Cardiovascular Disease in HIV

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Epidemiological Data: CVD Events in HIV-Patients[1]

- Retrospective cohort studies
- Prospective HIV cohort studies
- Administrative/clinical databases
- Randomized clinical trails of ART

	No. of patients/ No. of events	Event rate per 1,000 HIV+	Event rate per 1,000 HIV-
DAD I[2]	23,468/126	3.5	NA
DAD I[3]	23,437/345	3.6	NA
VA[4]	36,766/1,207	8.1	NA
Kaiser 2002[5]	4,159/47	4.3	2.9
Kaiser 2007	5,000/162	3.7	2.2
MGH[6]	3,851/189	11.13	6.98
MediCal[7]	28,512/294	4.12	3.32

[1]Currier Circulation 2008; [2]Friis-Moller N Engl J Med 2003; [3] Friis-Moller N Engl J Med 2007; [4]Bozette N Engl J Med 2003; [5]Klein J AIDS 2002; [6]Triant J Clin Endocrinol Metab 2007; [7]Currier J AIDS 2003

CVD Events in HIV-Patients: Veterans Aging Cohort Study Virtual Cohort, 2003-2009, n=82,459)

HIV		Age Group, y				
		40-49	50-59	60-69	70-79	80-89
no	AMI rates per 1000 person-years (95% CI)	1.5 (1.3-1.7)	2.2 (1.9-2.5)	3.3 (2.6-4.2)	6.7 (4.8-9.2)	21.5 (12.7-36.4)
yes	AMI rates per 1000 person-years (95% CI)	2.0 (1.6-2.4)	3.9 (3.3-4.5)	5.0 (3.8-6.7)	10.0 (6.7-14.7)	13.5 (4.3-42.0)

„Infection with HIV is associated with a 50% increased risk of AMI beyond that explained by recognized risk factors."

Freiberg et al JAMA 2013

Cause of Death in D:A:D

Cause of death	Percentage[1]	
AIDS-related	29	
Liver-ralated	13	
Non-AIDS cancers	15	
CVD-related	11	7.9 (ATCC)[2]
Non-natural	10	
Bacterial infections	7	
Renal	1	
Lactic acidosis/pancreatitis	<0.5	
Others/Unknown	15	

[1]Smith Lancet 2014; [2]ATCC, Clin Infect Dis 2010

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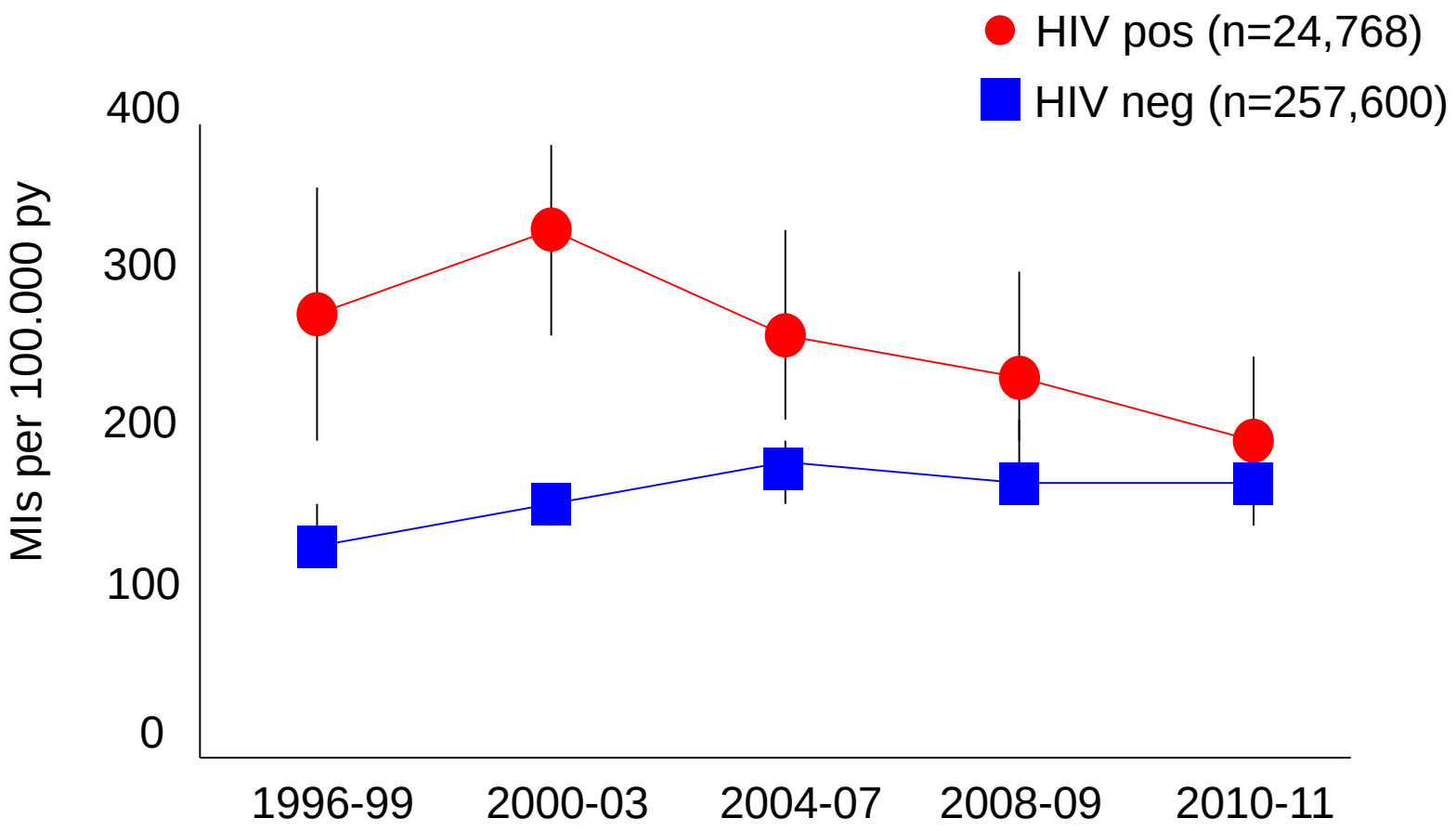
[1]Smith Lancet 2014

No Differences in Incidence of MI for HIV+ and HIV- Individuals in Recent Years



Role of Traditional Risk Factors in HIV+ and HIV- [1]

		% increase in risk per unit for each study		
		HIV+		
	Unit	Iloeje[2]	Friss-Møller[3]	HIV-
Age	Per 1 y ↑	9%	6%	6-9%
Sex	Male vs female	NS	110%	110-160%
Diabetes mellitus	Yes vs No	260%	90%	140-252%
Smoking	Yes vs No	140%	290%	70-290%
Hypertension	Yes vs No	30%	80%	80-90%
Total cholesterol	Per 1 mm/L ↑	…	26%	25-33%
HDL cholesterol	Per 1 mm/L ↑	…	-28%	-52%

[1]Currier Circulation 2008; [2]Iloeje HIV Med 2005; [3] Friis-Moller N Engl J Med 2007

Prevalence of Cardiovascular Risk Ractors in HIV

Traditional risk factors

- Smoking (47-71%) [1,2]
- Obesity (40-60%) [3]
- Hypertension (31%) [4]
- Dyslipidemia (40-60%) [5]
- Glucose intolerance
- Type 2 diabetes

Traditional risk factors powerfully predict cardiovasular risk in HIV patients

BUT: Lack of specificity

[1]Saves Clin Infect Dis 2003; [2]Gritz Nicotine Tob Res 2004; [3]Kaplan Clin Infect Dis 2007; [4]Seaberg AIDS 2005; [5]Samaras Diabetes Care 2007

Incidence of the Metabolic Syndrome in HIV

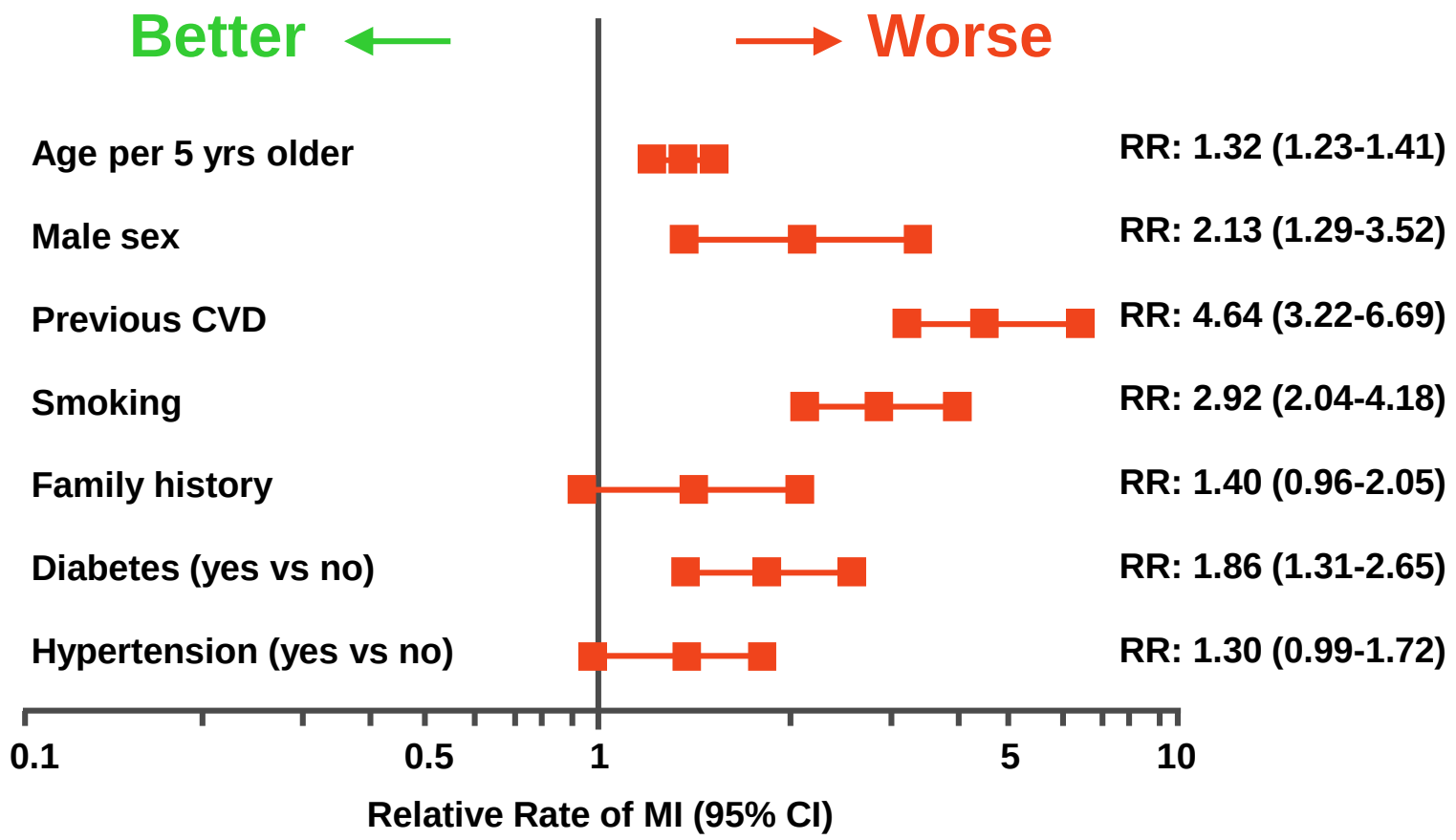
Reference	Incident metabolic syndrome cases	Person-years	Incidence rate (per 100 person-years)	Timeframe of study
Palacios et al. 2007 [23]	7	50	14	2002-2003
Wand et al. 2007 [25]	234	2223	12	2001-2004
Krishnan et al. 2012 [32]	478	5617	8.5	2001-2009
Bonfanti et al. 2012 [20]	14	539	2.6	2007-2010

Incidence of Type 2 Diabetes in HIV

Reference	Incident DM cases	Person-years	Adjusted risk estimates* (95 % confidence interval)	Timeframe of study
Brown et al. 2007 [40]				1999-2003
HIV-infected	47	100	4.11 (1.85, 9.16)	
HIV-uninfected	14	100	ref	
Tien et al. 2012 [46]				2000-2006
HIV-infected	76	4905	1.90 (1.04, 3.48)	
HIV-uninfected	15	1774	ref	
Rasmussen et al. 2012 [42••]				1996-1998
HIV-infected	18	4,768	2.83 (1.57, 5.09)	
HIV-uninfected	29	20,992	ref	
Rasmussen et al. 2012 [42••]				1999-2010
HIV-infected	87	23,574	0.90 (0.72, 1.13)	
HIV-uninfected	499	115,374	ref	
Tripathi et al. 2014 [47]				1994-2011
HIV-infected	491	39,737	0.55 (0.46, 0.65)	
HIV-uninfected	595	39,994	ref	

Nix & Tien Curr HIV/AIDS Rep 2014

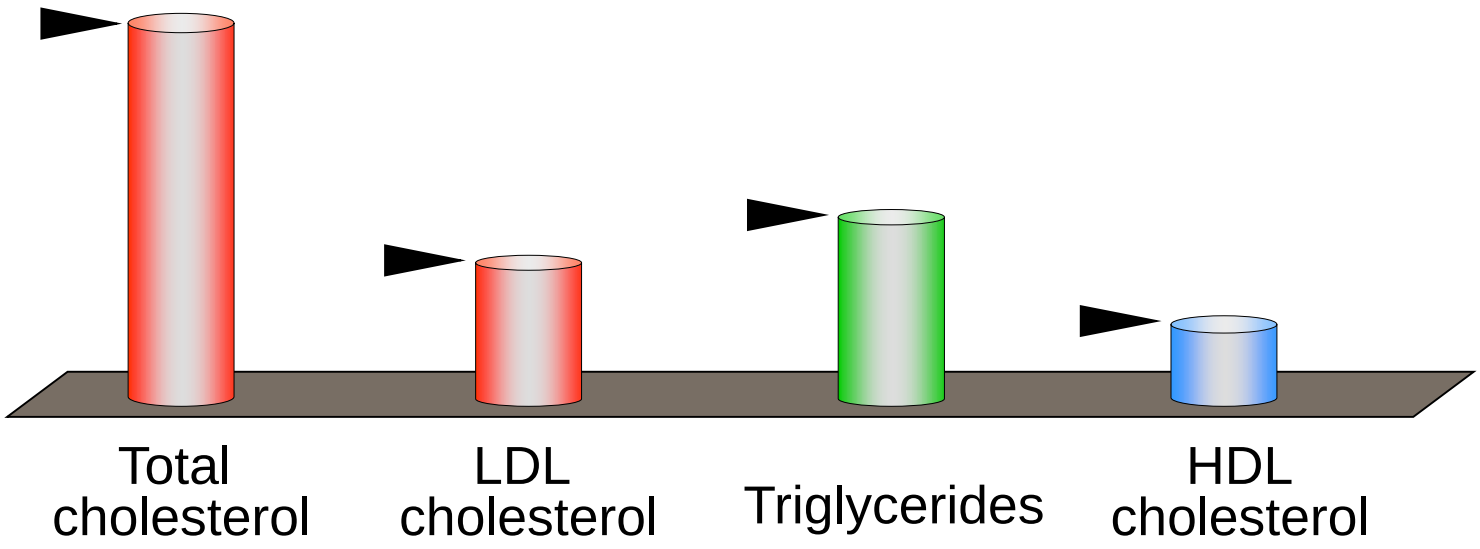
D:A:D: Traditional Risk Factors for CHD in an HIV-infected Population



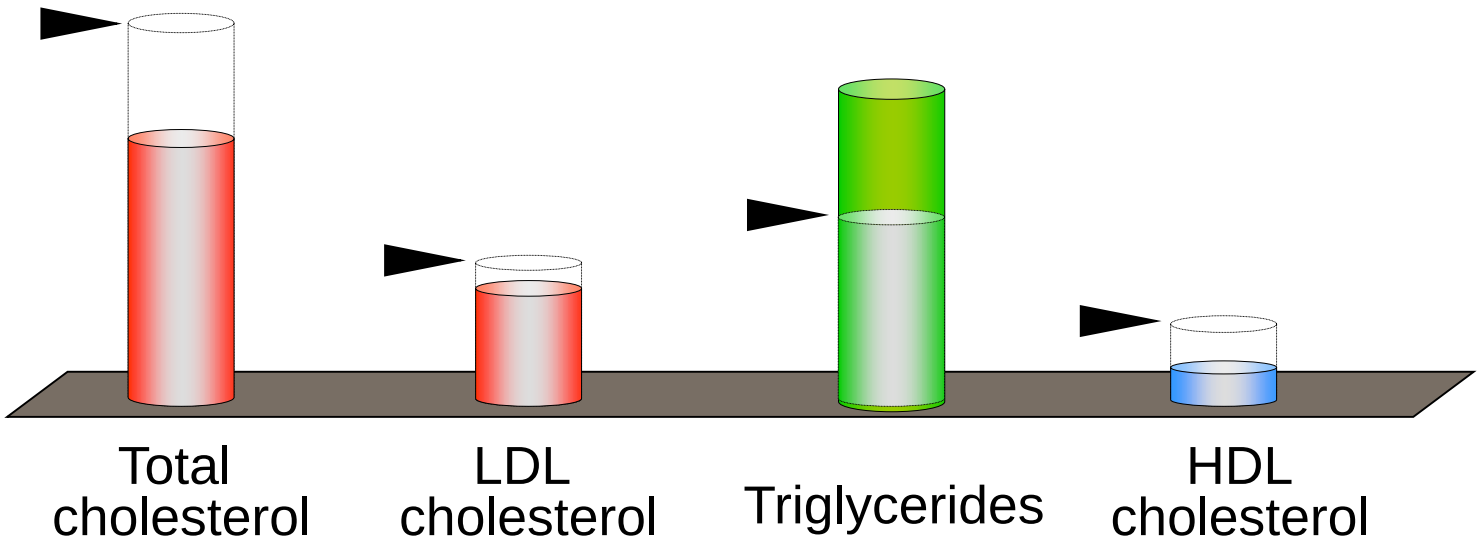
Multivariable Poisson model adjusted for age, sex, BMI, HIV risk, cohort, calendar year, race, family history of CVD, smoking, previous CVD event, TC, HDL, hypertension, diabetes.

Friis-Møller N et al. *N Engl J Med.* 2007;356:1723-1735.

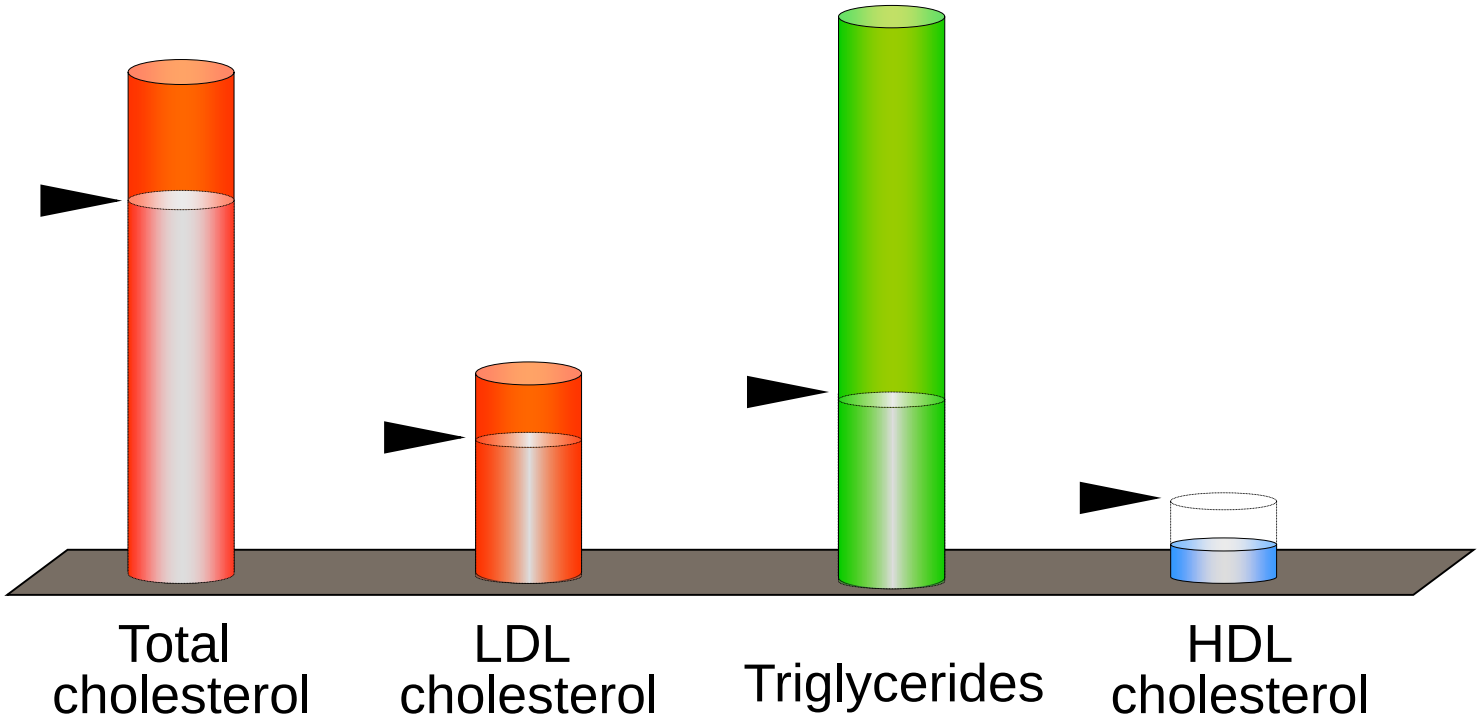
Lipid >Profile *before* HIV Infection



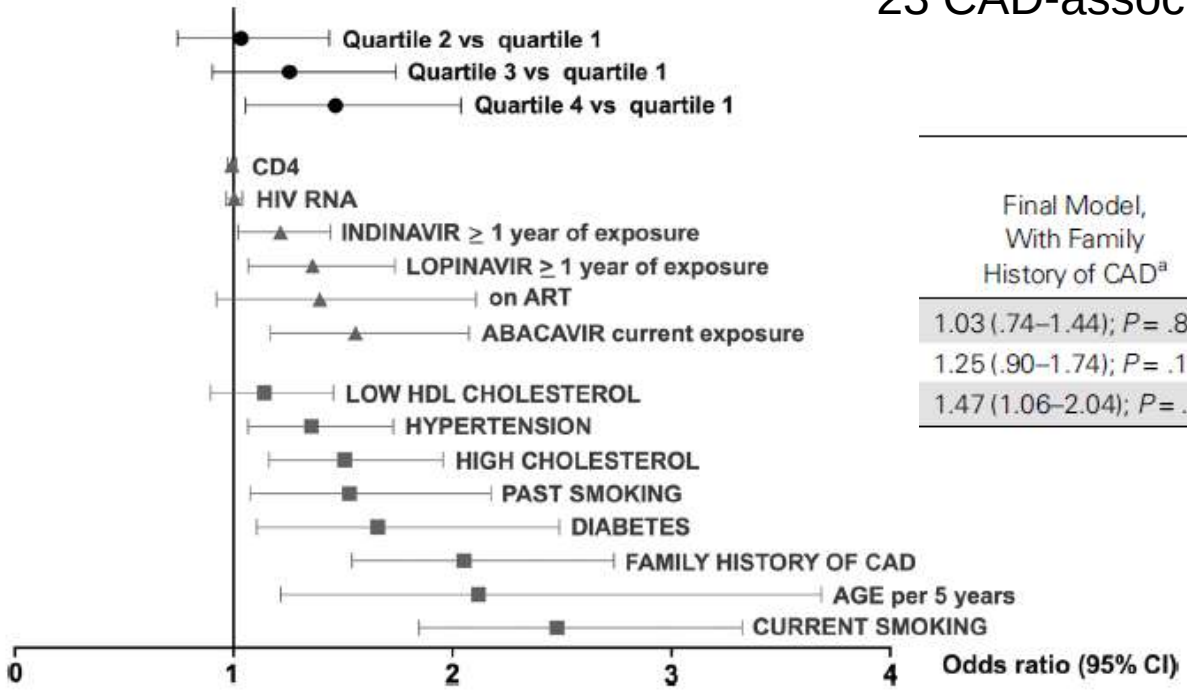
Lipid Profile *due to* HIV Infection



Lipid Profile *due to* Several ARTs



Contribution of the Genetic Background to CAD in HIV Patients

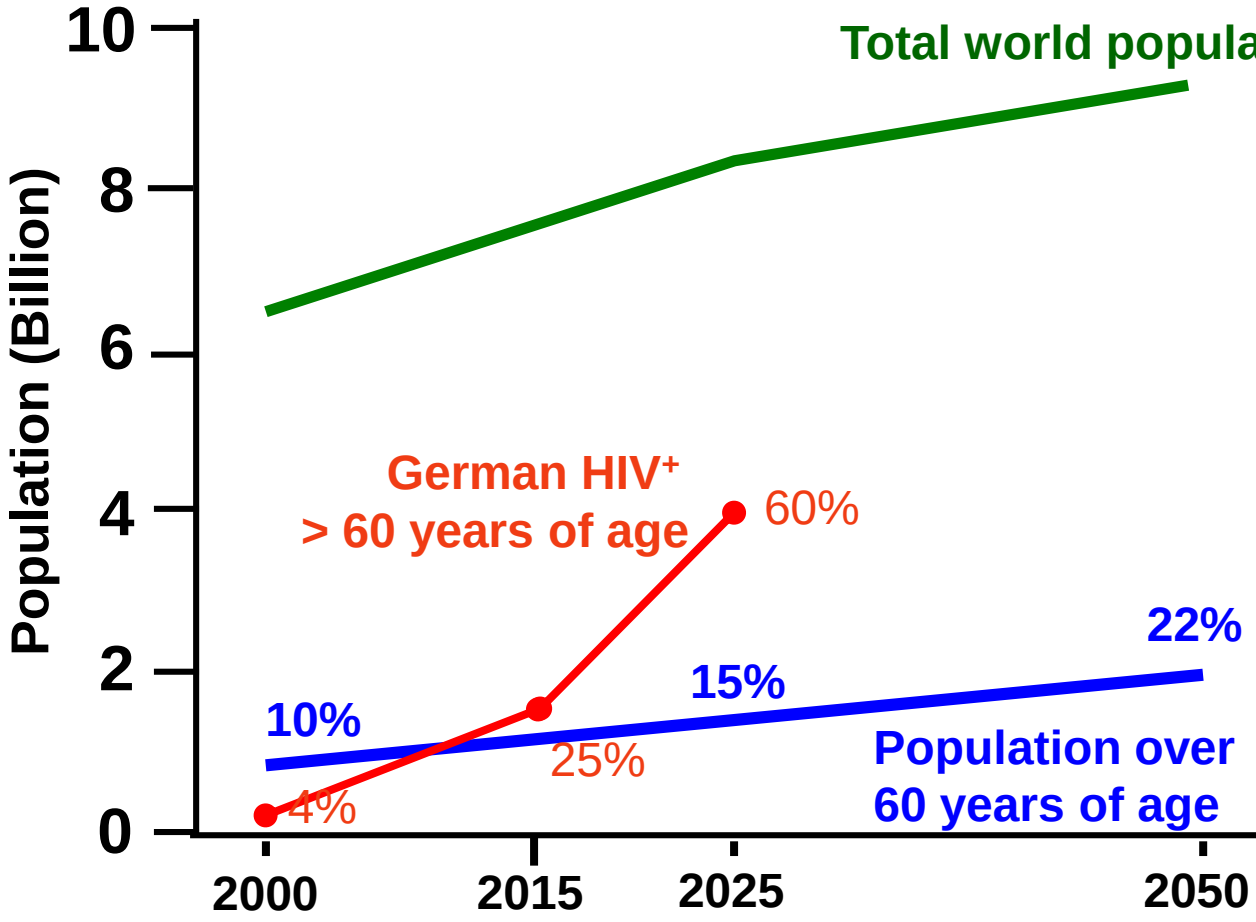


23 CAD-associated SNPs

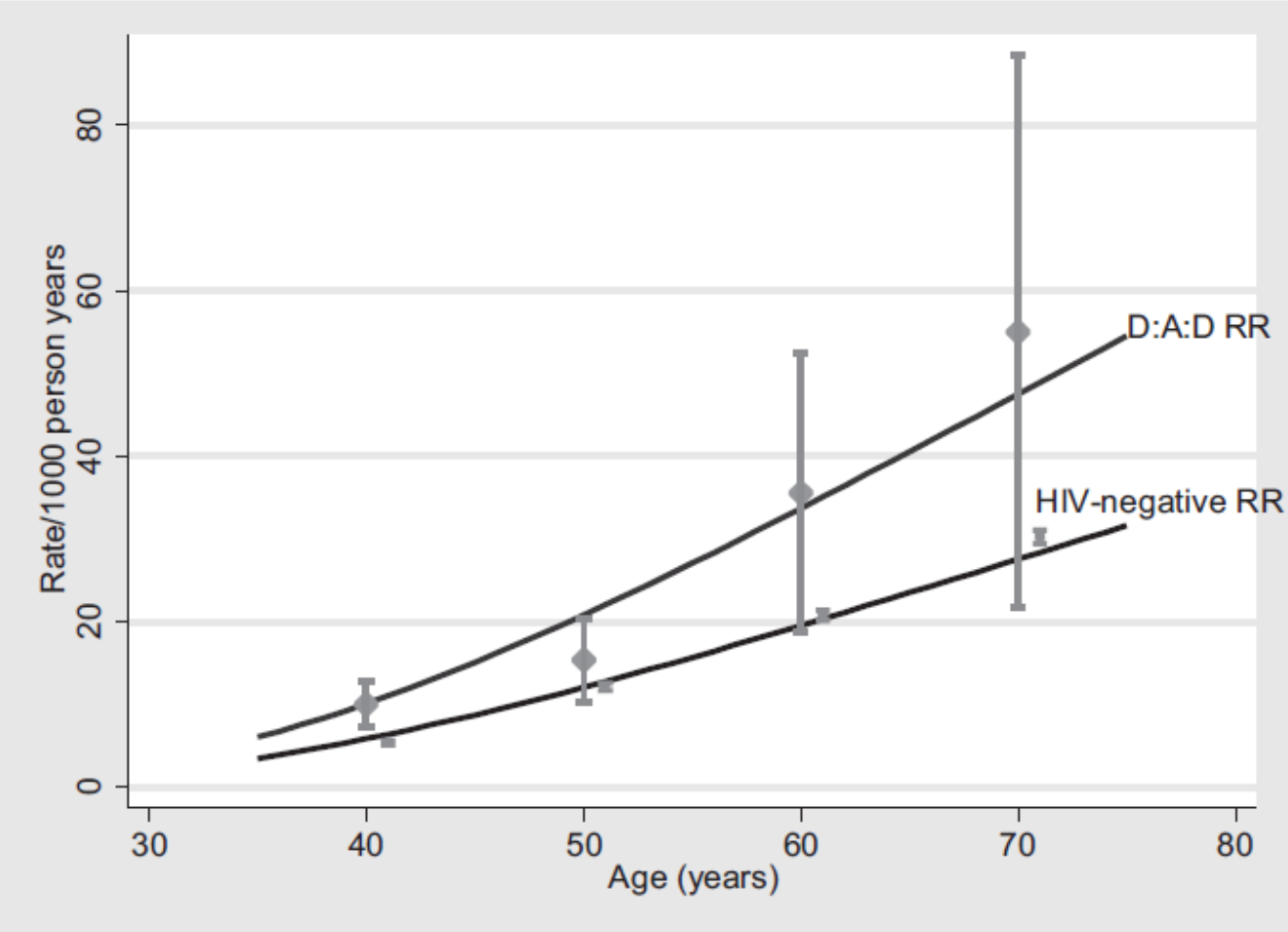
Final Model, With Family History of CAD[a]	Final Model, Without Family History of CAD[b]
1.03 (.74–1.44); $P = .84$	1.04 (.75–1.44); $P = .82$
1.25 (.90–1.74); $P = .18$	1.25 (.90–1.72); $P = .18$
1.47 (1.06–2.04); $P = .02$	1.47 (1.06–2.03); $P = .02$

571 HIV+ with first MI, 1304 matched HIV neg. controls

HIV, ART and Aging: A Rough Estimate



Increased Risk for CVD with Age in HIV



Petoumenos et al., HIV Med 2014

HAART and Cardiovascular Disease

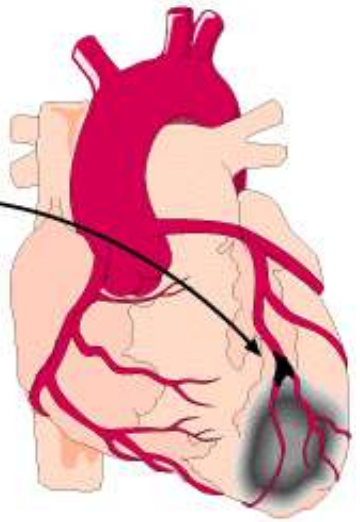
HAART

Insulin resistance
Type 2 diabetes

Dyslipidemia
High FFA
Small dense LDL
Low HDL
High TG

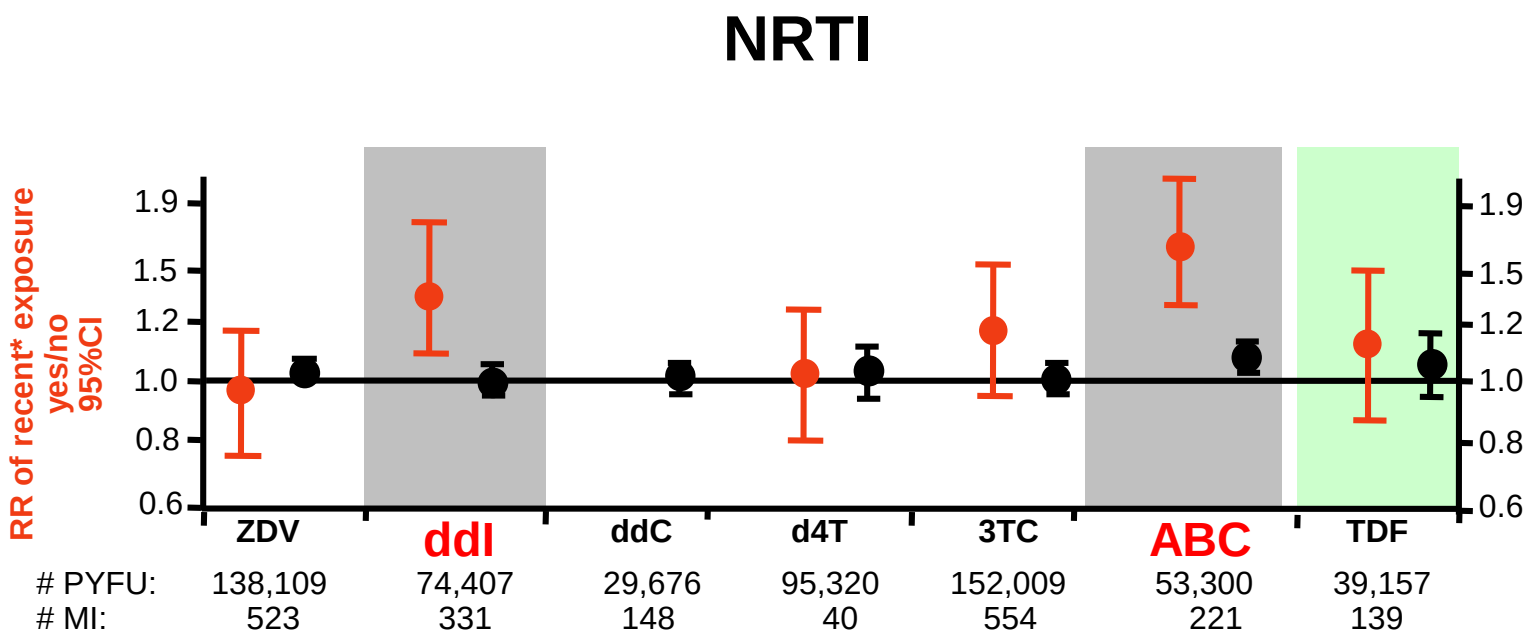
Central obesity

CVD



Age, genetics, diet, hypertension, sedentery life style, renal disease…

D:A:D: Recent and/or Cumulative Antiretroviral Exposure and Risk of MI

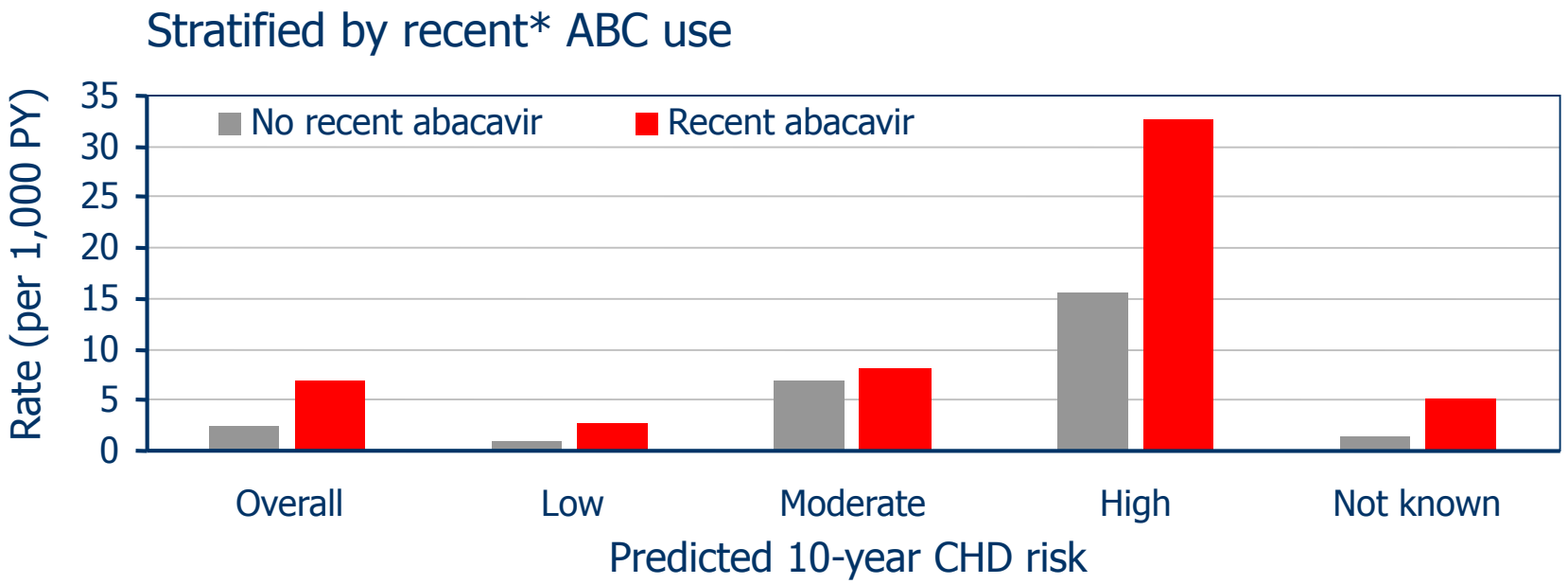


*Current or within last 6 months. †Approximate test for heterogeneity: *P* = 0.02

Lundgren JD, et al. CROI 2009. Abstract 44LB.

Only >30,000 PY of follow up

D:A:D : Abacavir and Myocardial Infarction



Events	325	192	60	42	79	33	100	68	86	49
PY	126581	27728	57628	14754	13372	4300	6293	2095	49288	10182

Sabin CA et al. 15th CROI; Boston, MA; February 3-6, 2008. Abstract 957c.

HIV Drug-Specific Associations to CVD

HAART

Abacavir
Didanosine
Indinavir
Lopinavir

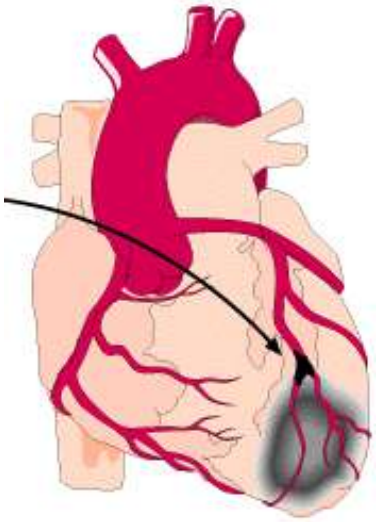
Insulin resistance
Type 2 diabetes

Dyslipidemia
High FFA
Small dense LDL
Low HDL
High TG

Central obesity

Inflammation ?

CVD



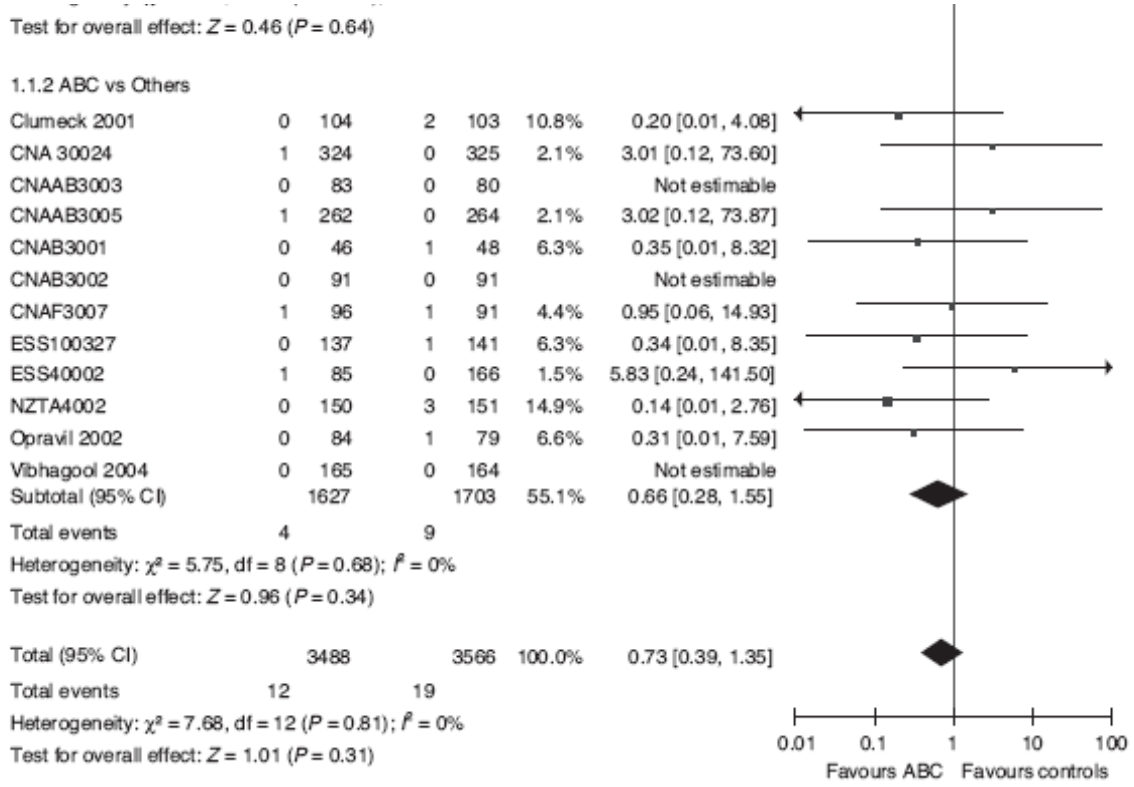
Abacavir and Myocardial Infarction

Study	Design	Event Ascertainment	Patients (n=)	MI (n=)	Abacavir-effect?
D:A:D	Prospective observ. cohort	Prospective predefined	33,347	580	**Yes**
FHDB	Case control in observ. cohort	Prospective, MI retrospectively validated	289 cases 884 control	289	**Yes**, first year of exposure
SMART	RCT, Oberserv. analysis	Prospective predefined	2,752	19	**Yes**
STEAL	RTC	Prospective	357	3	**Yes**
QPHID	Case control in observ. cohort	ICD 9 code acute MI Not validated	142 cases 1,420 controls	142	**Yes**
GSK Analysis	RCT (n=54)	Retrospective Data base search	14,174	11	**No**
ALLRT ACTG	Long term follow up of 5 RCT	Retrospective 2 independent reviewer	3,205	27	**No**
VACCR	Retrospective observ. cohort	ICD 9 code acute MI Not validated	19,424	278	**No**

Behrens & Reiss Curr Opin Infect Dis 2010

Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data

Mario Cruciani[a], Veronica Zanichelli[b], Giovanni Serpelloni[a], Oliviero Bosco[a], Marina Malena[a], Romualdo Mazzi[a], Carlo Mengoli[b], Saverio G. Parisi[b] and Graeme Moyle[c]



Test for overall effect: $Z = 0.46$ ($P = 0.64$)						
1.1.2 ABC vs Others						
Clumeck 2001	0	104	2	103	10.8%	0.20 [0.01, 4.08]
CNA 30024	1	324	0	325	2.1%	3.01 [0.12, 73.60]
CNAAB3003	0	83	0	80		Not estimable
CNAAB3005	1	262	0	264	2.1%	3.02 [0.12, 73.87]
CNAB3001	0	46	1	48	6.3%	0.35 [0.01, 8.32]
CNAB3002	0	91	0	91		Not estimable
CNAF3007	1	96	1	91	4.4%	0.95 [0.06, 14.93]
ESS100327	0	137	1	141	6.3%	0.34 [0.01, 8.35]
ESS40002	1	85	0	166	1.5%	5.83 [0.24, 141.50]
NZTA4002	0	150	3	151	14.9%	0.14 [0.01, 2.76]
Opravil 2002	0	84	1	79	6.6%	0.31 [0.01, 7.59]
Vibhagool 2004	0	165	0	164		Not estimable
Subtotal (95% CI)		1627		1703	55.1%	0.66 [0.28, 1.55]
Total events	4		9			
Heterogeneity: $\chi^2 = 5.75$, df = 8 ($P = 0.68$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.96$ ($P = 0.34$)						
Total (95% CI)		3488		3566	100.0%	0.73 [0.39, 1.35]
Total events	12		19			
Heterogeneity: $\chi^2 = 7.68$, df = 12 ($P = 0.81$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.01$ ($P = 0.31$)						

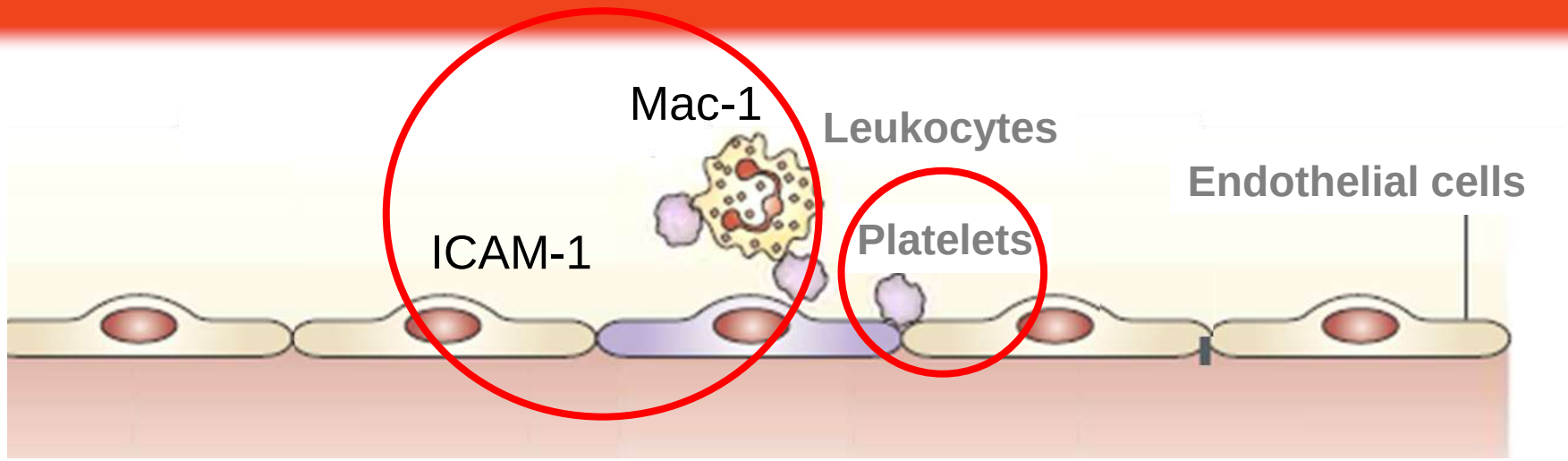
The Cruciani Meta Analysis

- No channelling bias!

  But

- Low baseline cardiovascular risk
- Low event rates
- Comparator arm +/- PI/r?
- No data on viral replication at the time of the event
- Mostly first line therapy

ABC + Inflammation: More data, more Questions?



ABC *in vitro*:

- induces Mac-1 on leukocytes, which interacts with ICAM-1 on endothelial cells[1]
- increases platelet activity through inhibition of soluble guanylyl cyclase[2]
- facilitates collagen-induced platelet aggregation[3]

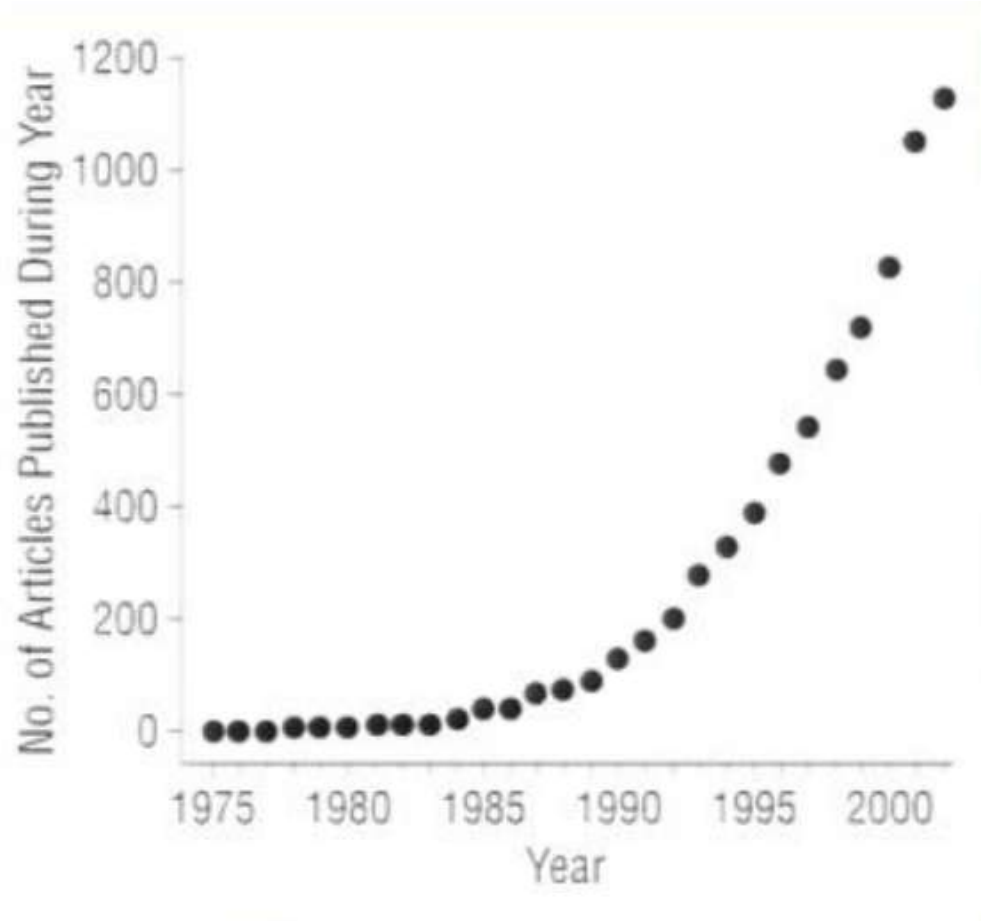
ABC in patients:

- STEAL Study[4]
- WIHS and HOPS Cohort[5]
- BICOMBO Study[6]
- HEAT Study[7]

No differences in biomarkers
(hsCRP, IL-6, D-dimer, MCP-1…)

[1]de Pablo CROI 2010 #716; [2]Baum CROI 2010 #717; [3] Satchell CROI 2009 #151LB7; [4]Martin CROI 2010, #718; [5]Palella AIDS 2010; [6]Martinez AIDS 2010; [7]McComsey CROI 2009 # 732

Search for Independent CVD Risk Factors

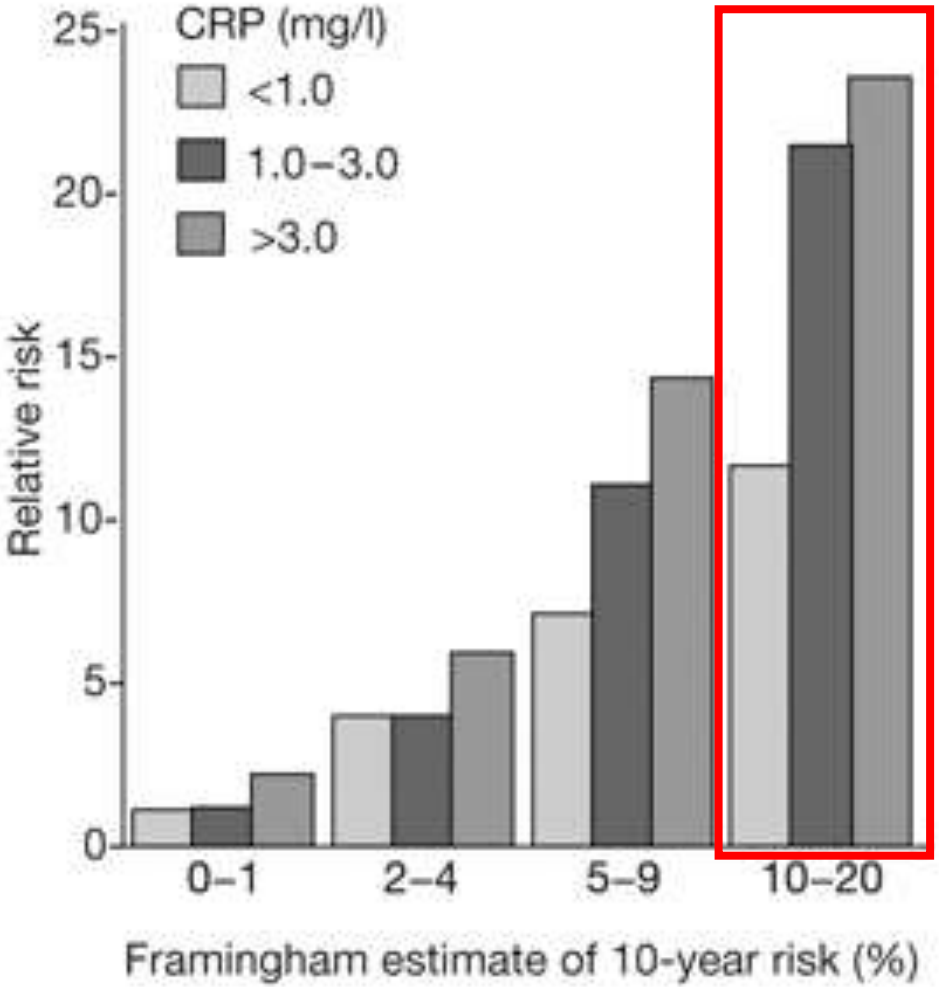


Brotman DJ, et al. Arch Intern Med 2005; 165:138

Challenges of Useful Independent Risk Factors for CVD (Biomarkers)

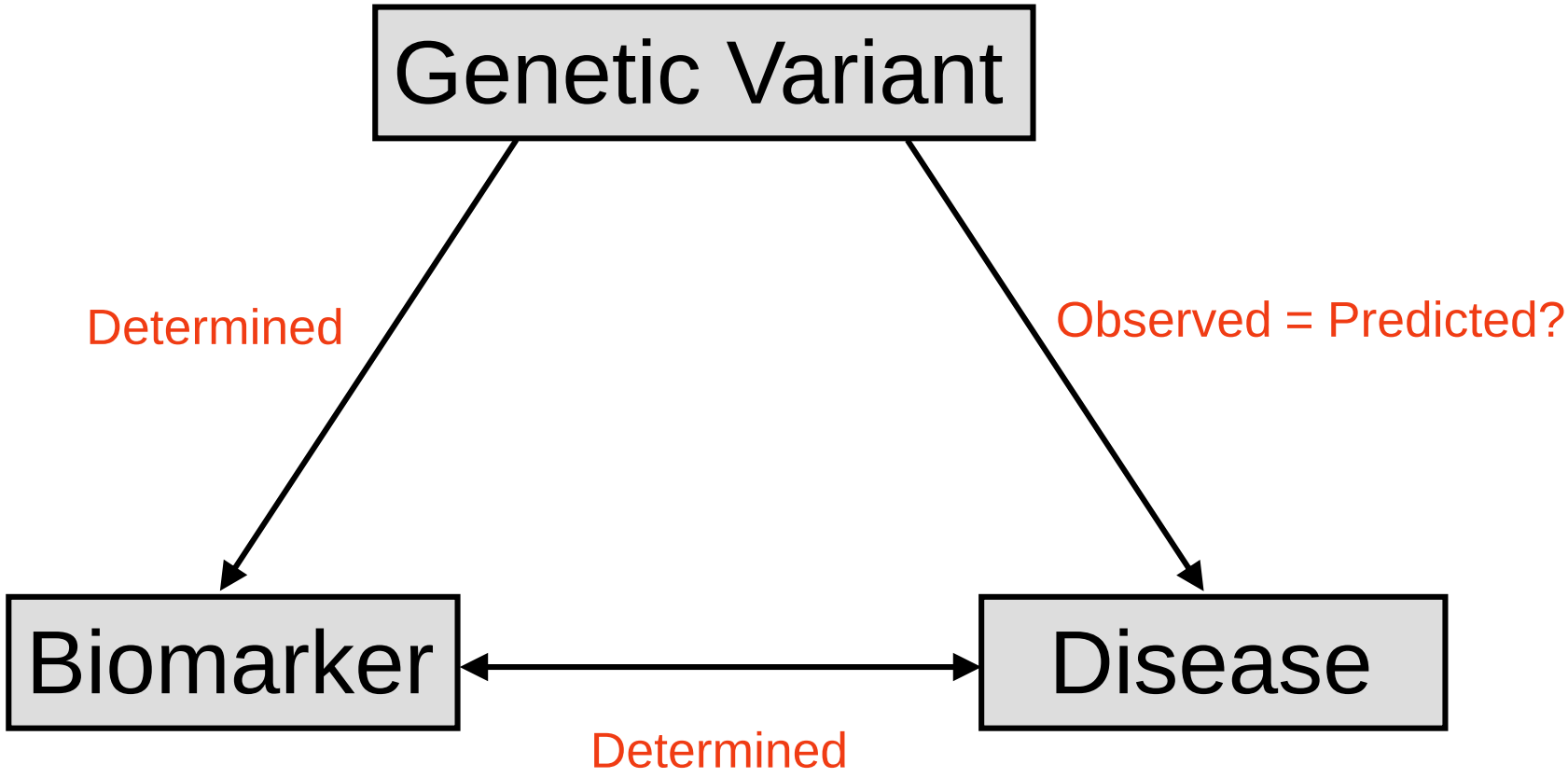
- Tells you nothing about clinical utility
- Scientifically: Tells you nothing about causality
- Markers with strong independent associations (adj. RR 2-3) usually will not improve discriminaton for CVD
- Biggest challenge: Showing that therapy based on identification of a new marker must improve long-term outcomes (RCT)

Predictive Value of High-Sensitivity C-Reactive Protein



Verma S et al.. Nat Clin Pract Cardiovasc Med 2004

The Mendelian Randomization Approach to Identifying a Causal Association



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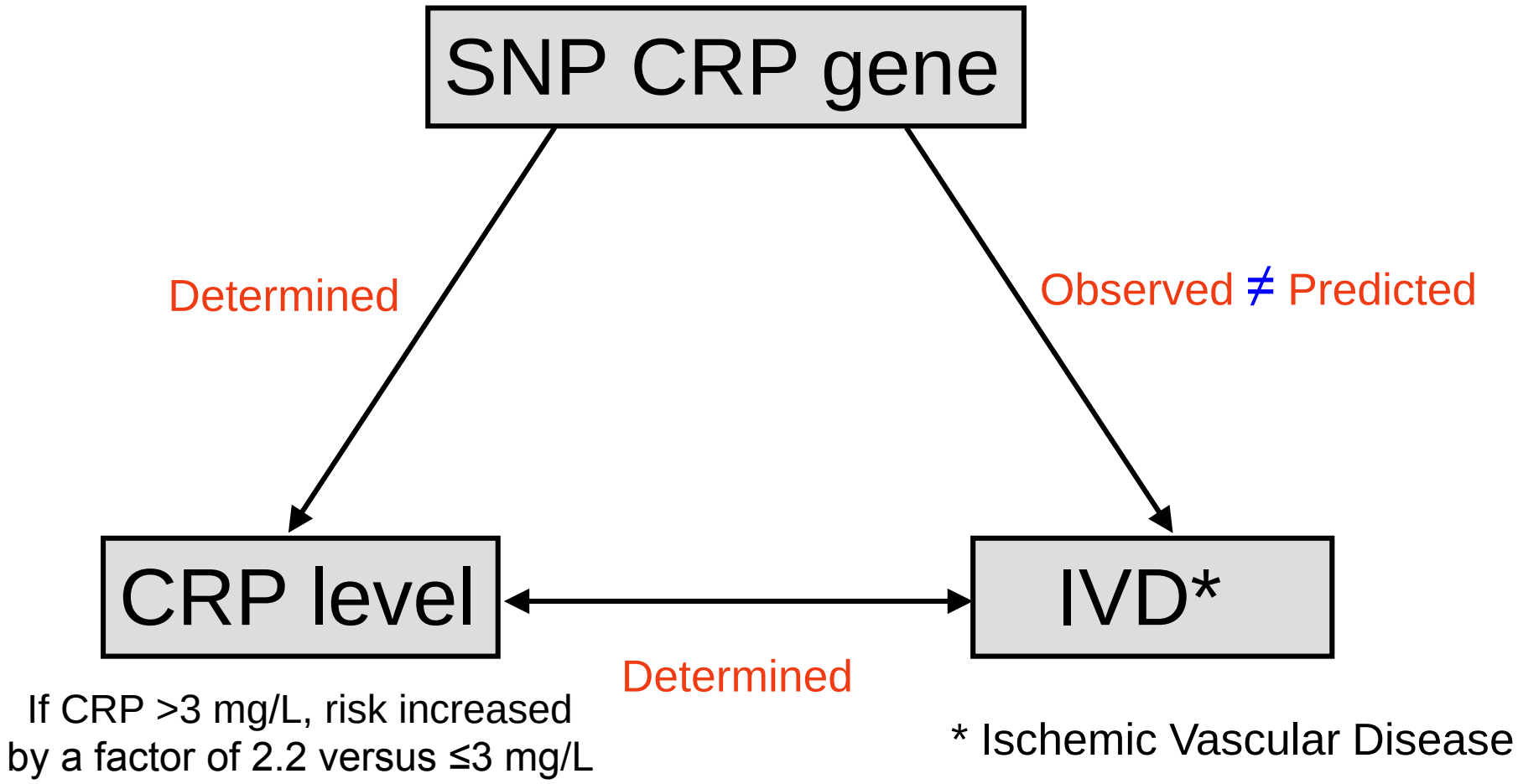
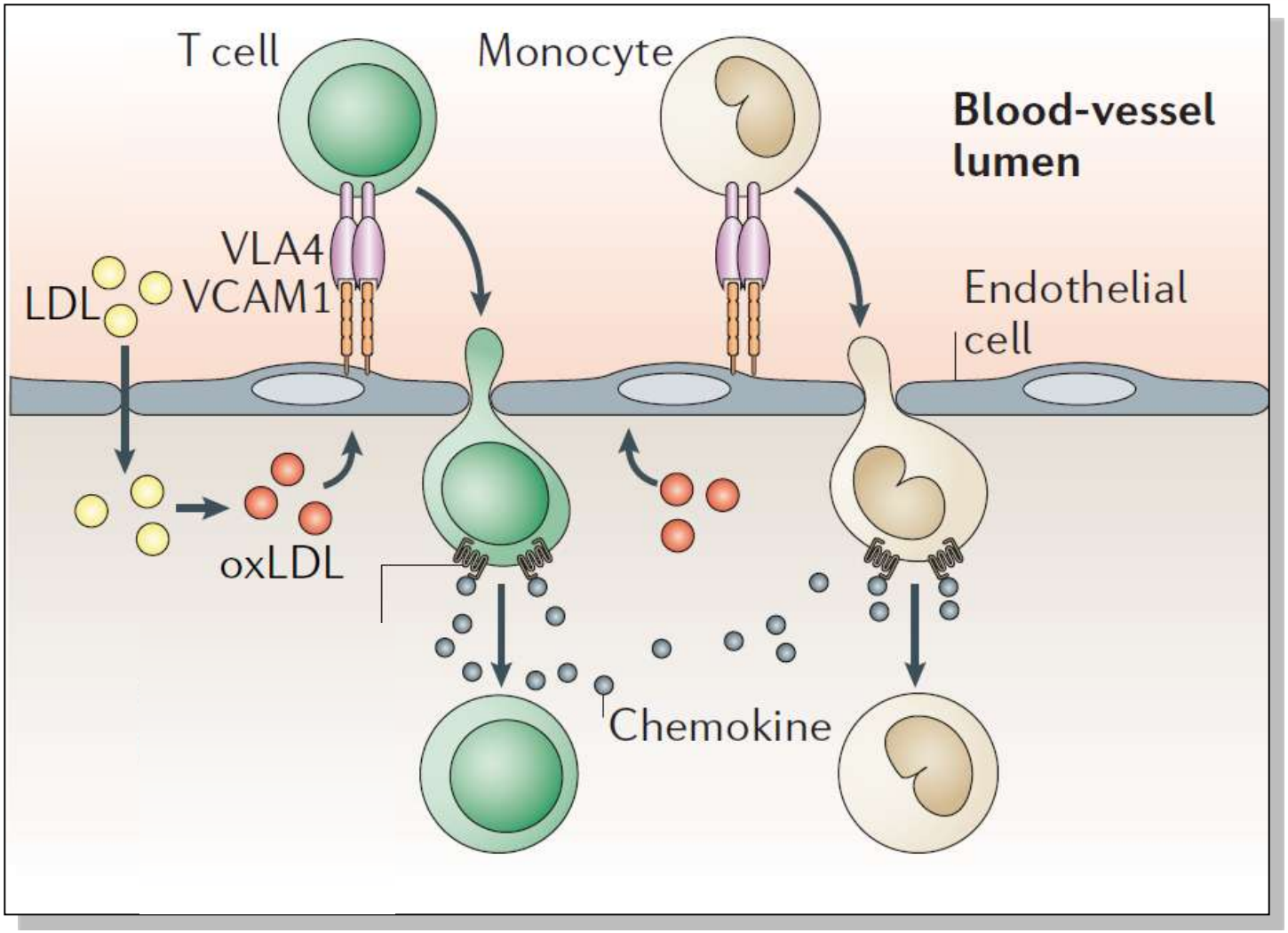
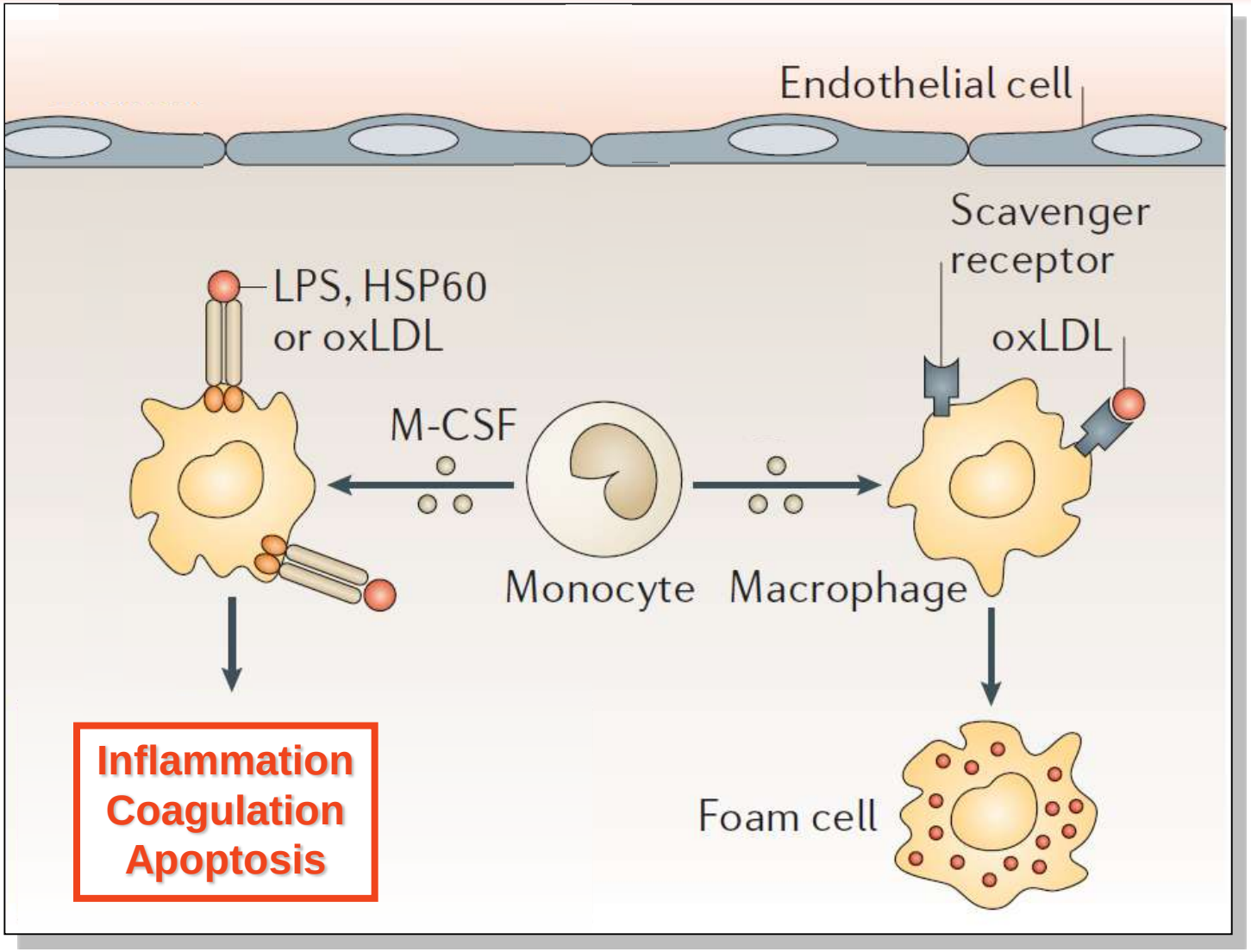


Atherosclerosis and Immune Cells



Modified from Hansson & Libby.
The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006

Atherosclerosis and Immune Cells



Modified from Hansson & Libby.
The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006

HIV and Cardiovascular Risk

HIV induces

- Apoptosis ↑ in endothelial cells (gp120, Tat)[1-3]
- Endothelial dysfunction[4]
- Leukocyte activation[5]
- HDL ↓, IL-6 ↑, sICAM ↑, D-dimer ↑
- MCP-1-CCR2 axis activation[6]
- MCP-1 polymorphism associated with atherosclerosis in HIV[7]
- a distinct (inflammatory) atherosclerosis process?[8]

MCP-1: Monocyte chemotactic protein-1

[1]Sudano, Am Heart J 2006; [2]Huang, J AIDS 2001; [3]Jia, Biochem Biophys Res Commun 2001; [4]Solages, CID 2006; [5]de Gaetano, Lancet Infect Dis 2004; [6]Park Blood 2001; [7]Alonso-Villaverde Circulation 2004; [8]Mehta, Angiology 2003, Baker CID 2010

HIV and Cardiovascular Risk

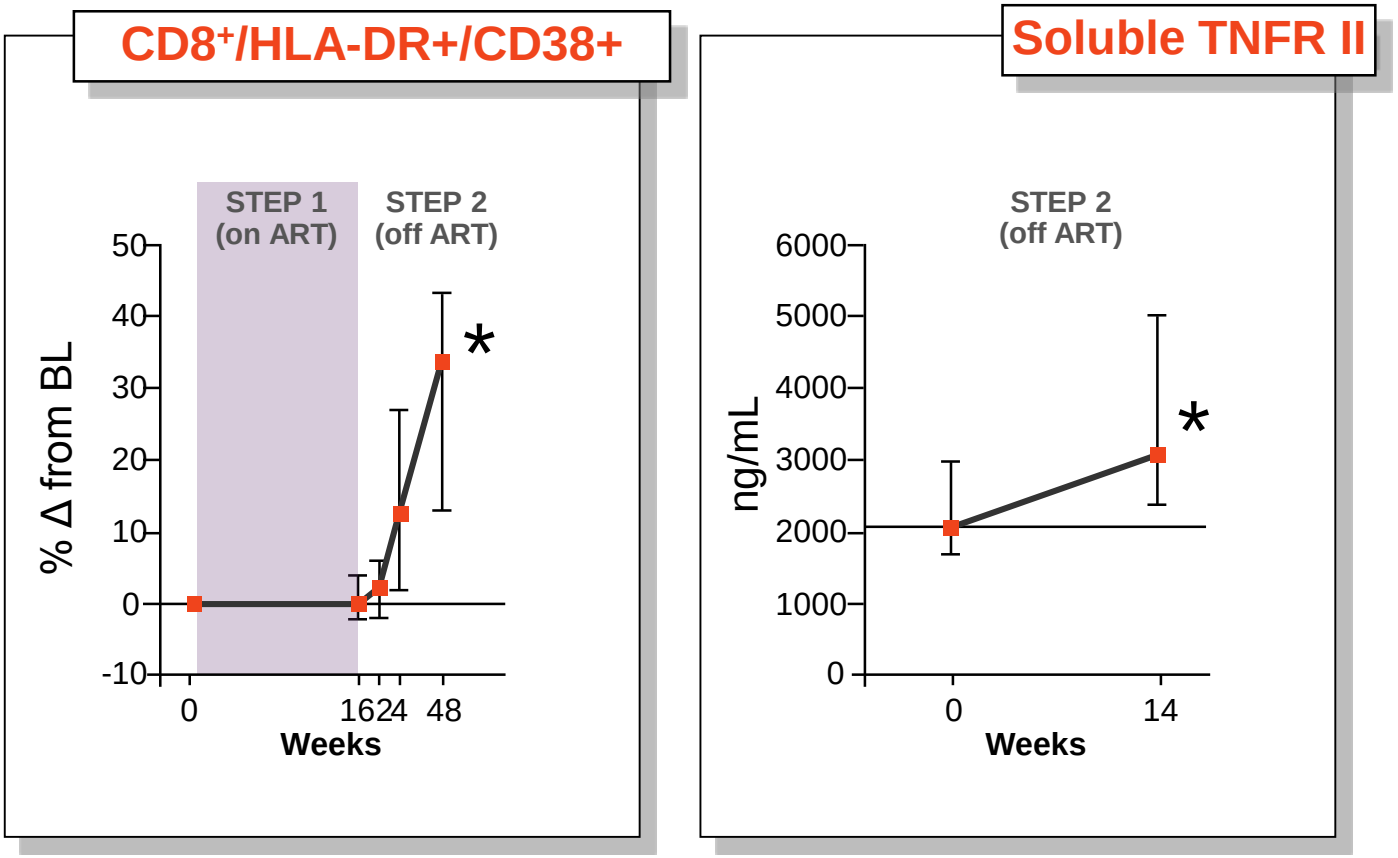
HIV as a risk factor

- HIV**+HCV**: - sICAM-1 + sVCAM-1 ↑[1]
  - endothelial dysfunction[1]
  - increased risk for MI[2]
- Low CD4 count is risk factor for MI[3] and carotid leasons
- Low CD4 nadir is associated with reduced arterial stiffness[4]
- HAART improves FMD, but not to normal (ACTG 5152s)[5]
- HIV is an independent predictor of increased carotid IMT[6,7]
- HIV increases tissue factor expression on monocytes[8]

FMD: Flow-mediated dilatation

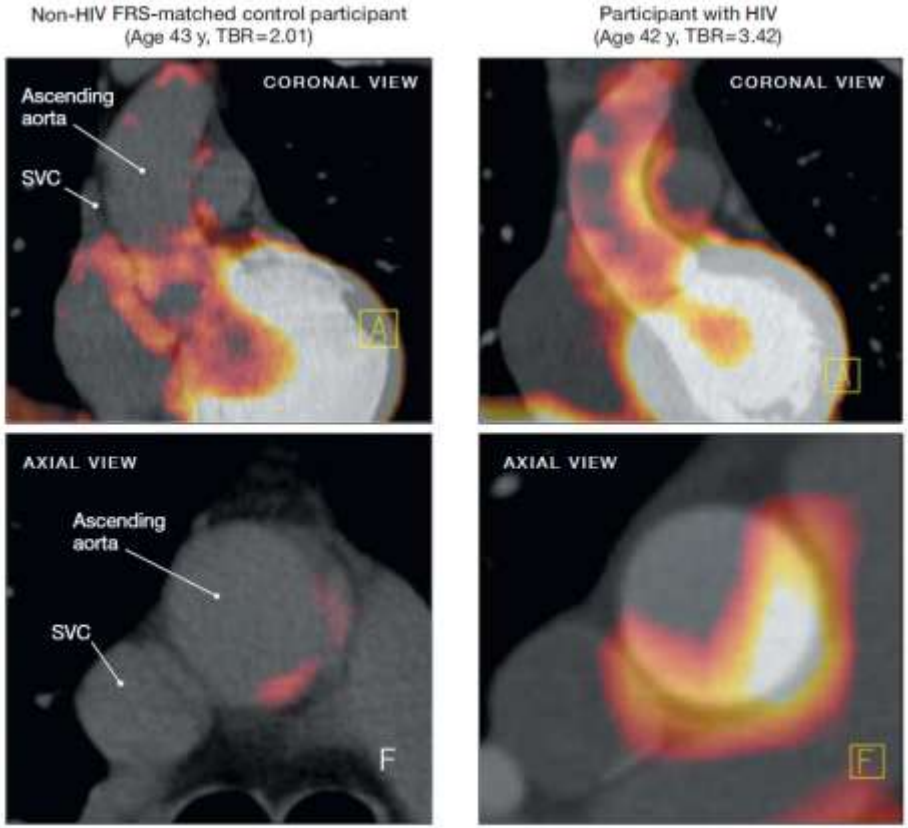
[1]Castro, AIDS 2010; [2]Bedimo, HIV Med 2010; [3]Lichentstein, Clin Infect Dis 2010; [4]Ho, AIDS 2010; [5]Torriani Am J Coll Cardiaol 2008; [6]Hsu, Circulation 2004; [7]Grunfeld AIDS 2009; [8]Funderburg Blood 2010

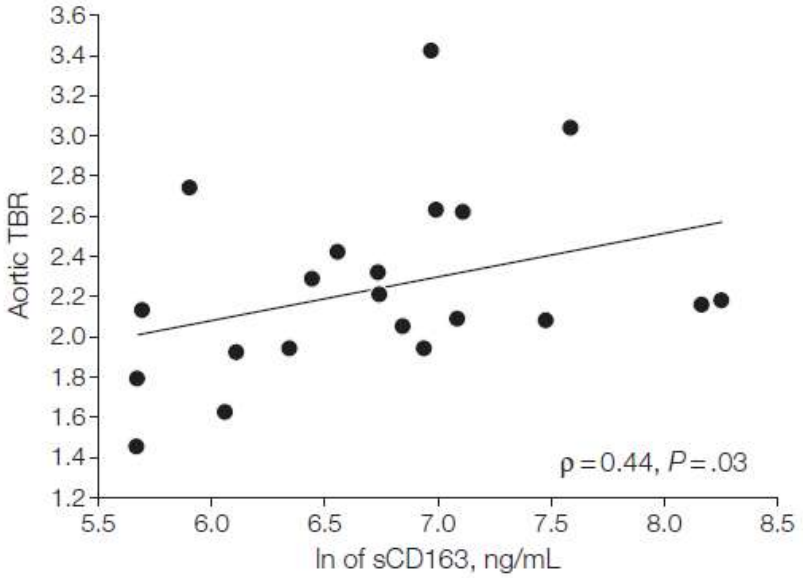
Changes in Immune Activation with Treatment Interruption (ATG 5102)



Conclusion for treatment interruption: Lipids ↓, immune activation ↑

Arterial Inflammation in Patients With HIV





Subramanian et al JAMA 2012

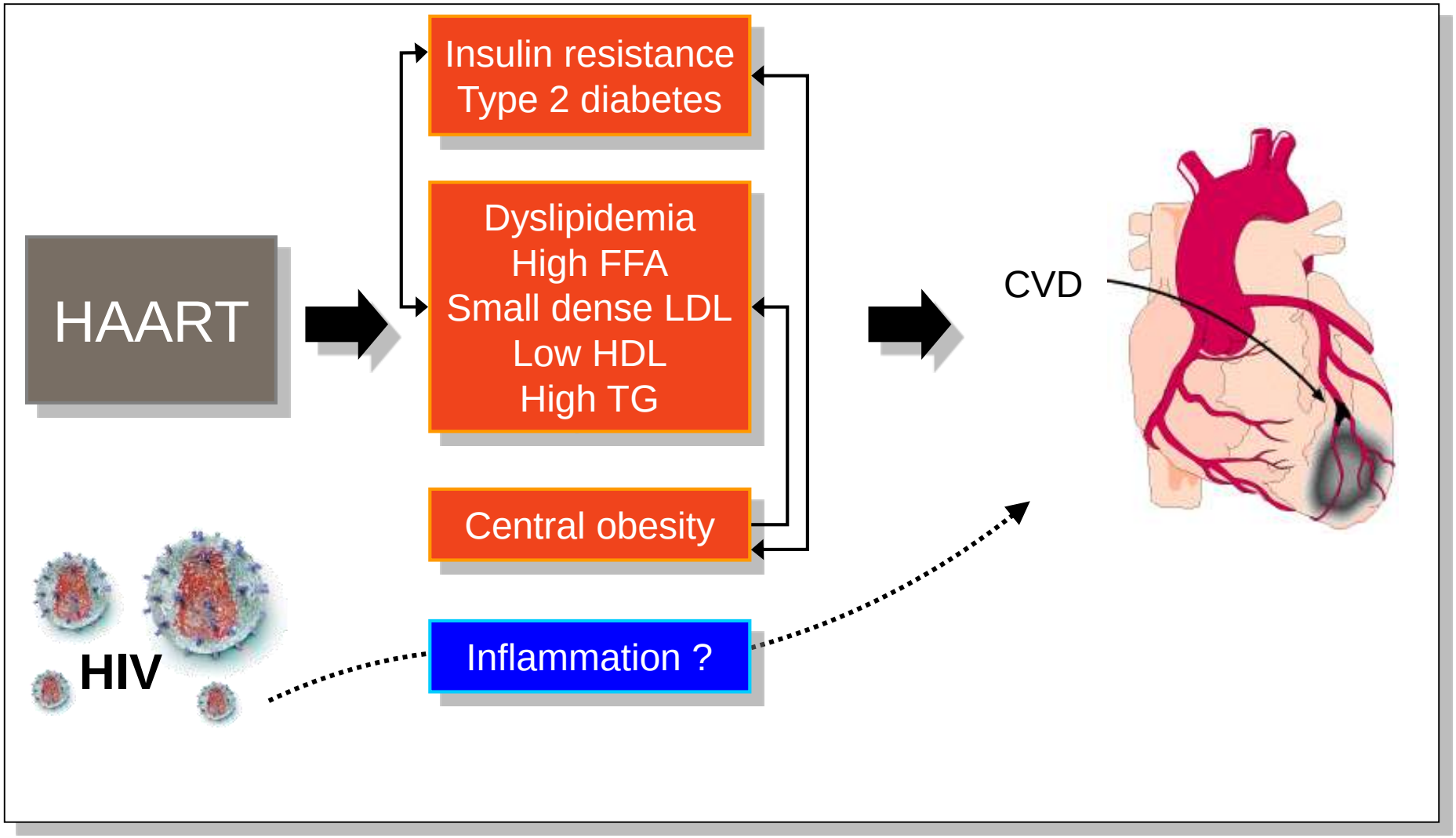
Signs for CVD in Elite Controllers

	Elite Controllers (n=10)	Chronic HIV (n=103)	HIV negative (n=43)	P-value
Coronary plaques*	**78%**	60%	42%	0.049
Total plaque segements	**2.5** (0.3, 6.6)	1 (0, 3)	0 (0, 3)	0.14
sCD14 (ng/ml)	**1530** (499, 1919)	416 (218, 1614)	241 (134, 395)	0.001
sCD163 (ng/ml)	**2841** (1722, 3427)	1247 (829, 1883)	847 (624, 1230)	0.0002
hsCRP (mg/l)	**0.4** (0.3, 2.4)	1.4 (0.6, 3.9)	1.2 (0.5, 3.1)	0.25

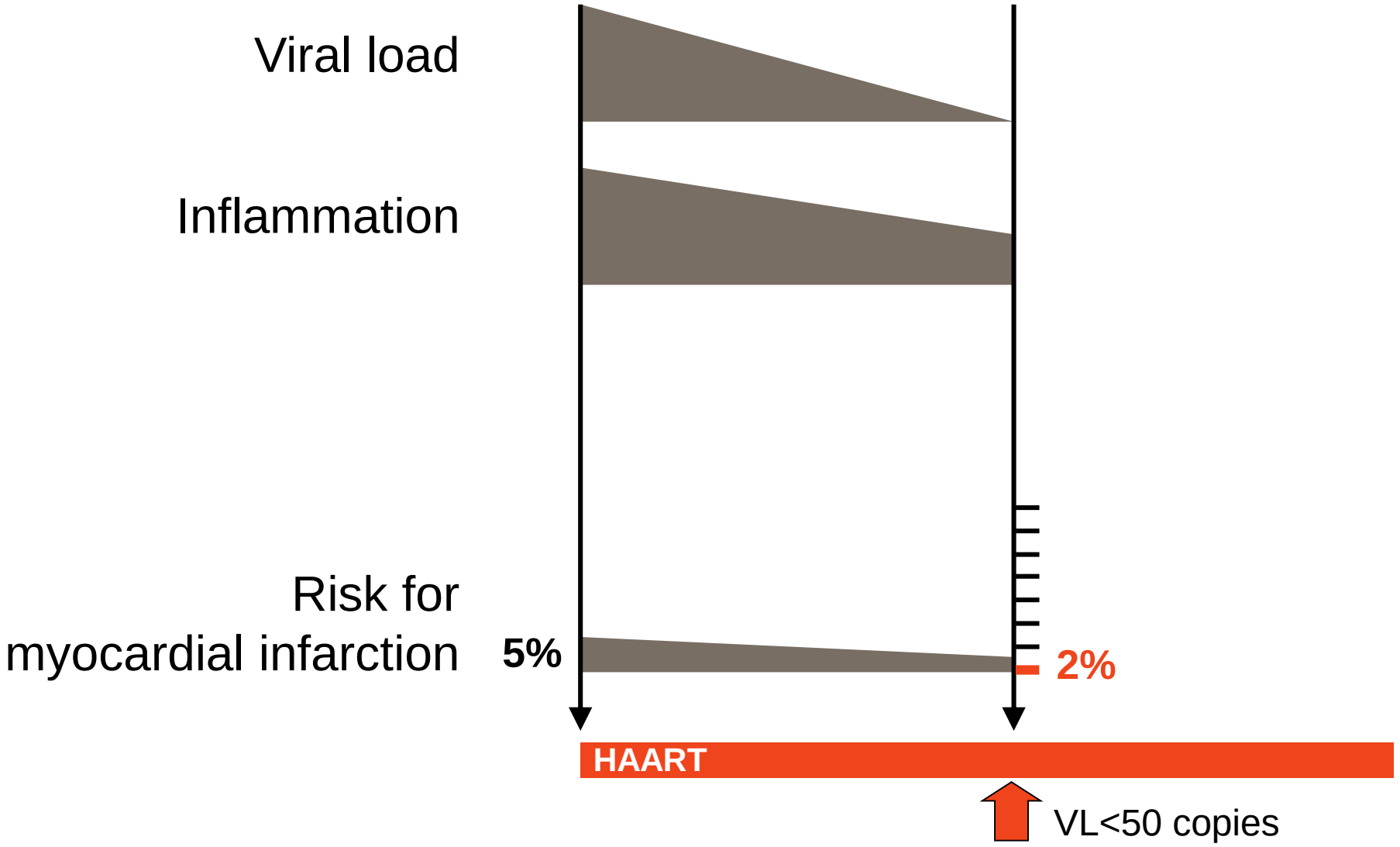
Pereyra et al. AIDS 2012

***CT Angiopgraphy**

Inflammation and Cardiovascular Disease



What Does it Mean for Clinical Care?



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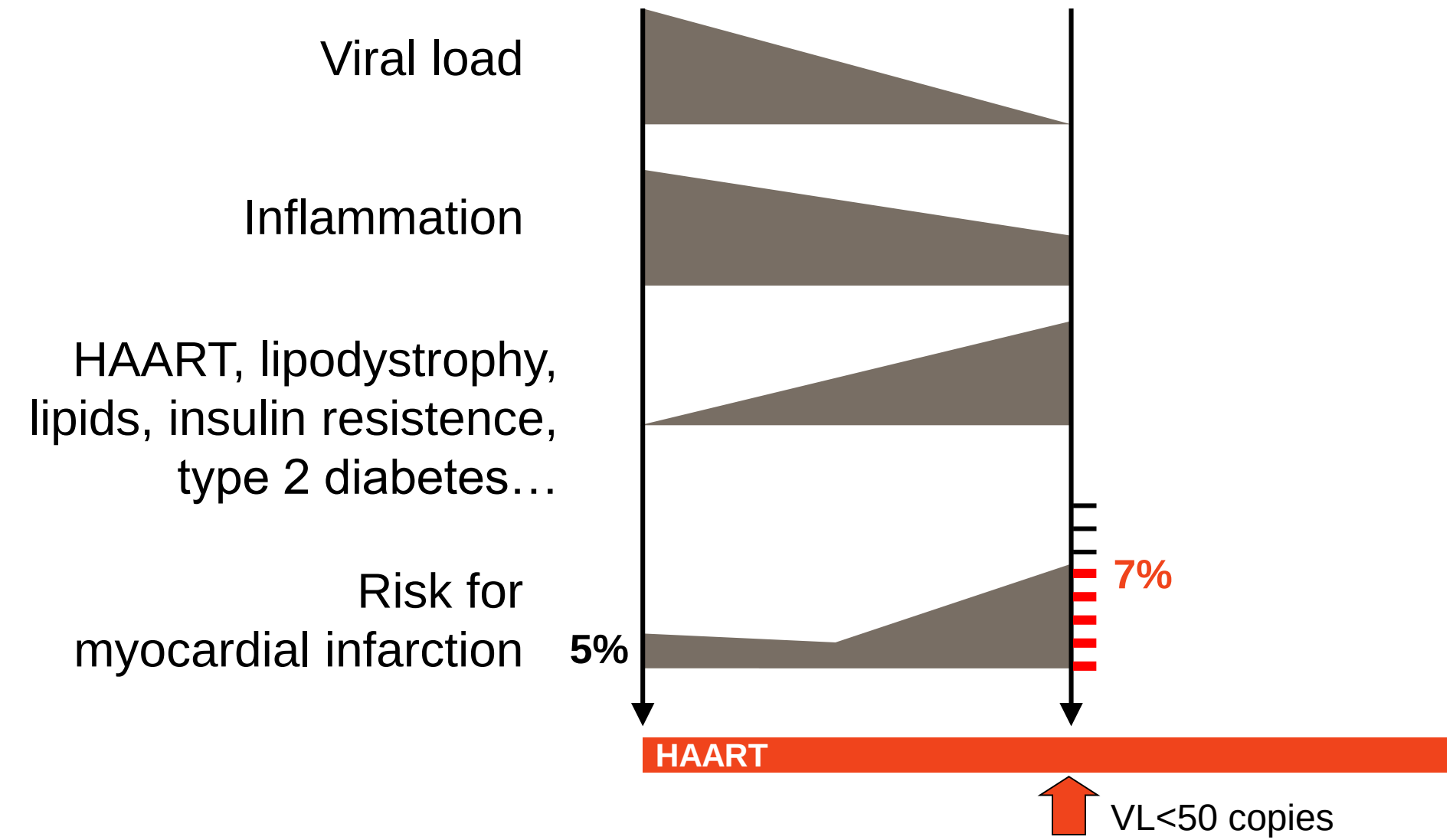

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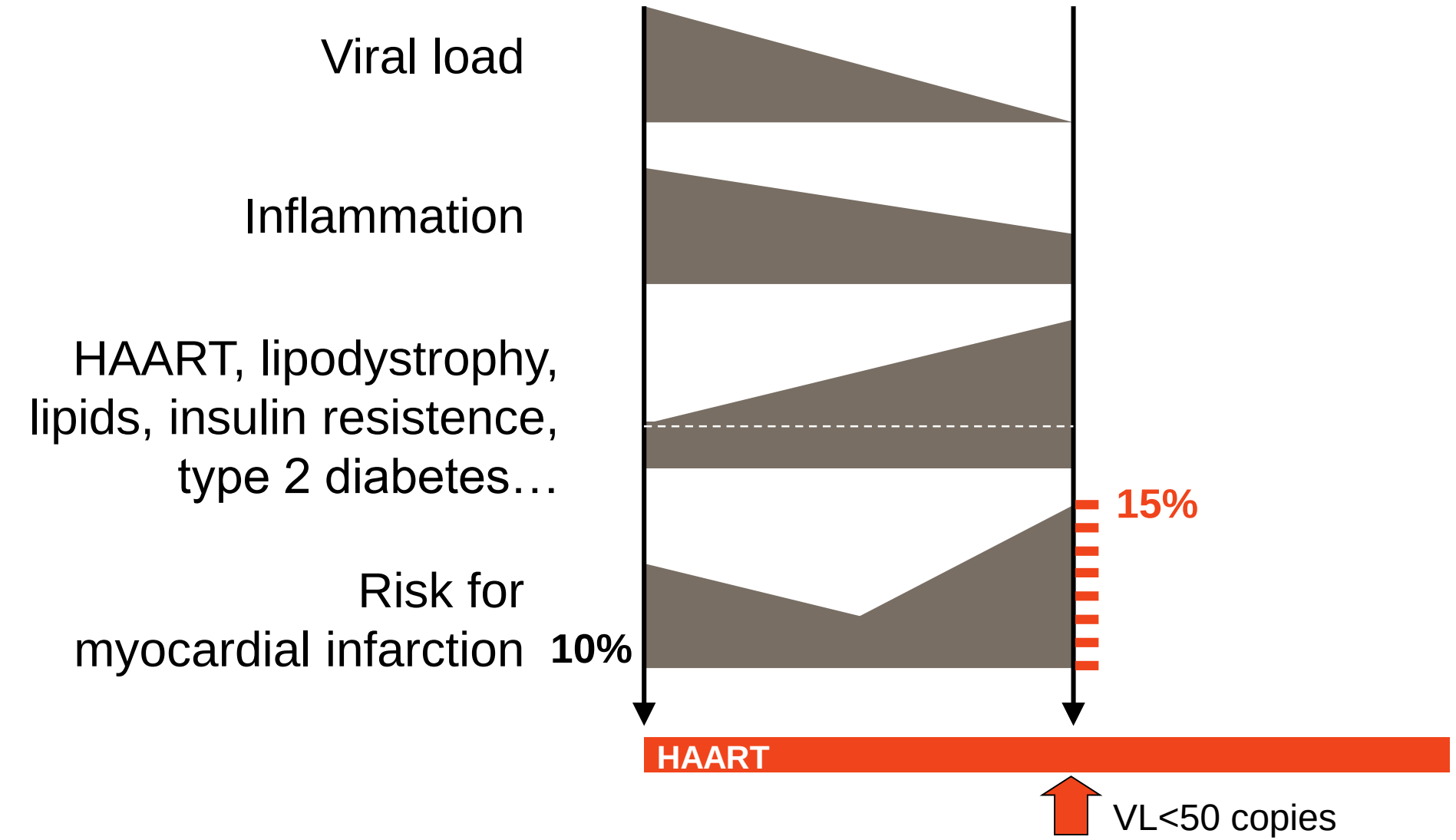
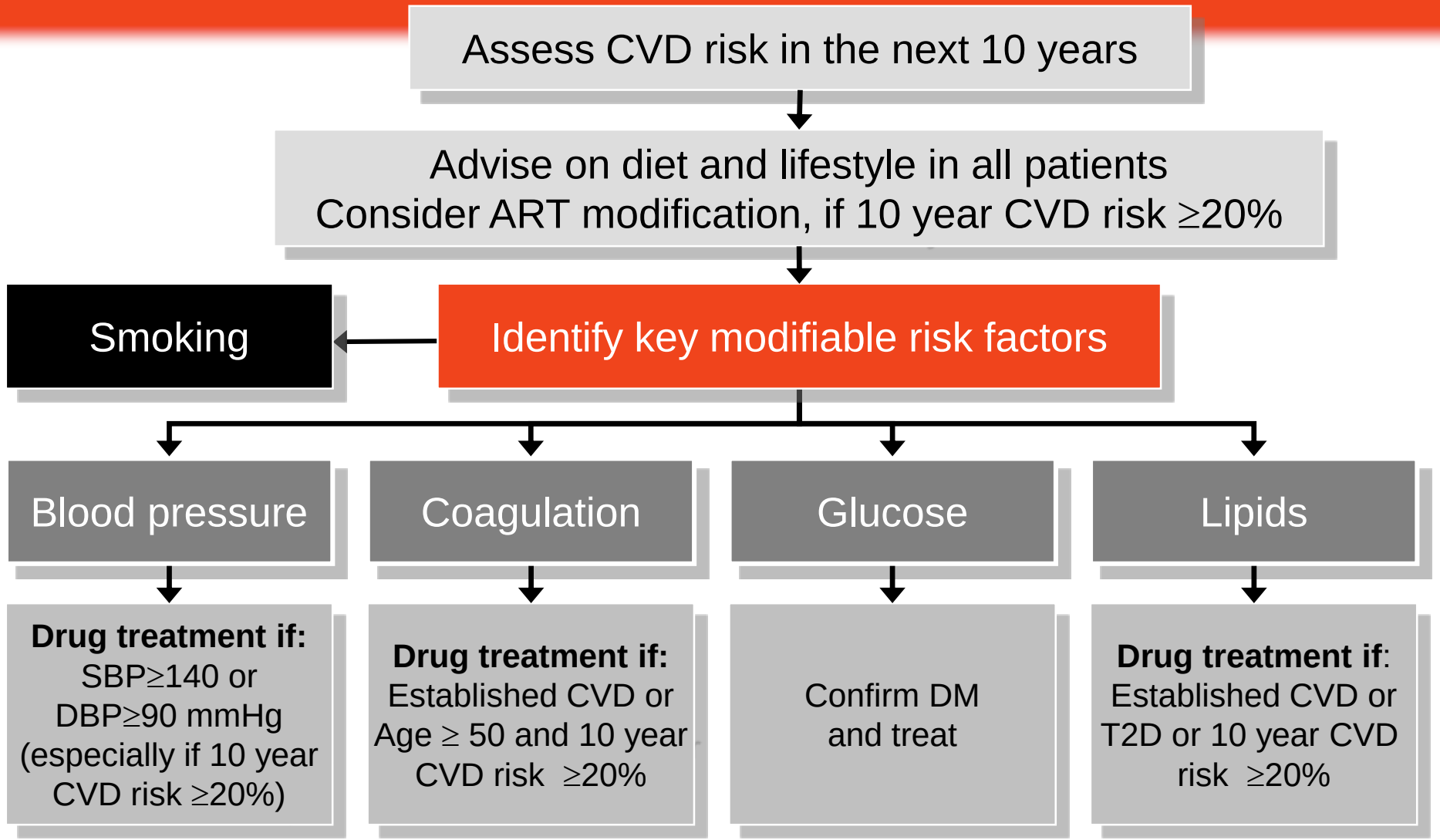


EACS Guidelines 2014



EACS Guidelines 2014

Assess CVD risk in the next 10 years

Advise on diet and lifestyle in all patients
Consider ART modification, if 10 year CVD risk ≥20%

Smoking

Identify key modifiable risk factors

Blood pressure

Target	
If T2D or prior CVD or CKD + proteinuria	Others
SBP<130	<140
DBP<80	<90

Coagulation

Target
N/A

Consider to treat with acetylsalicylic acid 75-150mg

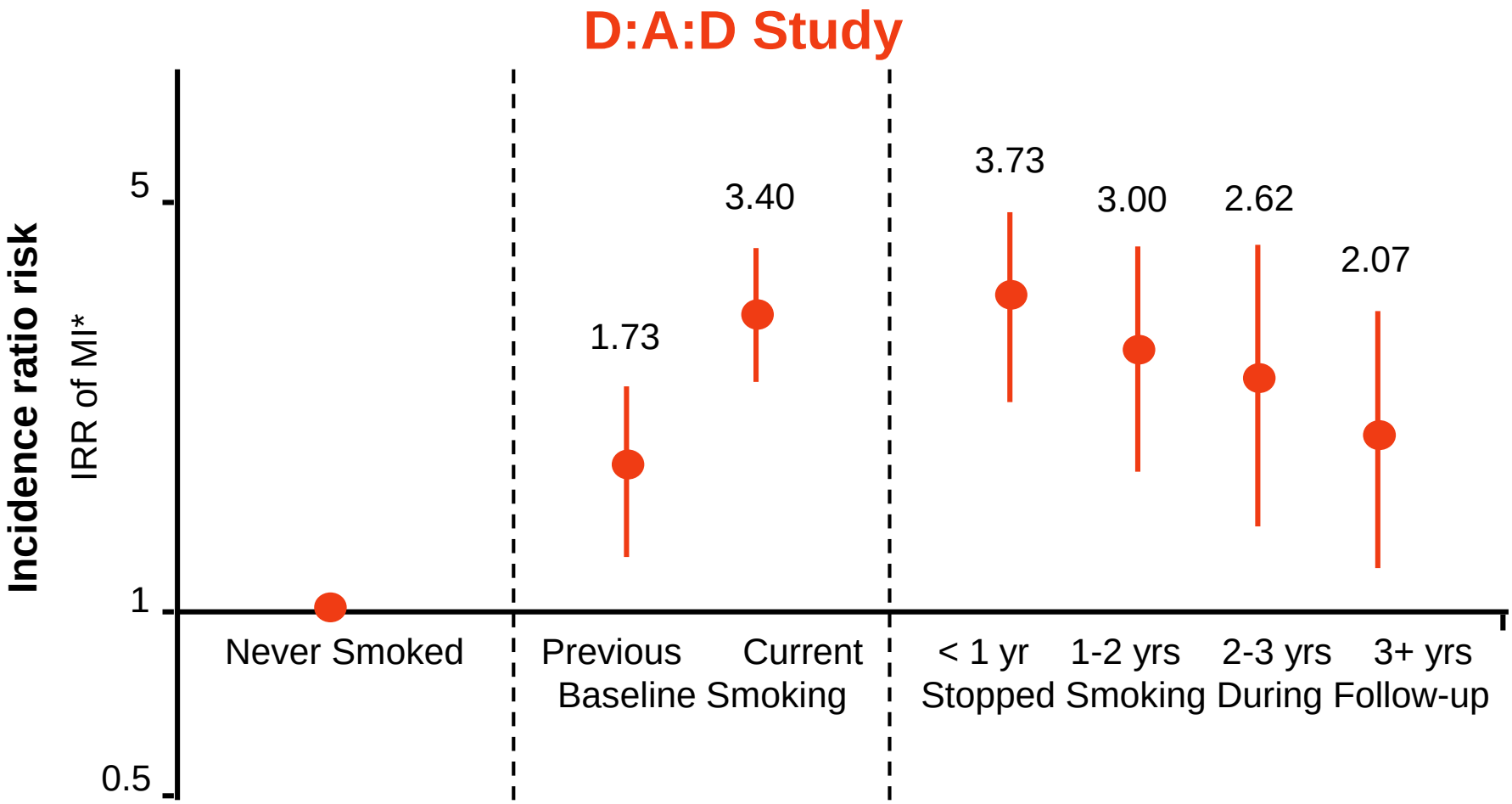
Glucose

Target
HbA1c <6.5-7%

Lipids

Target		
	Best	Standard
TC	≤4 (155)	≤5 (190)
LDL	≤2 (80)	≤3 (115)

Smoking Cessation Decreases Risk of CVD in HIV-infected Patients



*Adjusted for: age, cohort, calendar yr, antiretroviral treatment, family history of CVD, diabetes, time-updated lipids and blood pressure assessments.

Petoumenos et al. HIV Medicine 2011

The ART Drug Profile

Antiviral activity

Metabolisation

Resistence profile

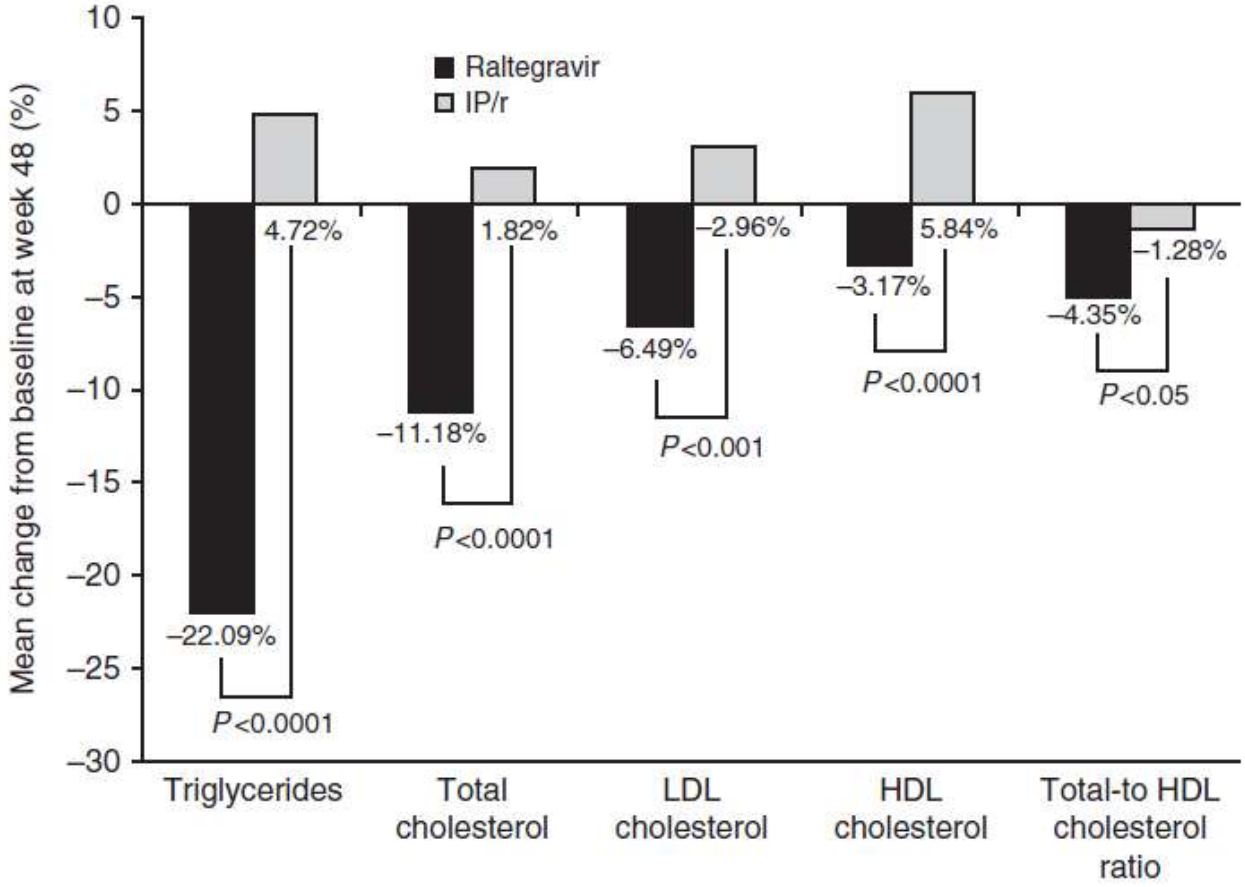
Pharmacokinetics

Drug-drug interaction

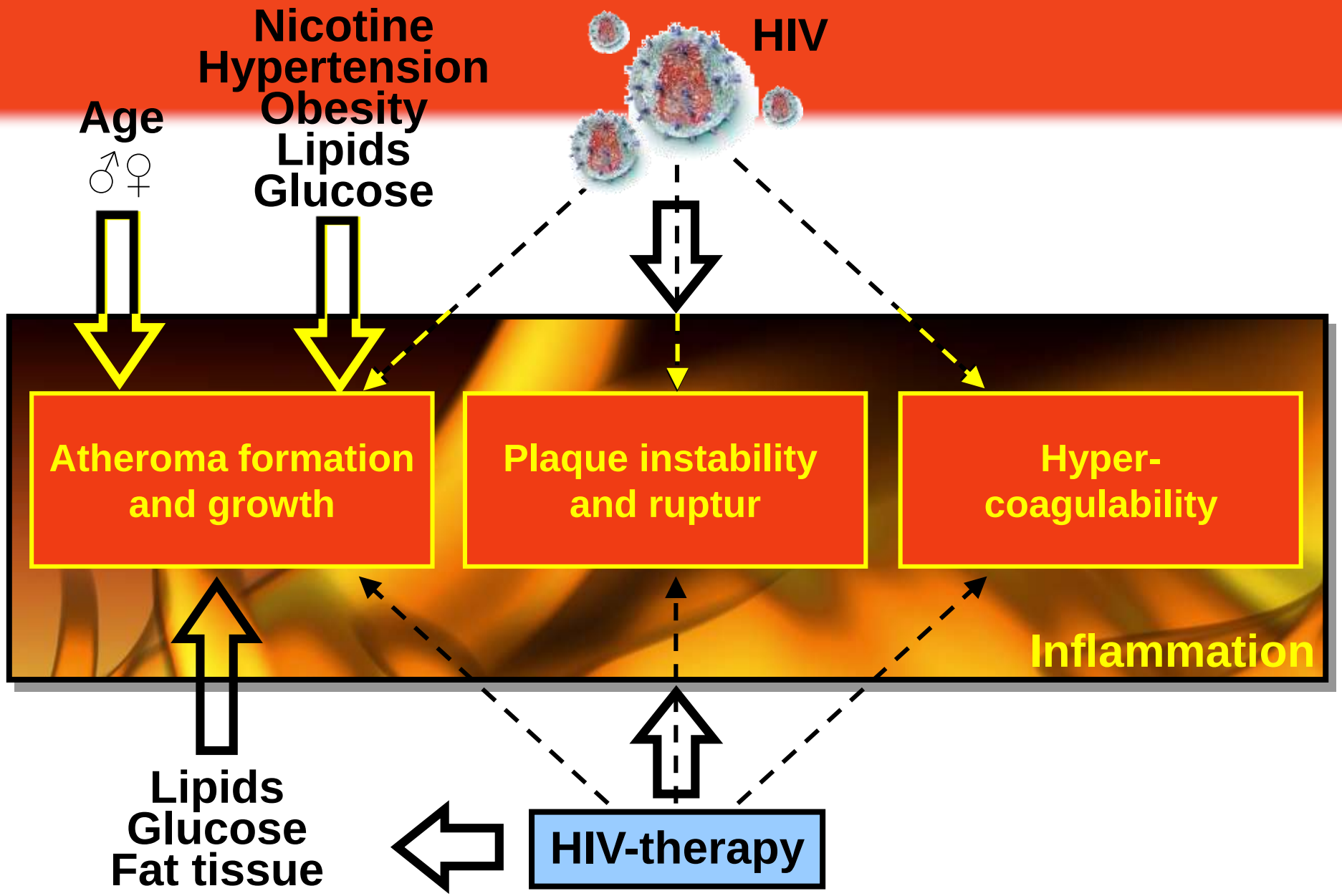
C_{max}

Lipid profile…

SPIRAL Study

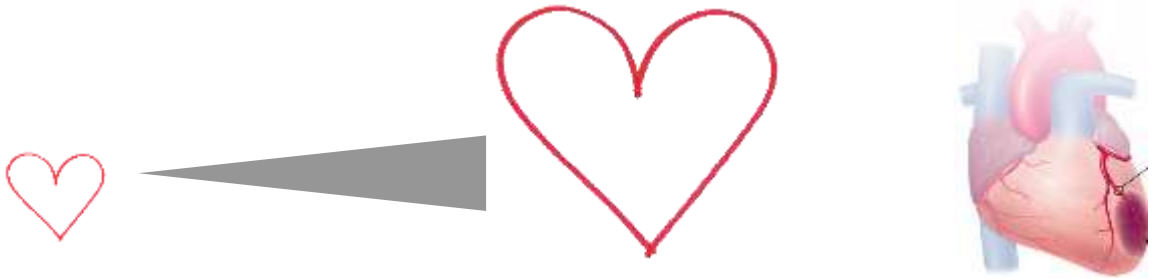


Martinez et al., AIDS 2010



Behrens & Reiss Curr Opin Infect Dis 2010

Summary



1995 2005 2015 2025

Drug-associated „Metabolics“

Inflammation

Clinical end points

Ageing