HIV and cardiovascular disease

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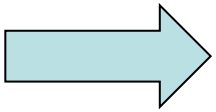
Overview

- Control of HIV replication and its consequences
- Exposure to ART and cardiovascular risk
- Management of CHD risk in HIV infection
- HIV infection, chronic inflammation and endothelial inflammation

Achievements of ART

- Undetectable viral load in >90% of HIV-infected individuals (SHCS)
- HIV-infected non-IDU individuals with CD4cell > 500 cells/µL over 3 years have SMR similar to non-HIV infected peers (*Int J Epidemiology 2012;41:433–4*)
- MTC of HIV in Switzerland <1.0%
- HIV pos. women with undetectable viral load can have a normal sexual and reproductive life
- Early TX of HIV protects discordant partners from HIV infection (*N Engl J Med 2011;365:493)*



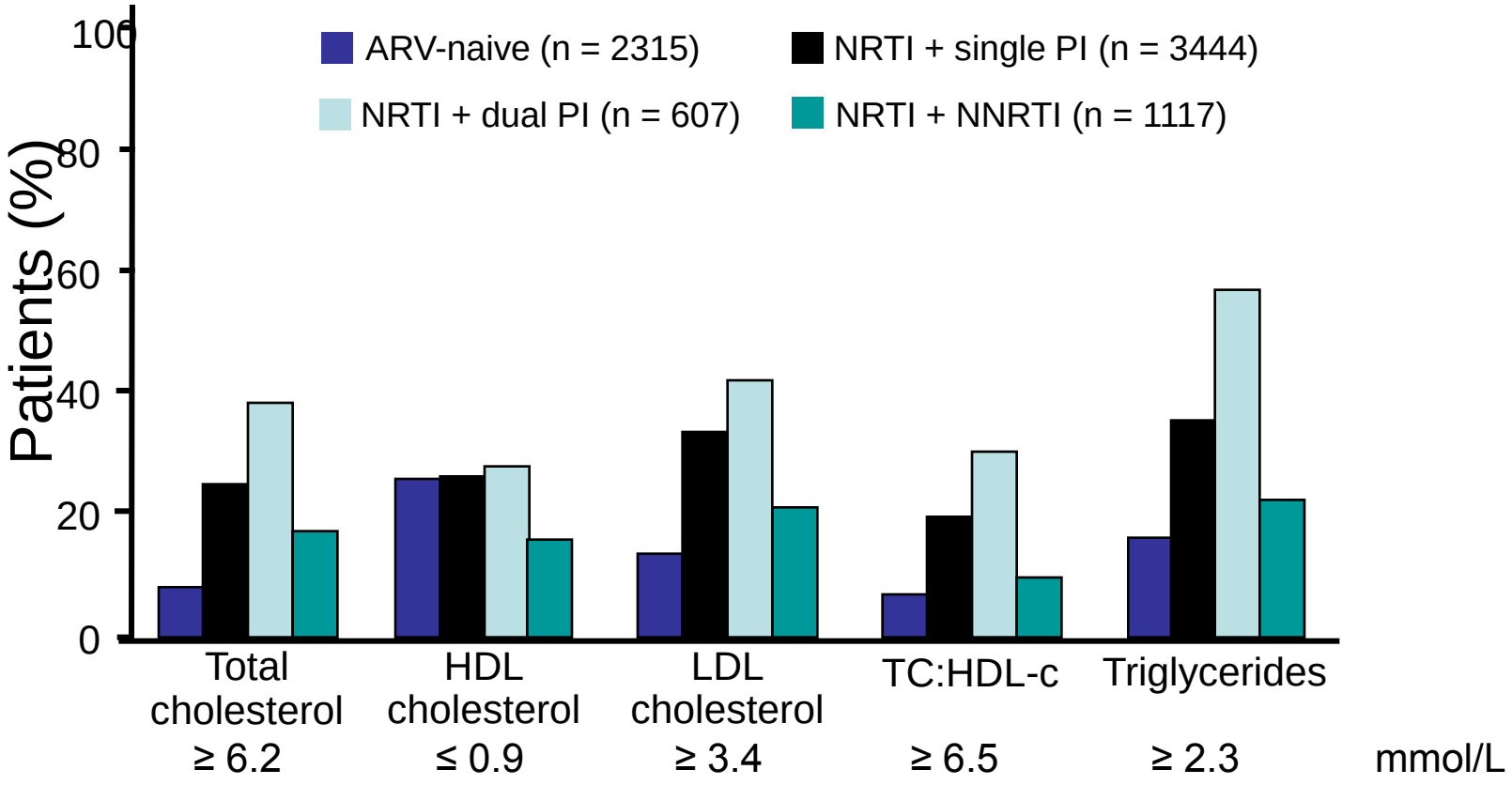
Leading to the strategy of treating all at earliest time point

What mechanisms drive CHD in HIV infection?

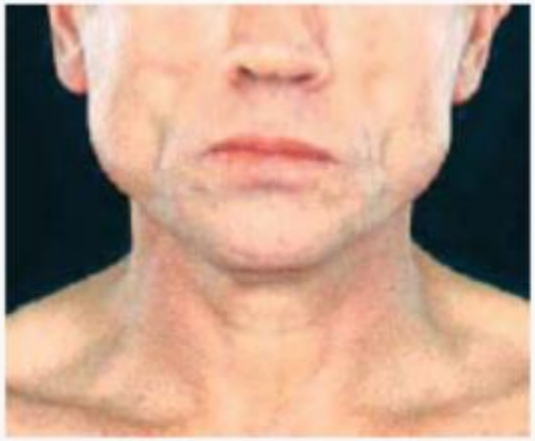
1. Exposure to ART and in particular to some older proteinase inhibitors and abacavir (NRTI)
2. Unfavorable constellation of traditional risk factors for CHD
3. Accumulation of highly atherogenic particles
4. Chronic inflammation
5. Microbial translocation

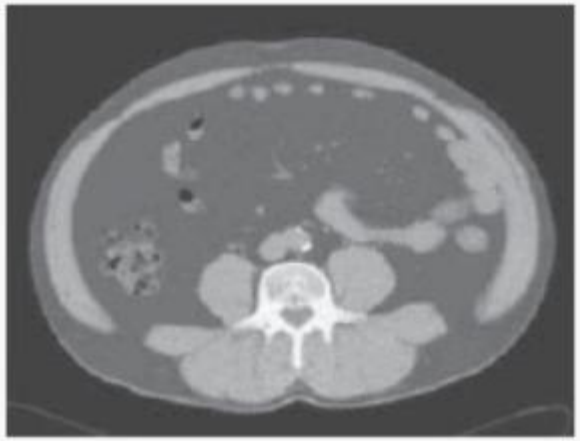
Prevalence of dyslipidemia by type of antiretroviral regimen at study start (n = 7483)

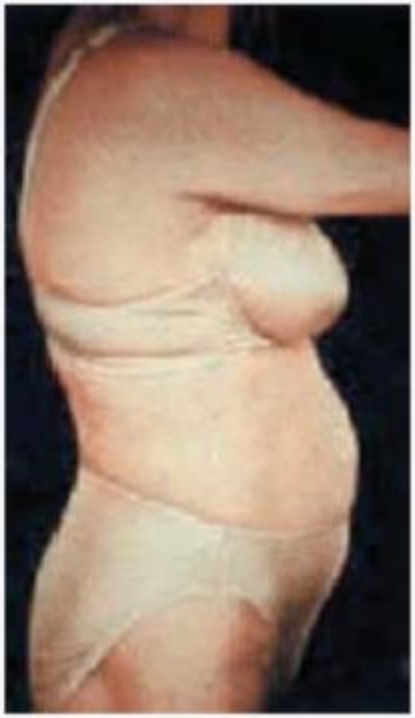
Fontas E J Infect Dis. 2004;189:1056

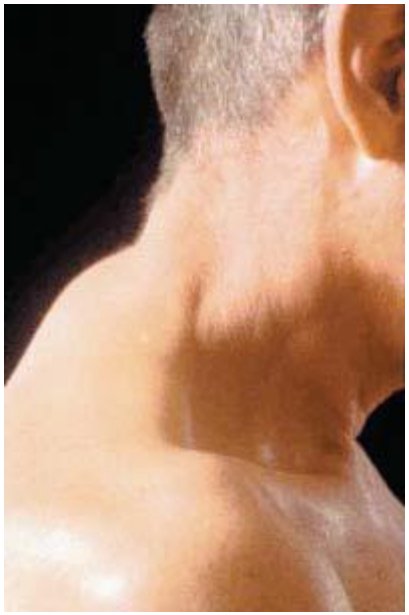


Lipoatrophy and fat accumulation in HIV-infected patients *S Greenspoon N Engl J Med 2005; 352: 44*

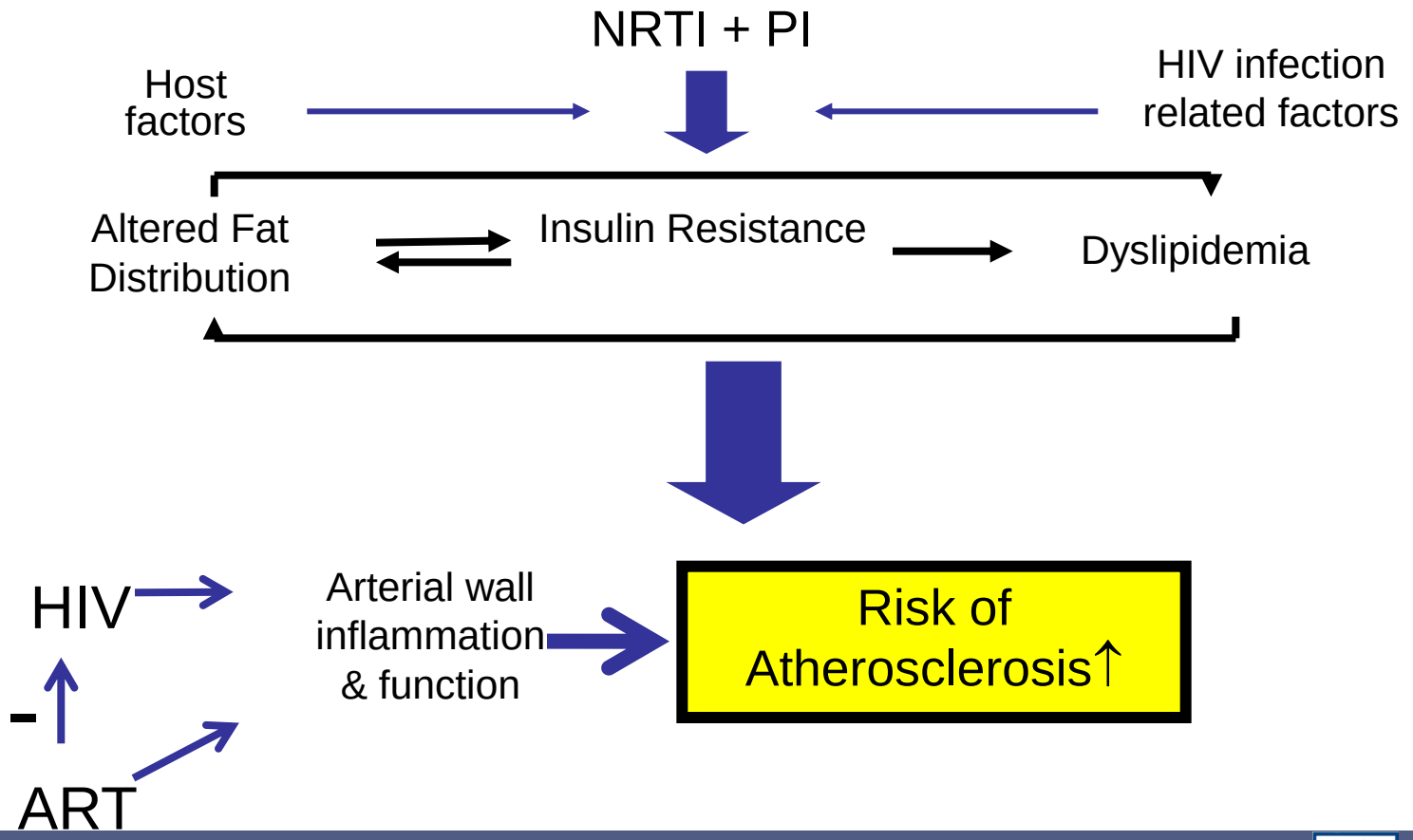




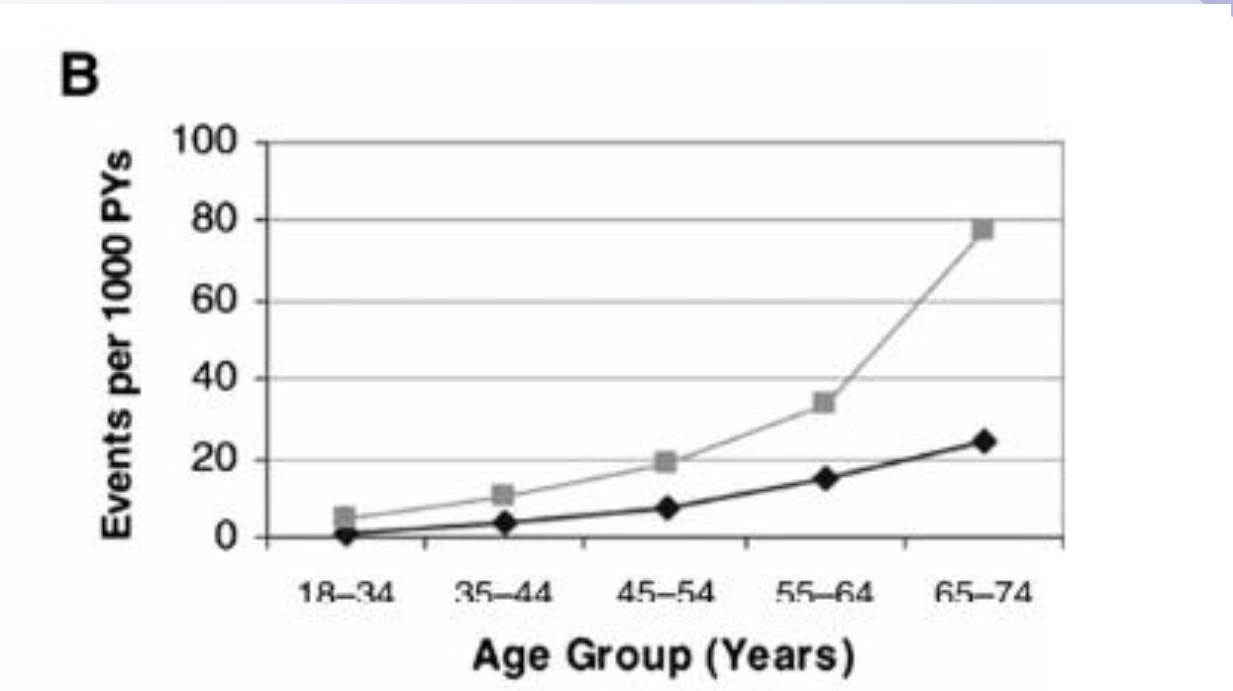




Antiretroviral therapy related metabolic complications potentially contributing to CVD risk



Risk of MI in HIV-infected and HIV-uninfected populations in the US



Data from Partners in System Health Care Boston
dark uninfected light HIV infected individuals
Triant V J Clin Endocrinol Metabol 2007;92:2506

Prevalence of risk factors in patients with and without myocardial infarction D.A.D. Study

Worms SM J Inf Diseases 2010; 201:318–30

Characteristic	No. (%) of patients	
	With MI (n = 580)	Without MI (n = 32,728)
Male sex	526 (90.7)	24,143 (73.8)
Age, median years (IQR)	49 (43–65)	44 (38–50)
BMI >26	109 (18.8)	5675 (17.3)
Current smoker	260 (44.8)	9386 (28.7)
Ex-smoker	173 (29.8)	9850 (30.1)
Cardiovascular disease		
In own history	116 (20.0)	823 (2.5)
In family history	79 (13.6)	2707 (8.3)
Diabetes mellitus	96 (16.6)	1730 (5.3)
Hypertension		
Using antihypertensive medication	198 (34.1)	3602 (11.0)
Any hypertension	252 (43.5)	6290 (19.2)
Latest lipid levels		
Total cholesterol level, median mmol/L (IQR)	5.7 (4.7–6.6)	4.8 (4.1–5.6)
HDL cholesterol level, median mmol/L (IQR)	1.1 (0.9–1.3)	1.2 (1.0–1.5)
Triglyceride level, median mmol/L (IQR)	2.2 (1.5–3.9)	1.6 (1.0–2.4)
Using lipid-lowering medication	209 (36.0)	4084 (12.5)
Any dyslipidemia	434 (74.8)	14,506 (44.3)
Lipodystrophy	243 (41.9)	8566 (26.2)

Incidence of MI according to exposure to PI or NNRTI D.A.D. Study

N Engl J Med 2007;356:1723-35

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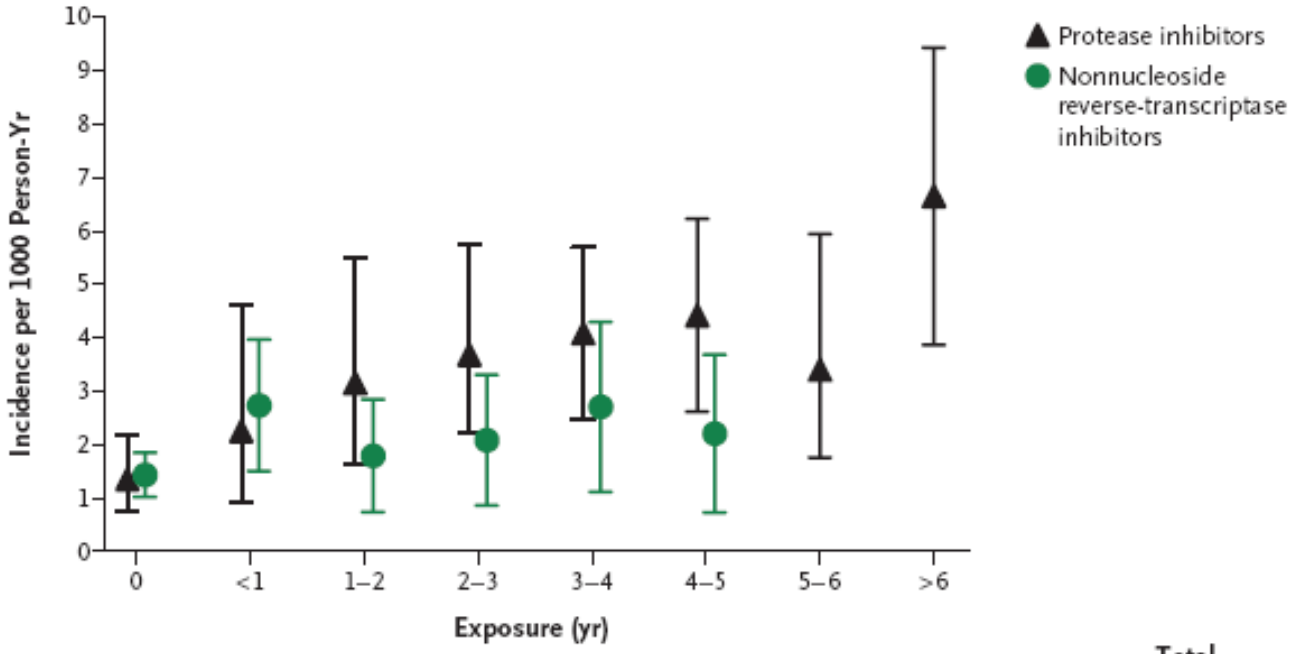


									Total
Protease Inhibitors									
No. of events	16	7	12	19	25	23	12	22	136
No. of person-yr	11,815	3108	3808	5144	6108	5199	3525	3306	42,013
Nonnucleoside Reverse-Transcriptase Inhibitors									
No. of events	16	6	3	3	3	2	—	—	33
No. of person-yr	11,815	2585	2294	1980	1525	1424	—	—	21,623

Exposure to antiretroviral drugs and risk of myocardial infarction D.A.D. Study

Worms SM J Inf Diseases 2010; 201:318–30

Characteristic	RR of myocardial infarction (95% CI)				
	Abacavir, recent exposure	Abacavir, cumulative exposure (per year)	Didanosine, recent exposure	Indinavir, cumulative exposure (per year)	Lopinavir-ritonavir, cumulative exposure (per year)
Estimates from main model	1.70 (1.17–2.47)	1.07 (1.00–1.14)	1.41 (1.09–1.82)	1.12 (1.07–1.18)	1.13 (1.05–1.21)
Further adjustment					
Latest total cholesterol, HDL cholesterol, and triglyceride levels	1.73 (1.33–2.24)	1.07 (1.00–1.14)	1.30 (0.97–1.74)	1.08 (1.02–1.14)	1.09 (1.01–1.17)

178,835 person-years of follow-up, 580 patients developed MI

Management of risk factors for CHD in HIV

How well are risk factors for CVD managed in HIV-infected patients?

Predictors for normalisation of total cholesterol in the SHCS *TR.Glass HIV Clin Trials 2007;8:77*

	Patients n	Events n (%)	Relative Hazard (95% CI)
Age in years 53 – 85	240	87 (36)	0.40 (0.29-0.54)
Baseline total cholesterol (mmol/L)			0.78 (0.71-0.86)
Diabetes	93	27 (29.0)	0.39 (0.26-0.59)
Prior history of CHD	11	5 (45.5)	0.27 (0.10-0.71)
Switched ART when viral load was undetectable			1.48 (1.14-1.91)
Time on PI only (years)			0.39 (0.33-0.46)
Time on NNRTI only (years)			0.35 (0.29-0.43)
Time on PI/ NNRTI baseline (years)			0.34 (0.26-0.43)
Time on lipid-lowering medication (years)			1.11 (0.90-1.38)

Extent of blood pressure control in the SHCS

R. Nüesch JAIDS 2013 (in press)

- Hypertension was diagnosed in 2595 of 10,361 eligible patients
- Of those 869 initiated antihypertensive treatment
- Mean (95% CI) decrease in systolic and diastolic blood pressure of -0.82 (-1.06, -0.58) mmHg and -0.89 (-1.05, -0.73) mmHg per year

Risk factors for cardiovascular events in hypertensive HIV-infected individuals in the SHCS

R. Nüesch JAIDS 2013 (in press)

Parameter	Cardiovascular events	
	Multivariate HR (95% CI)	p-value
Systolic blood pressure per 10 mmHg increase	1.18 (1.06, 1.32)	<0.01
Age per 10 year increase	1.71 (1.39, 2.10)	<0.01
Total cholesterol per 1 mmol/l increase	1.16 (1.07, 1.26)	<0.01
HDL cholesterol per 1 mmol/l increase	0.62 (0.39, 1.00)	0.05
GFR < 50 ml/min/1.73m^2	2.10 (0.97, 4.57)	0.06
Smoker	1.95 (1.28, 2.96)	<0.01
Cumulative time on PI per 1 year increase	1.11 (1.02, 1.21)	0.02
Cumulative time on Triple-NRTI per 1 year increase	1.28 (1.09, 1.49)	<0.01

Drug interactions of antiretroviral drugs

Be aware of potential DI between statins and PIs!

Nested case control study in patients with cardiovascular events: SHCS

HC Bucher JAIDS 2012

Variable	Cases	Controls
N	98	392
General Characteristics		
Caucasian - %	94.9	92.9
Past or current injecting drug users - %	**27.6**	23.9
BMI – mean (SD)	24.1 (3.8)	23.0 (3.8)
Cardiovascular Disease Characteristics		
Family history of premature coronary heart disease - %	**19.4**	11.0
Waist-hip ratio – mean (SD)	0.95 (0.07)	0.92 (0.08)
Metabolic syndrome - %	**41.1**	22.0
Hypertension - %	**68.0**	52.9
Diabetes - %	**14.4**	8.5
Abdominal obesity - %	**44.2**	29.1
Lipid measurements (mg/dL) – median (IQR)		
Total cholesterol	**145.5** (112 – 177)	129.5 (106 – 168.5)
HDL	26 (20 – 35)	27.5 (21 – 37)
Triglycerides	**137.5** (88 – 246)	120 (81.5 – 190.5)
LDL	**87** (68 – 107)	77.5 (59 – 105.5)
Small-dense LDL	**8.2** (4.0 – 11.9)	5.4 (3.4 – 9.0)
Apo A-1	150 (116 – 193)	146 (112 – 192.5)
Apo B	**72** (54 – 104)	62 (46 – 87)

Odds ratio for coronary event in relation to small dense lipoproteins, and Apo B in 98 cases and 392 matched controls all treated with ART

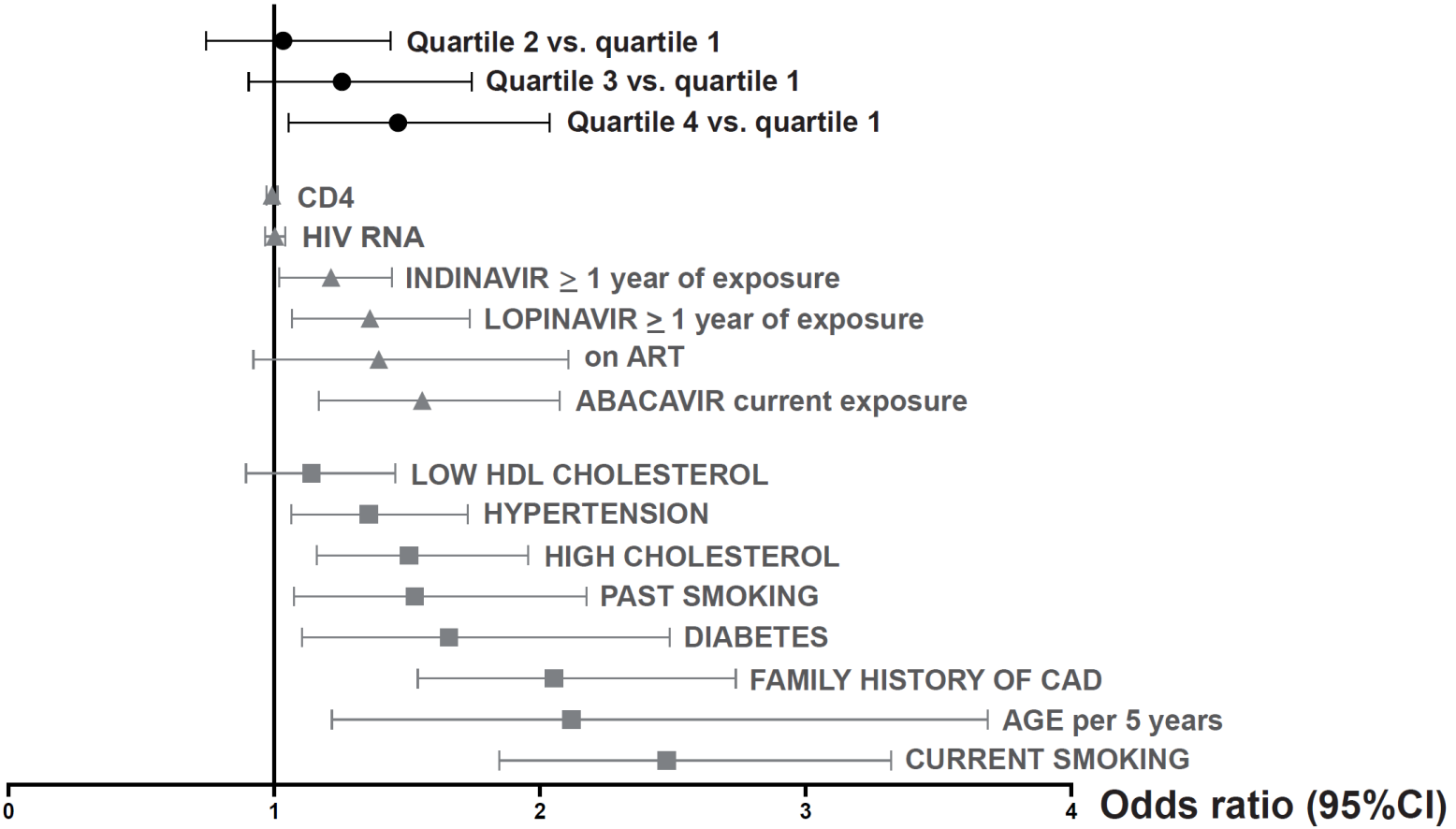
Models	OR (95%CI)	OR (95%CI)
Sd LDL	1.06 (1.00 – 1.11)	1.04 (0.99 – 1.10) ●
Sd LDL /Apo A-1	1.26 (0.96 – 1.67)	1.17 (0.87 – 1.58) ●
Apo B	1.16 (1.02 – 1.32)	1.13 (0.99 – 1.30)
Apo B / Apo A-1	1.02 (0.98 – 1.07)	1.01 (0.97 – 1.07) ●
Cholesterol/HDL-c	0.99 (0.98 – 1.00) ●	0.99 (0.98 – 1.00) ●
● Cholesterol remained statistically significant in model	Adjustment for: cholesterol, triglycerides HDL, systolic blood pressure, abdominal obesity, diabetes family history of premature CHD	Plus adjustment for: IDU, years on abacavir and boosted PI, viral load, CD4 nadir, weeks between plasma sample and event

Genetics and risk of CHD in HIV infection

M. Rotgers (CROI 2012)

- MAGNIFICENT consortium of 24 HIV observational studies from Europe, the USA, Australia and Argentina
- Nested case control study of 571 patients with a first CAD event and 1304 matched controls during a 9-year study period
- 23 SNPs were shown to be associated with CAD through genome-wide association analysis from the general population were analysed

Genetic risk score of 23 CAD-associated SNPs (P=2.9x10-4) and risk for a coronary event in HIV infected patients receiving ART *M. Rotgers (CROI 2012)*



Does HIV promote coronary heart disease

- Immune activtion is increased in HIV
  - residual HIV infection
  - other viruses (CMV) reactivation
  - Increased bacterial translocation
  - Altered gut permeability

- Markers of these processes (solid CD14, polis-accharide) have been linked to CHD and overall mortality also in patients with controlled HIV infection

Severe Complications Endpoint and Components Smart Study

N Engl J Med 2006;355:2283

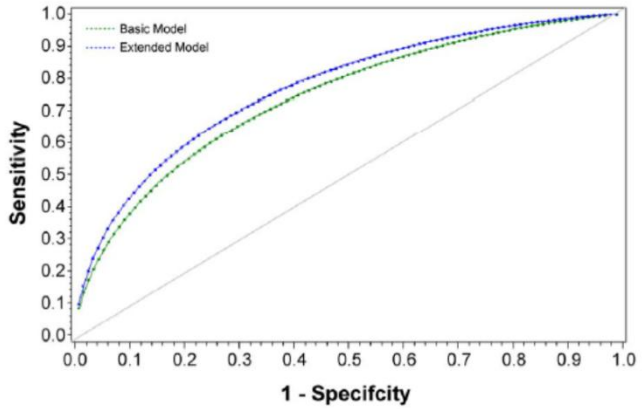
Table 2. Primary and Major Secondary End Points.*

End Point	Drug Conservation Group (N=2720)		Viral Suppression Group (N=2752)		Hazard Ratio for Drug Conservation Group vs. Viral Suppression Group (95% CI)	P Value
	No. of Participants with Event	Event Rate (per 100 Person-Yr)	No. of Participants with Event	Event Rate (per 100 Person-Yr)		
Primary end point	120	3.3	47	1.3	2.6 (1.9–3.7)	<0.001
Death from any cause	55	1.5	30	0.8	1.8 (1.2–2.9)	0.007
Opportunistic disease						
Serious	13	0.4	2	0.1	6.6 (1.5–29.1)	0.01
Nonserious	63	1.7	18	0.5	3.6 (2.1–6.1)	<0.001
Major cardiovascular, renal, or hepatic disease	65	1.8	39	1.1	1.7 (1.1–2.5)	0.009
Fatal or nonfatal cardiovascular disease	48	1.3	31	0.8	1.6 (1.0–2.5)	0.05
Fatal or nonfatal renal disease	9	0.2	2	0.1	4.5 (1.0–20.9)	0.05
Fatal or nonfatal liver disease	10	0.3	7	0.2	1.4 (0.6–3.8)	0.46
Grade 4 event	173	5.0	148	4.2	1.2 (1.0–1.5)	0.13
Grade 4 event or death from any cause	205	5.9	164	4.7	1.3 (1.0–1.6)	0.03

Chronic inflammation marker and risk of CHD In the SMART trial Plos one 2012

Table 1. Baseline characteristics: Demographics, HIV factors, CVD risk factors and biomarkers for SMART participants who developed a CVD event and those who did not.

	Participants with CVD event (N = 252)	Participants without CVD event (N = 4846)	p-value[1]	p-value[2]
Inflammation and Coagulation Biomarkers				
hsCRP (µg/mL) (median, IQR)	3.34 (1.47, 7.51)	1.67 (0.70, 4.02)	<0.001	<0.001
IL-6 (pg/mL) (median, IQR)	3.07 (1.87, 4.83)	1.72 (1.07, 2.92)	<0.001	<0.001
D-dimer (µg/mL) (median, IQR)	0.31 (0.18, 0.59)	0.20 (0.13, 0.36)	<0.001	<0.001



Chronic inflammation and factors related to cell senescence in HIV

HIV related

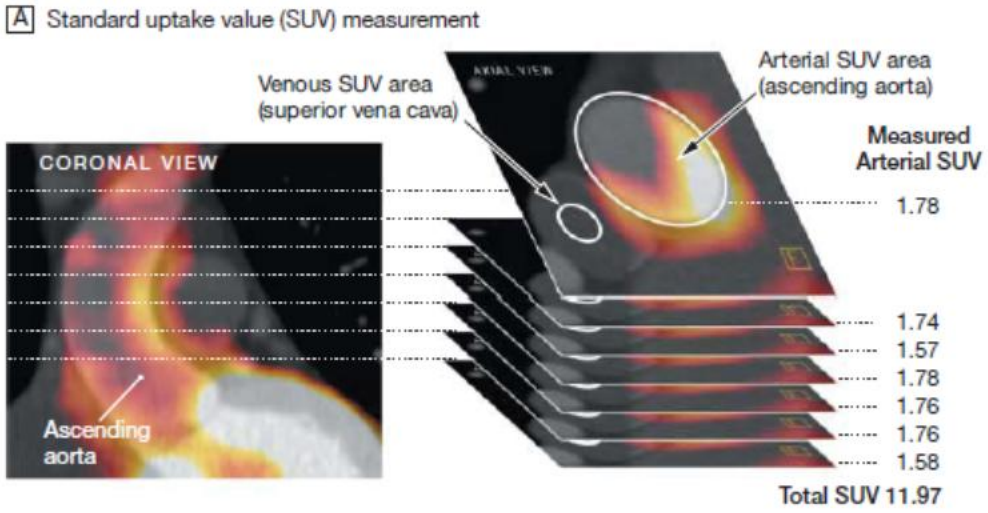
- Increased proportion of CD28-, CD57+ memory CD8+ T cells with reduced capacity to produce interleukin 2 (IL-2)
- Increased production of interleukin 6 (IL-6)
- Resistance to apoptosis, and shortened telomeres
- Massiv increased peripheral CD8+ T cells activation

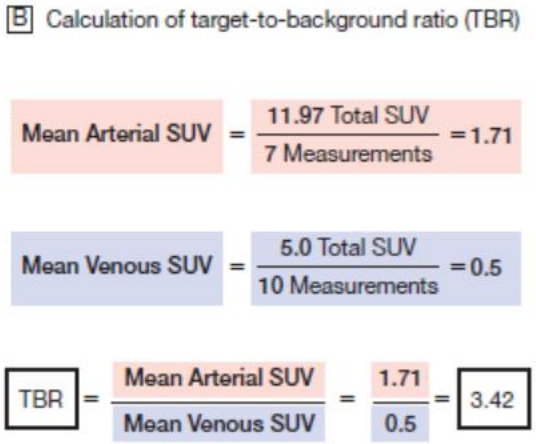
ART related

- Thymidine analogues have been associated with mitochondrial dysfunction and telomere shortening
- Prelamin A accumulation, is a promotor of oxidative stress, inflammation, and cell senescence in vitro (but not in vivo in HIV-infected individuals)

Chronic inflammation and CHD risk in patients with suppressed HI viral load

^{18}Fluorine-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) and soluble CD163 (sCD163), a marker of monocyte and macrophage activation *S. Subramainian JAMA. 2012;308:379*





Target to background ratio of ^{18}F-FDG-PET/CT imaging of the aorta in stratified analysis of HIV-infected individuals free of CHD treated with ART and matched HIV-negative controls *S. Subramainian JAMA. 2012;308:379*

	Participants With HIV		Non-HIV FRS-Matched Control Participants		
	Sample Size, No.	Mean (95% CI)	Sample Size, No.	Mean (95% CI)	*P* Value[a]
No coronary calcium	10	2.30 (1.92-2.69)	18	1.91 (1.81-2.01)	.009
Low FRS (0-10)	21	2.24 (2.05-2.43)	23	1.92 (1.83-2.00)	.002
Low LDL-C (<100 mg/dL)	8	2.30 (2.09-2.52)	6	1.91 (1.65-2.17)	.01
No statin use	27	2.23 (2.07-2.40)	20	1.88 (1.79-1.97)	.001
No smoking	21	2.23 (2.04-2.43)	25	1.90 (1.81-1.99)	.001
Undetectable viral load in the HIV-infected group	21	2.24 (2.03-2.45)	27	1.89 (1.80-1.97)	<.001

Correlation of soluble CD163 and aortic target to background ratio with 18F-FDG-PET in HIV infected patients *S. Subramainian JAMA. 2012;308:379*

Table 4. Correlations of sCD163 and Other Inflammatory Parameters With Aortic TBR in Participants With HIV[a]

	Participants With HIV	Sample Size, No.	Correlation With Aortic TBR	*P* Value
Marker of monocyte/macrophage activation				
sCD163, median (IQR), ng/mL	855 (451-1543)	27	$\rho = 0.31$	.04
Markers of generalized inflammation and hemostasis				
hs-CRP, median (IQR), mg/L	1.2 (0.4-3.6)	27	$\rho = -0.04$	.65
D-dimer, mean (SD), ng/mL	246 (100)	14	$r = 0.48$	.08

Summary & take home messages

- Prevalence of conventional risk factors for CHD remains high in HIV-infected individuals and risk factor control is insufficient
- First generation protease inhibitors and abacavir increase the risk of MI
- This risk has to be balanced against the apparent benefit of ART

Summary & take home messages

- Growing evidence that
  - Risk of CHD in HIV infected is higher than in the general population
  - HIV triggers endothelial inflammation and atherosclerosis

- Serious concerns that HIV may promote immunoscenesence
  - Atherosclerosis
  - Dementia
  - Osteoporosis

Outlook

- Better integrated care models of specialists are needed to tackle an imminent epidemic of coronary heart disease in HIV infection

- More research is needed to increase our understanding of the mechanisms that promote CHD in HIV infection

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The SHCS members:
Barth J, Battegay M, Bernasconi E, Böni J, Brazzola P, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Cellerai C, Cheseaux JJ, Drack G, Duppenthaler A, Egger M, Elzi L, Fehr J, Fellay J, Flepp M, Francini K, Francioli P (President of the SHCS), Furrer H, Fux CA, Gorgievski M, Grawe C, Günthard H, Gyr T, Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Posfay-Barbe K, Rauch A, Regenass S, Rickenbach M, Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Scheibner K, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Wyler CA, Yerly S.

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