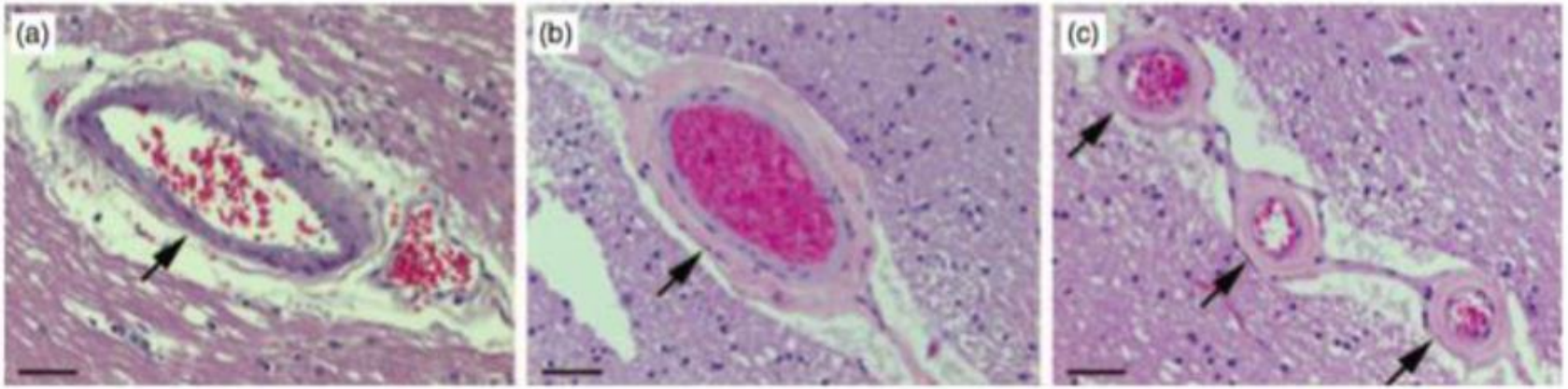
Association between cART and cerebrovascular events in cohort studies



Reference	Study	No. of patients	Results
D'Arminio Monforte, 2004	D:A:D	36145	Increased incidence of CVD with exposure to cART (no association bewteen cART and stroke)
Bozzette, 2003	Veterans	36766	No relation between cART (NRTI, NNRTI or PI) and risk of CV events
Rasmussen LD, 2011	Danish Cohort	5031	Abacavir associated with increased risk of CV events
Choi AI, 2011	Veterans	10931	Abacavir associated with increased risk of CV events

HIV protease inhibitor exposure predicts cerebral small vessel disease

Virawudh Soontornniyomkij[a,b], Anya Umlauf[a], Sandra A. Chung[a], Megan L. Cochran[a], Benchawanna Soontornniyomkij[b], Ben Gouaux[a], Will Toperoff[a], David J. Moore[a,b], Eliezer Masliah[a,c,d], Ronald J. Ellis[a,d],

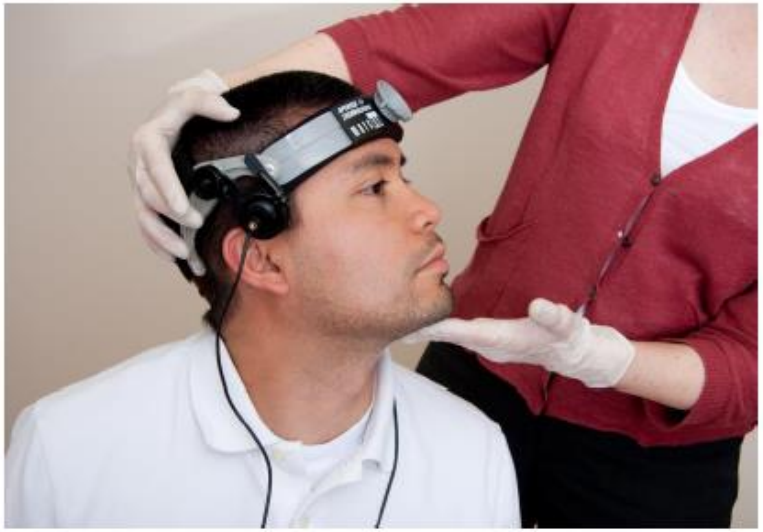


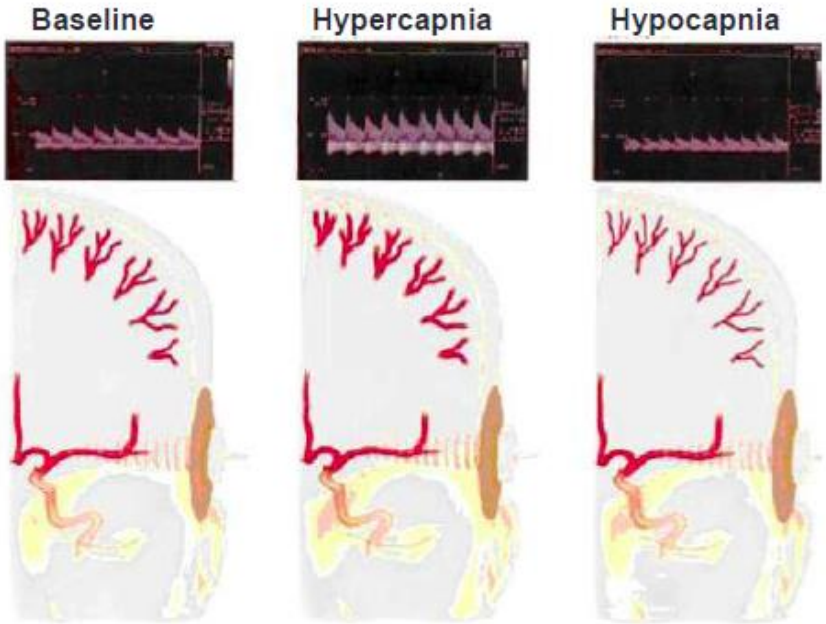
- Of 137 cases, 25% with mild cerebral SVD and 47% with moderate-severe SVD
- In multivariable analysis, PI-based regimen associated with significantly higher likelihood of mild (OR 2.7) and moderate (OR 2.4) SVD
- SVD at autopsy was associated with an antemortem diagnosis of cognitive impairment

Soontornniyomkij et al. AIDS 2014

Effect of ART on cerebral endothelial function

- 75 PLWH in Beijing (mean age, 41 yr; median time since diagnosis, 5 yr)
- 100% on ART and virally suppressed
- Majority of participants on 3TC + TDF or AZT + EFZ, NVP or LPV/r
- Measured cerebral vasoreactivity, marker of cerebrovascular endothelial function associated with large artery & small vessel disease, using transcranial Doppler breath-holding challenge

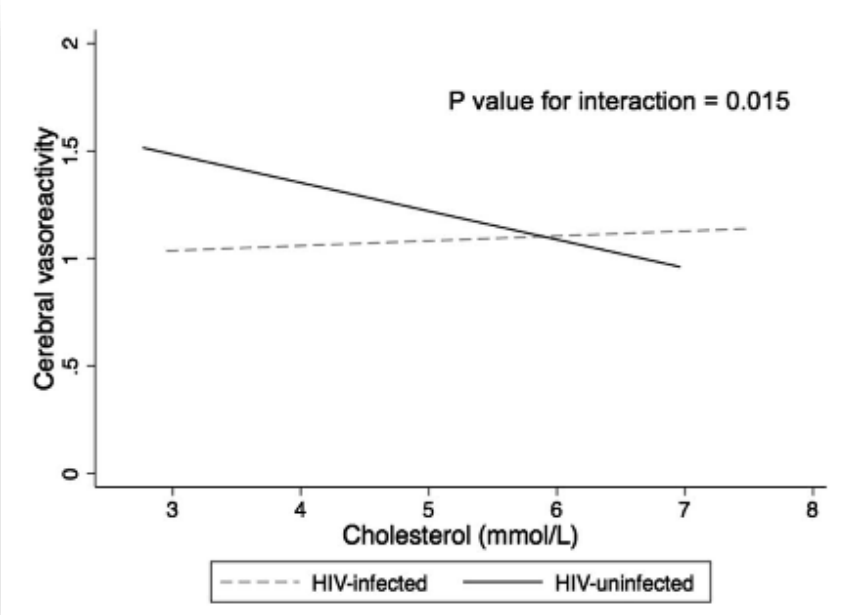


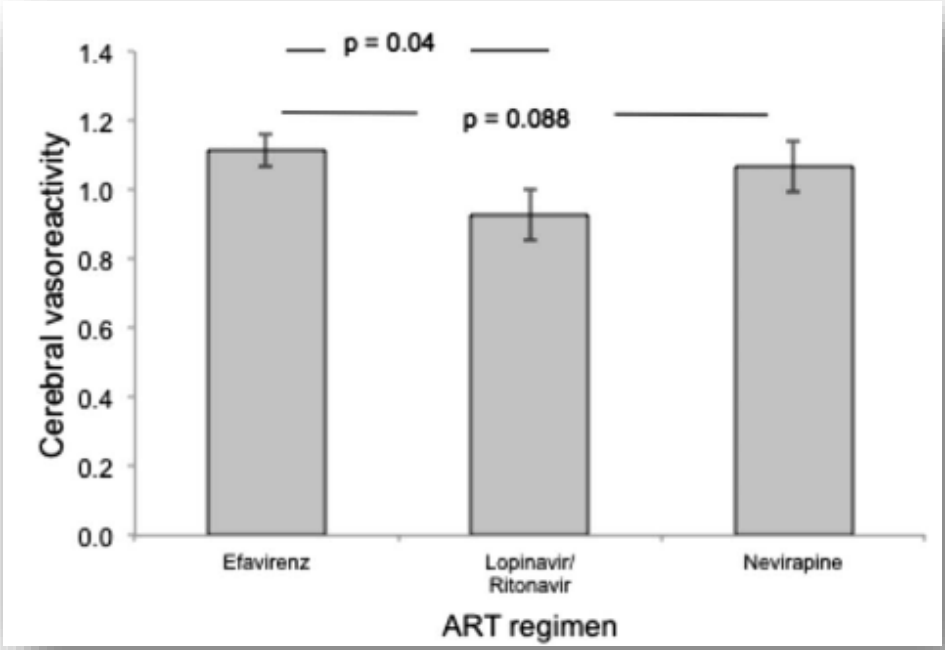


Chow et al. ANA 2016, Vernieri et al. 1999, www.swedish.org/services/neurosciences-institute

Relationship Between HIV Infection, Antiretroviral Therapy, Inflammatory Markers, and Cerebrovascular Endothelial Function Among Adults in Urban China

-Case control study
-78 HIV-positive patients on cART and with undetectable HIV RNA
-18 HIV-negative controls





(Chow FC et al., J AIDS 2017)

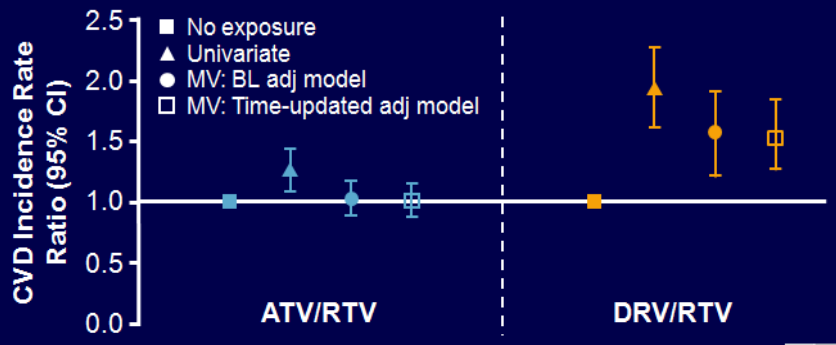
D:A:D: Exposure to ATV/RTV or DRV/RTV and Risk of CVD

- Prospective analysis of pts followed from 1/1/2009 (BL) to earliest CVD, last visit + 6 mos, or 2/1/2016 (N = 35,711)
  - 1157 pts (3.2%) developed CVD (MI, stroke, sudden cardiac death, invasive CV procedure)
- Cumulative expos. to DRV/RTV, but not ATV/RTV, assoc. with increased CVD risk in multivariate analysis: 59% risk increase per 5-yrs' DRV/RTV
  - Assoc. does not appear to be mediated through dyslipidemia, in contrast with first-generation PIs
- Limitations: potential for unmeasured confounding; observational study; unable to distinguish between DRV/RTV 800/100 mg QD vs DRV/RTV 600/100 mg BID

CVD Risk per 5 Yrs of ARV Exposure, IRR (95% CI)		
Model	**ATV/RTV**	**DRV/RTV**
Univariate	1.25 (1.10-1.43)	1.93 (1.63-2.28)
Multivariate		
▪ Baseline adjusted*	1.03 (0.90-1.18)	1.59 (1.33-1.91)
▪ Time-updated adjusted*	1.01 (0.88-1.16)	1.53 (1.28-1.84)

*Adjusted for: BMI, CKD, DM, CD4, dyslipidemia.

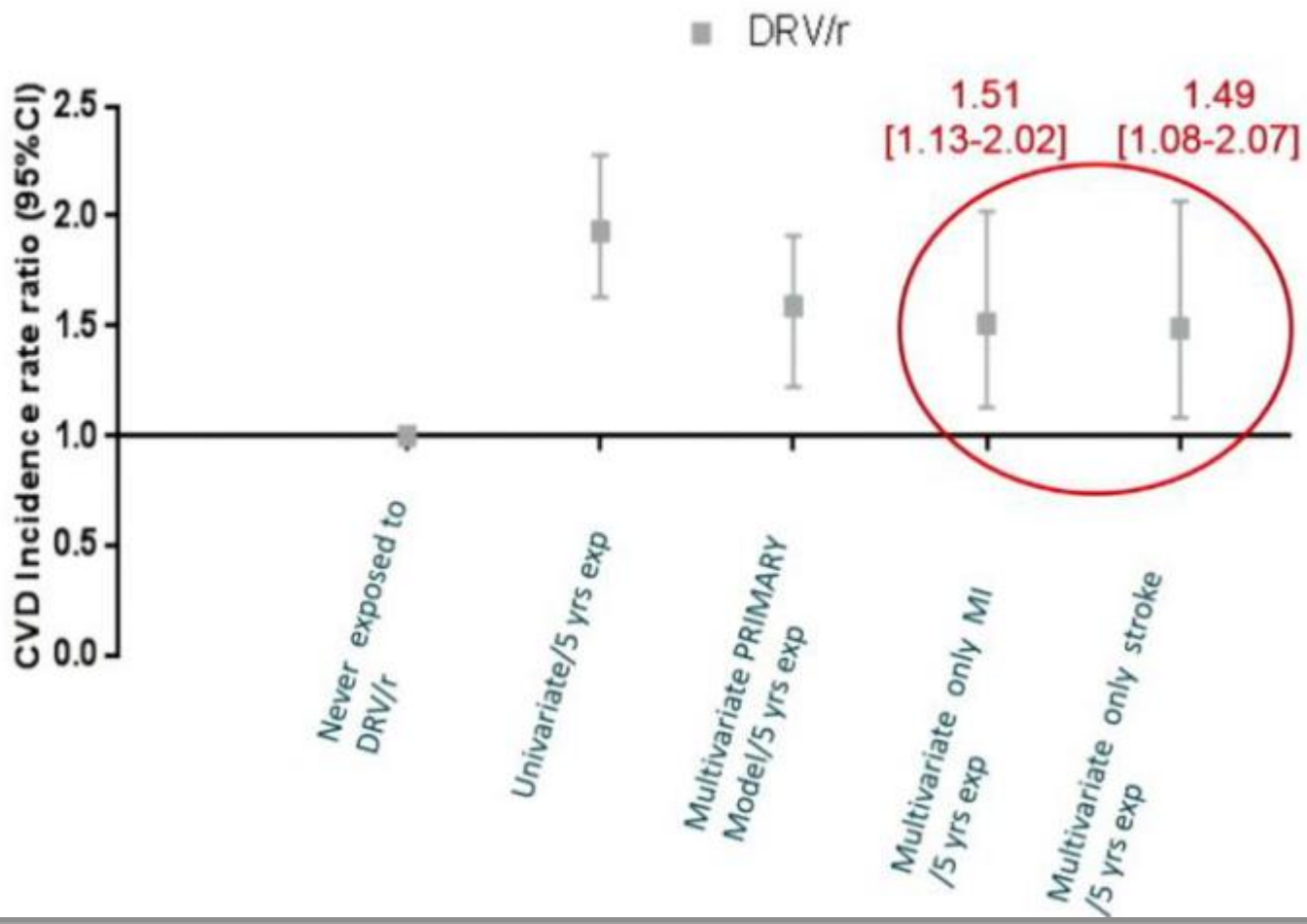
Relationship Between 5-Yr Exposure to ARVs and CVD



Ryom L, et al. CROI 2017. Abstract 128LB. Reproduced with permission.

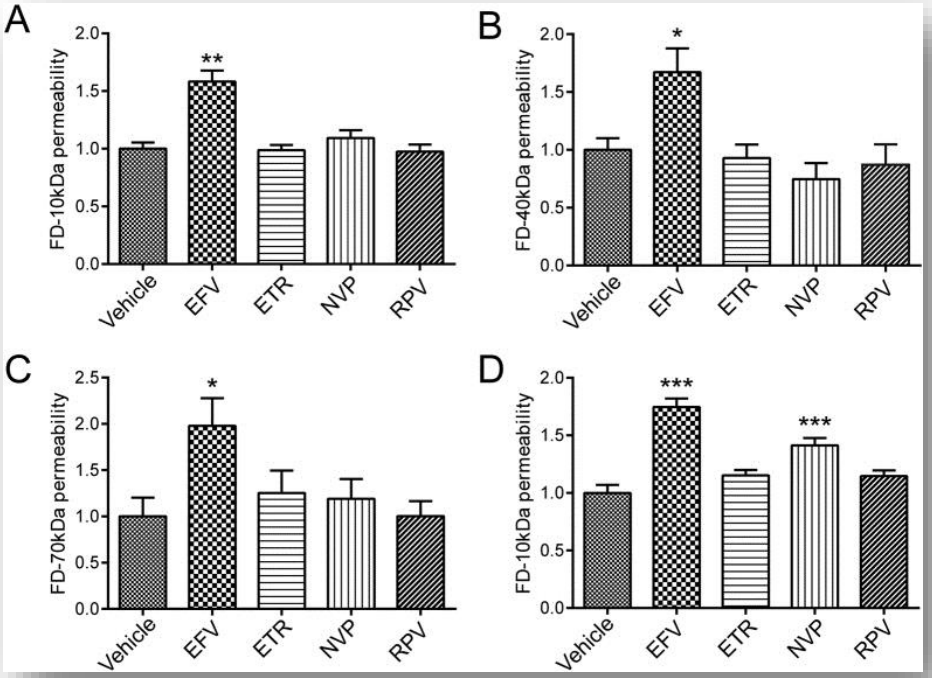
Slide credit: clinicaloptions.com

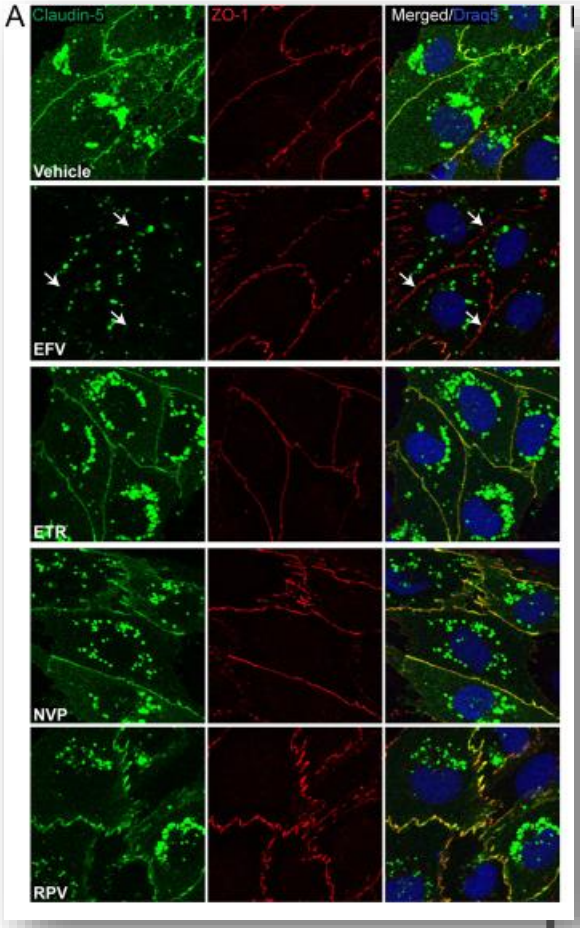
Association Between CVD & Cumulative DRV/r Use; MI (n=477) and Stroke (n= 395) Separately



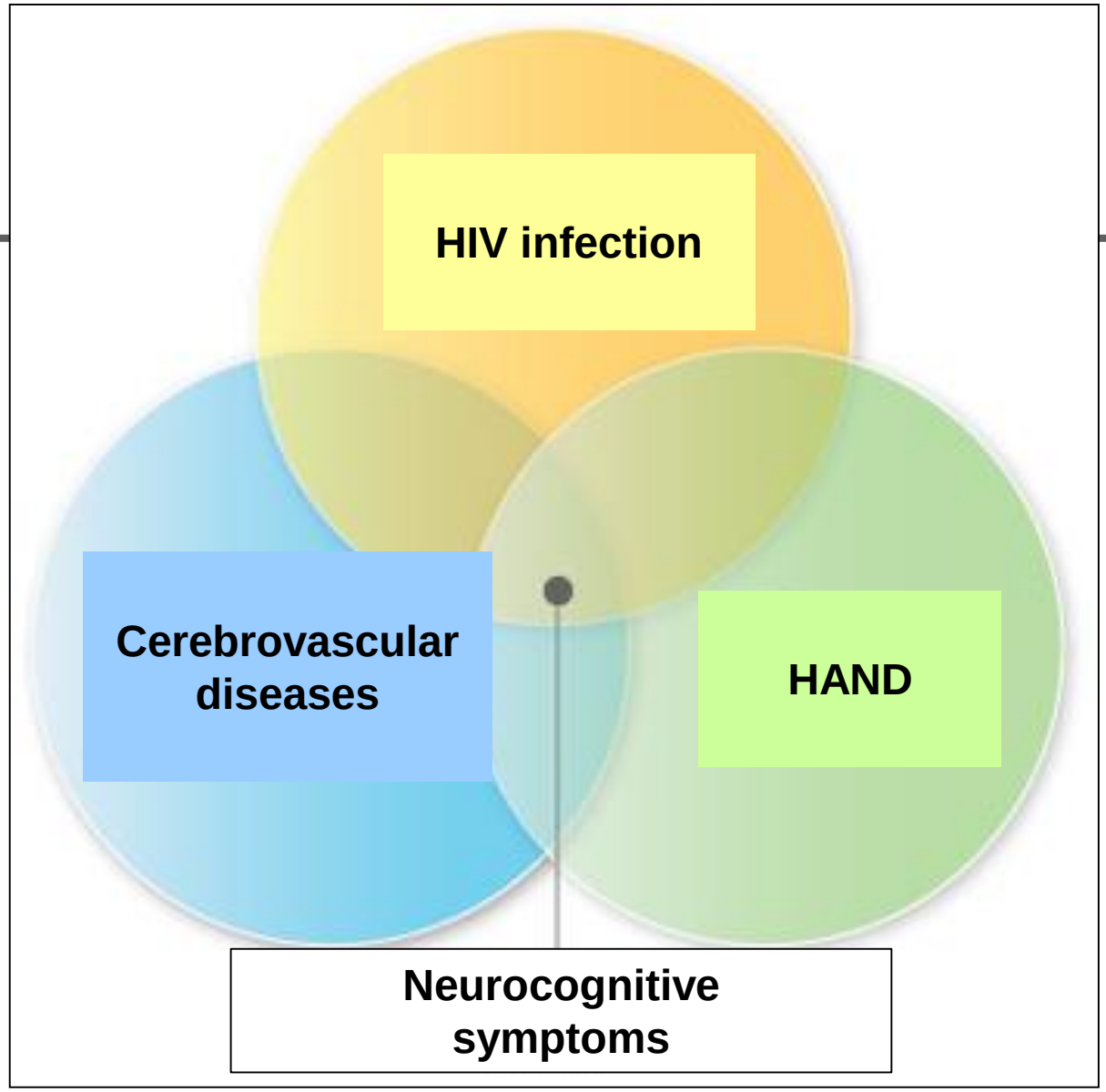
(Ryom L et al., Abstract 128LB, CROI 2017)

Antiretroviral Treatment with Efavirenz Disrupts the Blood-Brain Barrier Integrity and Increases Stroke Severity





(Bertrand L et al., Sci Rep 2016)



Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons

- SMART Substudy
- 292 HIV+ patients
- 92% on cART
- Median CD4 count: 536 cells/mm^3
- 88% with HIV RNA <400 cp/mL

Table 3 Association of participants' characteristics with neurocognitive performance: Regression coefficients and p values in multivariate linear (QNPZ-5) and logistic (NCI) regression[a]

				z Scores					Test scores (seconds or taps)				
Factors[b]	% of population	NCI[c]	QNPZ-5	GPB	CT1	CT2	TG	FTT	GPB	CT1	CT2	TG	FTT
Age (per 10 y)		NS	NS	NS	NS	NS	NS	NS	p=0.009[a] 4.5	p<0.001[a] 6.0	p<0.001[a] 12.2	NS	p=0.007[a] −1.5
Gender (female vs male)	41.7	NS	p=0.05[a] −0.21	NS	NS	NS	p<0.001[a] −1.13	p=0.05[a] 0.27	NS	NS	NS	p<0.001[a] 1.38	p<0.001[a] −5.2
Race/ethnicity (black vs other)	19.7	p=0.08 2.25	p<0.001[a] −0.48	NS	p<0.001[a] −1.10	p<0.001[a] −1.03	NS	NS	p=0.005[a] 11.6	p<0.001[a] 17.6	p<0.001[a] 33.4	NS	NS
Education (>12 y)	46.6	NS	NS	NS	NS	NS	p=0.002[a] −0.59	NS	NS	p<0.001[a] −10.4	p<0.001[a] −20.5	p=0.03[a] −0.51	p=0.007[a] 2.4
Location		NS	NS	p=0.007[a]	p=0.001[a]	p<0.001[a]	p=0.005[a]	p=0.004[a]	p=0.10	p<0.001[a]	p<0.001[a]	p=0.004[a]	p=0.003[a]
Brazil[d]	15.2			0.41	−0.97	−1.04	0.16	0.54	−4.0	15.5	35.9	−0.40	3.9
Thailand[d]	50.0			0.60	−0.29	−0.43	−0.72	−0.09	−9.0	5.3	16.3	0.76	−0.4
Prior AIDS	20.7	p=0.08 0.41	p=0.05[a] 0.24	—	p=0.08 0.36	—	p=0.03[a] 0.51	—	—	p=0.07 −5.6	—	p=0.05[a] −0.58	—
Hepatitis B	2.1	—	p=0.05[a] −0.66	p=0.03[a] −1.05	p=0.01[a] −1.41	p=0.08 −0.85	—	—	p=0.001[a] 30.7	p=0.06 15.5	NS	—	—
Prior CVD	3.5	p=0.01[a] 6.17	p=0.02[a] −0.65	p=0.06 −0.71	NS	—	p=0.08 −0.98	p=0.09 −0.62	p=0.001[a] 24.8	p=0.06 12.6	—	p=0.09 1.15	p=0.06 −4.6
Blood pressure-lowering drugs	11.0	—	p=0.03[a] −0.37	—	—	p=0.03[a] −0.53	p=0.01[a] −0.84	—	—	—	p=0.05[a] 15.4	p=0.03[a] 0.88	—
Total cholesterol (per 10 mg/mL)		p=0.06 1.08	p=0.02[a] −0.03	—	p=0.06 −0.04	p=0.06 −0.03	—	—	—	p=0.06 0.5	—	—	—
HDL (per 10 mg/mL)		—	—	p=0.03[a] −0.11	p=0.05[a] −0.12	—	—	—	p=0.02[a] 2.5	p=0.05[a] 1.9	NS	—	—
Depression (CES-D ≥ 16)	23.8	—	p=0.07 −0.21	—	—	—	p<0.001[a] −0.91	—	NS	—	—	p<0.001[a] 1.07	—

(Wright EJ et al., Neurology 2010)

Diabetes and cognitive decline in a French cohort of patients infected with HIV-1

- ANRS CO3 Aquitaine Cohort
- 2007-2009
- 400 HIV+ patients
- 2-year follow-up

Table 4 Multivariable analyses of the association between baseline glycemia status and change in cognitive performances, ANRS CO3 Aquitaine cohort, 2007-2011

		Glycemia status at baseline			
		Normal (n = 232)	Impaired glycemia (n = 24)	Diabetes (n = 27)	
Cognitive tests	Yearly mean change (SD)	Adjusted yearly mean change (SE)	Adjusted yearly mean change (SE)	Adjusted yearly mean change (SE)	p Value[a]
TMT, Part A[b]	−0.037 (0.31)	−0.068 (0.024)	0.068 (0.072)	0.078 (0.073)	0.04
TMT, Part B[b]	−0.22 (2.15)	−0.27 (0.17)	0.45 (0.53)	0.96 (0.51)	0.01
DSST score	0.27 (2.7)	0.29 (0.21)	0.44 (0.62)	0.24 (0.63)	0.97
FCSRT-immediate recall score	0.77 (2.34)	0.64 (0.19)	1.18 (0.55)	0.33 (0.56)	0.54
FCSRT-delayed recall score	0.29 (0.99)	0.27 (0.07)	−0.13 (0.22)	−0.54 (0.23)	0.03
IST score 30 s	0.77 (3.39)	0.79 (0.23)	0.90 (0.69)	0.58 (0.71)	0.94
ROCF-copy score	−0.47 (1.83)	−0.07 (0.14)	−0.55 (0.41)	−0.62 (0.41)	0.0002
ROCF-recall score	0.63 (2.15)	0.69 (0.16)	−1.25 (0.48)	−2.33 (0.48)	0.0002
Digit span score	0.04 (0.60)	0.05 (0.04)	−0.04 (0.13)	−0.09 (0.14)	0.53
PPT score	−0.03 (9.3)	0.02 (0.78)	−1.86 (2.29)	−2.82 (2.32)	0.07

(Dufouil C et al., Neurology 2015)

White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on combination antiretroviral therapy

- Cross-sectional study
- 103 aviremic HIV-infected men on cART vs 70 HIV-negative controls

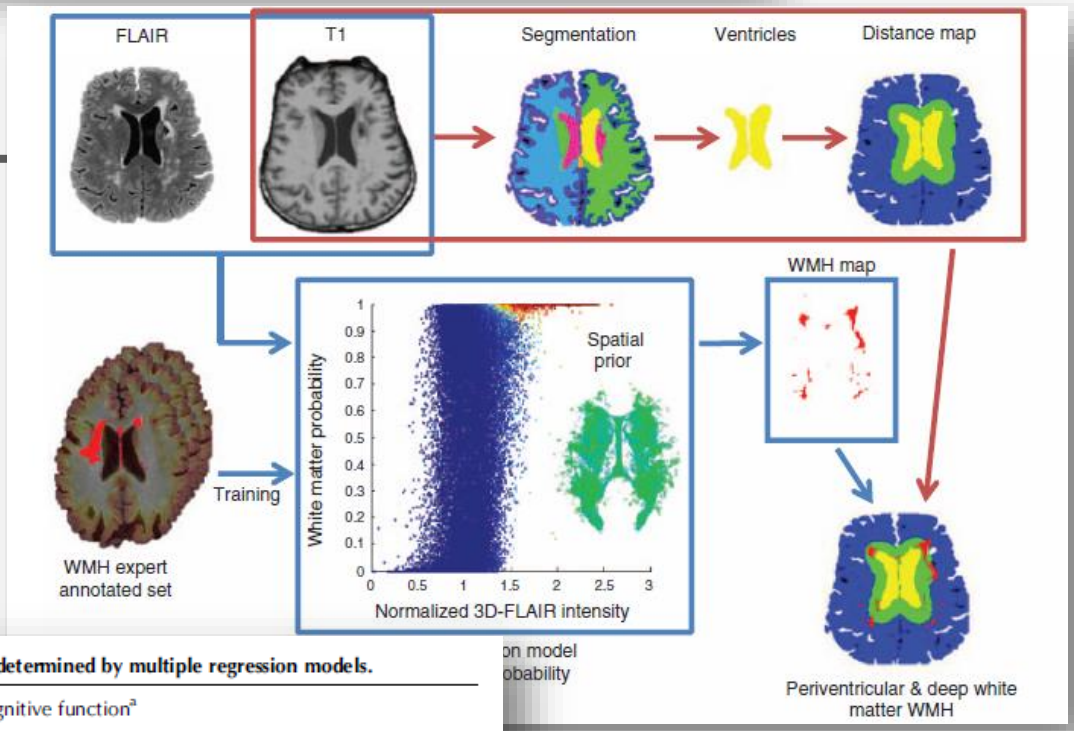


Table 4. White matter hyperintensity load in relation to global cognitive function as determined by multiple regression models.

	Outcome measure: cognitive function[a]								
	Model 1			Model 2*			Model 3#		
	ß (95% CI)	*P*	η^2	ß (95% CI)	*P*	η^2	ß (95% CI)	*P*	η^2
HIV serostatus (0/1)[b]	−0.29 (−0.55–−0.03)	0.03	0.03	−0.29 (−0.55–−0.04)	**0.03**	0.03	−0.23 (−0.49–0.02)	**0.07**	0.02
Diabetes mellitus (0/1)[c]	–	–	–	−0.60 (−1.17–−0.03)	**0.04**	0.02	−0.56 (−1.13–0.01)	**0.05**	0.02
Age (years)	–	–	–	−0.011 (−0.028–0.006)	0.20	0.01	0.00 (−0.020–0.020)	0.99	0.0001
D-dimer (mg/l)	–	–	–	−0.43 (−1.04–0.19)	0.17	0.01	−0.28 (−0.90–0.34)	0.37	0.005
DBP (mmHg)	–	–	–	0.004 (−0.010–0.017)	0.60	0.002	0.006 (−0.007–0.020)	0.35	0.005
Total WMH load[d]	–	–	–	–	–	–	−0.33 (−0.64–−0.02)	**0.04**	0.03

η^2, partial eta squared; CI, confidence interval; ß, beta coefficient. Bold indicates statistical significance. In all models, both HIV-infected patients and HIV-uninfected controls were included.
*Regression analyses were performed to assess effects of HIV serostatus and age on cognitive function, including previously identified determinants of cognitive function (i.e., reported cannabis use, past cardiovascular disease, diabetes mellitus type 2, having an abnormal waist-to-hip ratio, presence of depressive symptoms) [32].

(Su T et al., AIDS 2016)

Stroke prevention
Risk factor control

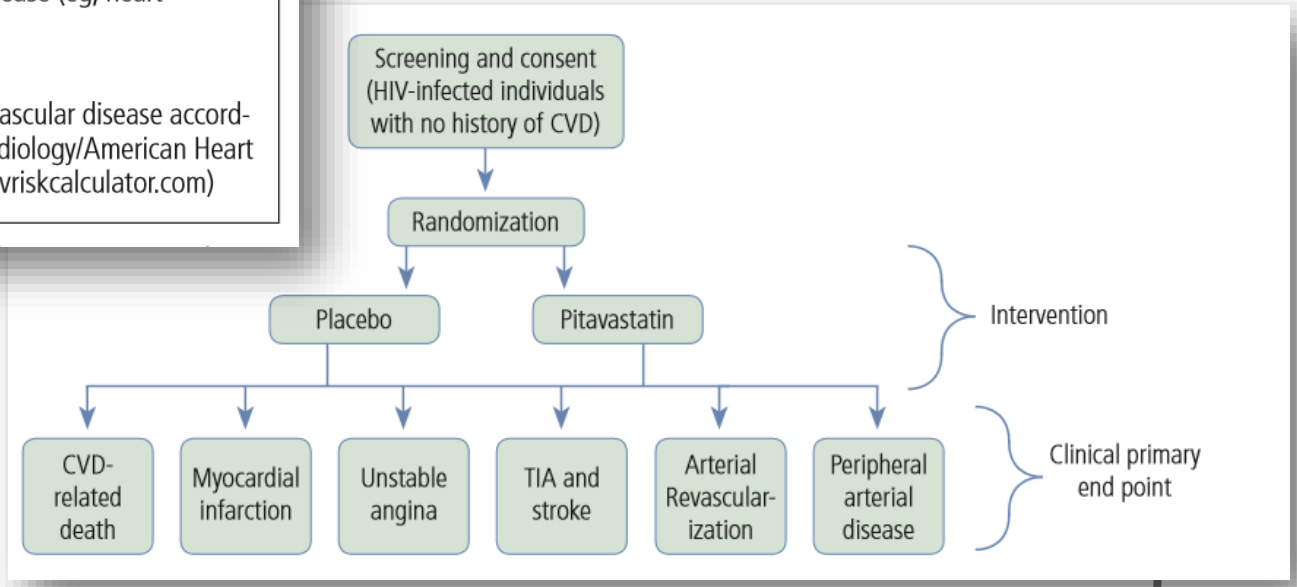
- Hypertension
- Cigarette smoking
- Dyslipidemia
- Diabetes mellitus
- Alcohol consumption
- Abdominal obesity and nutrition
- Physical inactivity
- Antithrombotic therapy

Special Contribution

HIV-Related Cardiovascular Disease, Statins, and the REPRIEVE Trial

Box. Eligibility Criteria for Participants in the REPRIEVE Trial

- Must have HIV infection
- Must be between age 40 years and 75 years
- Must have been taking antiretroviral therapy for at least 6 months
- Must have a CD4+ cell count greater than 100/μL
- Must have no history of cardiovascular disease (eg, heart attack or stroke)
- Must not be currently taking a statin
- Must have low or moderate risk of cardiovascular disease according to the 2013 American College of Cardiology/American Heart Association risk calculator (http://www.cvriskcalculator.com)



(Gilbert JM et al., Top Antivir Med 2015)

Open Access Full Text Article

REVIEW

Management of intracerebral hemorrhage – use of statins

Conclusion

Statin therapy is widely used and recommended by multidisciplinary guidelines for primary and secondary prevention of arteriosclerotic cardiovascular disease and ischemic stroke prevention. Despite proposed pharmacologic mechanisms for increased risk of ICH and clinical findings from the post hoc analysis of the SPARCL trail, the increasing body of clinical evidence does not support the theory that statins significantly increase the rates of ICH. Decreased total cholesterol and LDL have mixed data for increased risk of ICH, but this risk is not correlated with statin use. Further studies are required to delineate which ICH patients would benefit from statin therapy. Therefore, decisions regarding the use of statin therapy in patients with, or at risk for, ICH should be decided on an individual patient basis with statin therapy prescribed in situations where the potential to maximize benefits and minimize risk is greatest.

(Van Matre ET et al., Vasc Health Risk Manag 2016)

Conclusions

- Increasing incidence of cerebrovascular diseases in HIV-infected people
- Primary role of traditional cardiovascular risk factors
- Contribution of HIV and chronic inflammation
- Effect of specific antiretroviral drugs on vascular disease
- Association between cerebrovascular disease and neurocognitive disorders (mainly driven by cardiovascular risk factors)
- Risk factor control is mandatory