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XIV Congreso de la Sociedad Canaria de Medicina Interna
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HIV Infection and Cardiovascular Risk

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There are reasons to consider that the risk of CV disease may be increased in HIV-infected patients

Aging
Organ dysfunction: cardiovascular, kidney, etc

Drug consumption
Tobacco
Alcohol
Cocaine
Other?

Metabolic abnormalities
Dyslipidemia
Insulin resistance / DM

Body fat changes
Lipoatrophy
Lipoaccumulation

Degree of immunedeficiency
CD4 cells/μL

Patient

CV disease

Other?

Antiretroviral drugs

HIV (and other infections)

NRTIs
Dyslipidemia?
Insulin resistance ?
Body fat changes?
Other?

PIs
Dyslipidemia
Insulin resistance?
Body fat changes?
Other?

HIV, HCV, HBV?, other?
Dyslipidemia
Systemic inflammation
Inmune activation
Vascular infection

Contribution of PATIENT

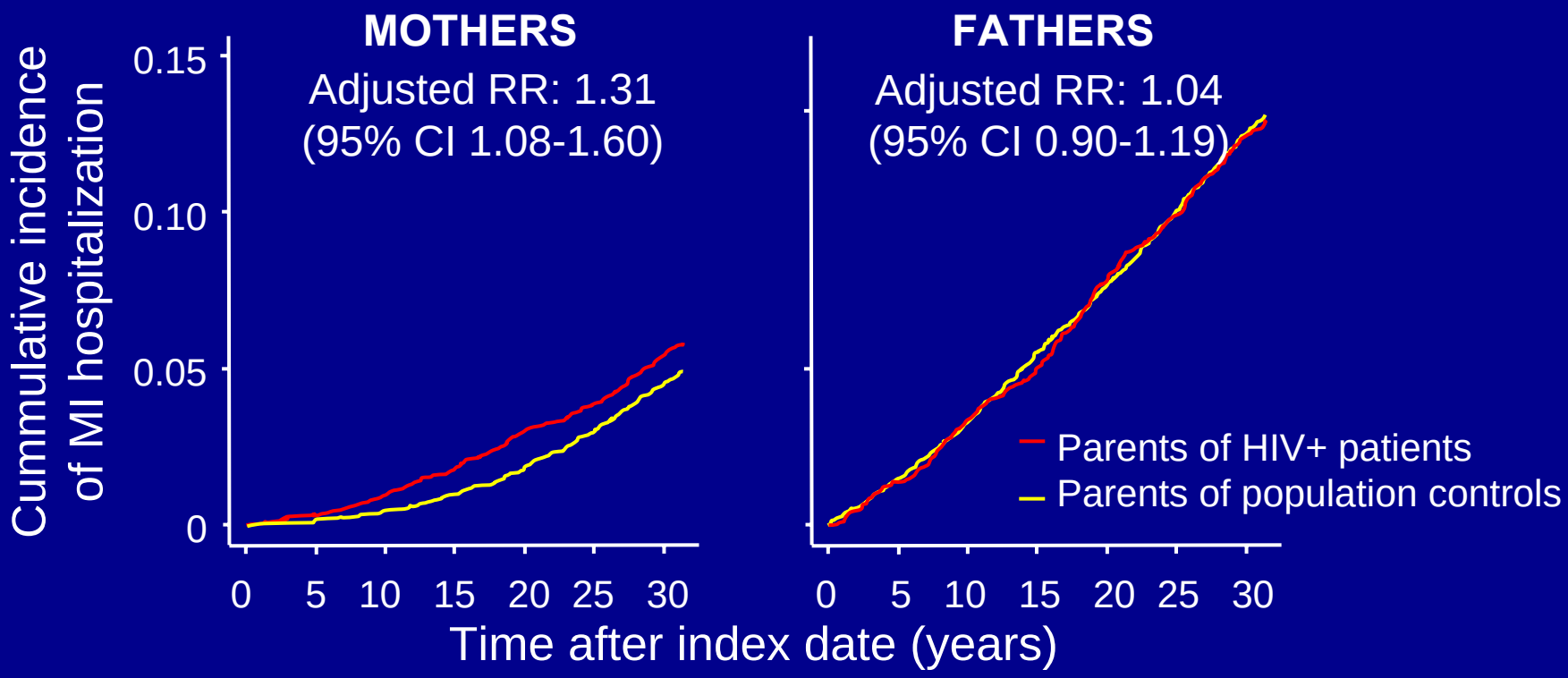
HIV+ patients with myocardial infarction have higher prevalence of traditional CV risk factors

	DAD		French Cohort	
	MI (n=580)	No MI (n=32728)	MI (n=289)	No MI (n=884)
Age (years) (median)	49	44	47	46 (matched)
Sex, male (%)	91	74	89	89 (matched)
Current smoker (%)	45	29	73	44
Previous CV disease (%)	20	3	0 (defined)	0
Family history CV disease (%)	14	8	19	7
Diabetes mellitus (%)	17	5	16	10
Hypertension (%)	44	19	21	12
Any dyslipidaemia (%)	75	44	-	-
Hypercholesterolaemia (%)	-	-	52	33
10-year Framingham score				
Moderate (10-20%) (%)	30	15	-	-
High (≥20%) (%)	18	4	-	-
Nr CV risk factors				
0 (%)	-	-	1	18
≥3 (%)	-	-	39	19

Lundgren, J & DAD Study Group *et al* CROI 2009 abstract 44LB; Lang *et al*, CROI 2009, abstract 43LB

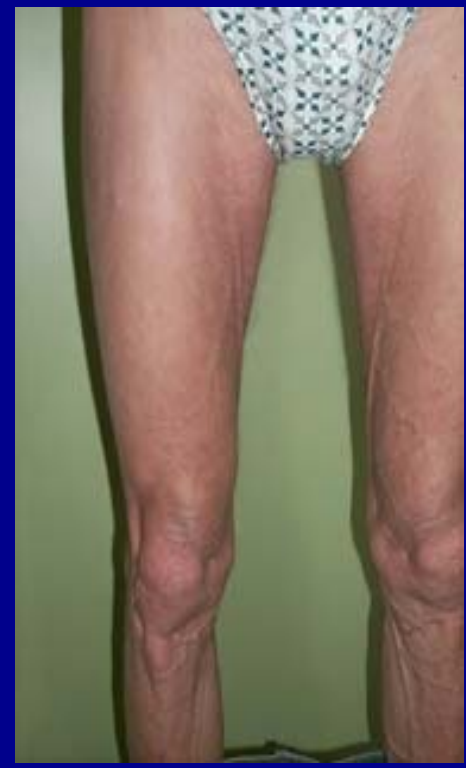
Mothers of HIV+ patients have an increased risk of MI: role of family life-style factors?

- Case-control Study (1:4)
- Danish HIV Cohort Study and Danish Civil Registration System
- Parents born in Denmark after 1952
- 2269 mothers and 2022 fathers of HIV+ patients
- 9076 mothers and 8460 fathers of control subjects



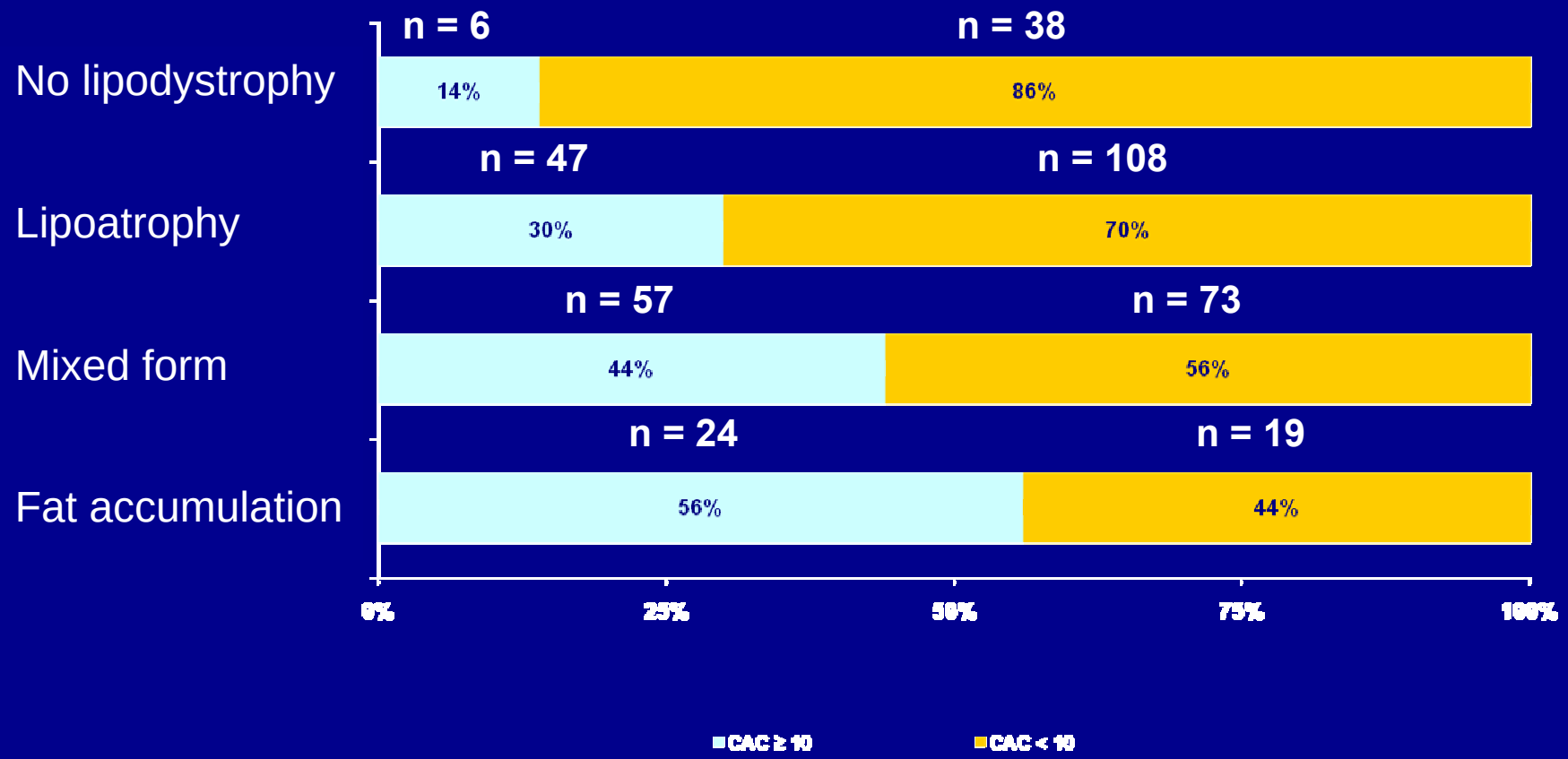
Rasmussen LD et al. BMC Infect Dis 2010

Lipodystrophy is a distinctive feature of HIV-infected patients



Lipodystrophy is a predictor of sub-clinical atherosclerosis

Prevalence of coronary artery calcium score > 10 according to different phenotypes of lipodystrophy



X^2-test *p*-value < 0,001

CAC : Coronary artery calcium

Guaraldi G et al. Atherosclerosis 2009

Lower CD4 cell counts associated with higher rates of CV disease and other non-AIDS events

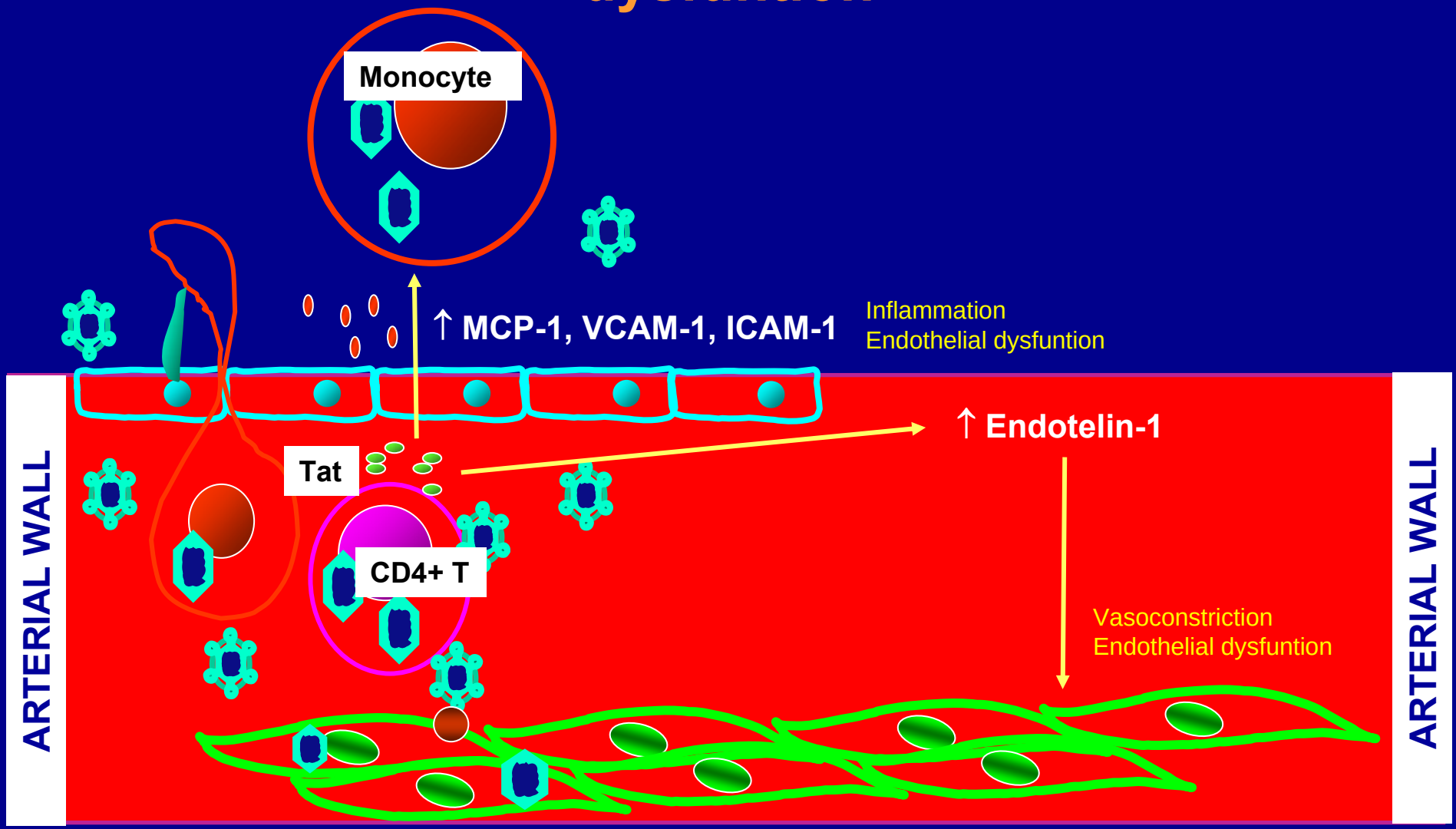
Causes of morbidity/ mortality:	Cardiovascular disease	Non-AIDS cancer	Liver Disease	Renal disease
Studies suggesting association with lower CD4+ count:	• SMART • D:A:D • CASCADE* • FIRST • VACS†	• D:A:D • CASCADE • FIRST • Aquitaine	• SMART • D:A:D • CASCADE • FIRST	• SMART • FIRST • VACS

* Cardiovascular disease or type 2 diabetes; † Vascular disease

Goulet JL, et al. Clin Infect Dis 2007;
Weber R, et al. 12th CROI;
CASCADE Collaboration, AIDS 2006;
Baker JV, et al. AIDS 2008;
Weber R, et al. Arch Intern Med 2006;
Bruyand M, et al. 15th CROI;
El Sadr WM, et al. N Engl J Med 2006

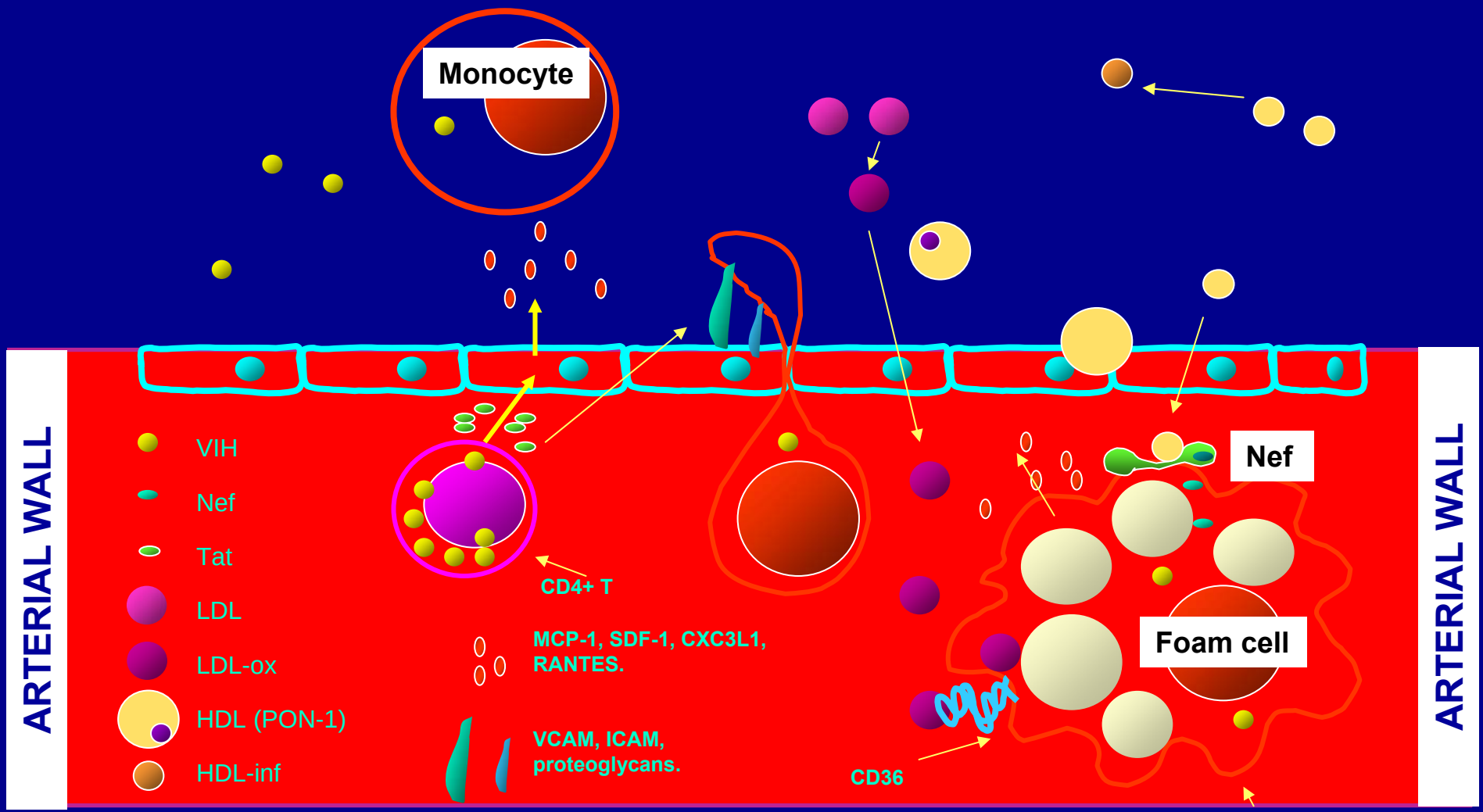
Contribution of VIRUS

HIV infects arterial wall, and Tat protein promotes vasocontriction, inflammation, and endothelial dysfuntion



1. Eugenin EA et al. Am J Pathol 2008; 2 Liu K et al. Am J Physiol Lung Cell Mol Physiol 2005;
3. Park IW et al. Blood 2001; 4. Kanmogne GD et al. Biochem Biophys Res Commun 2005

HIV infection of vascular wall promotes lipid storage and development of atherosclerotic plaque

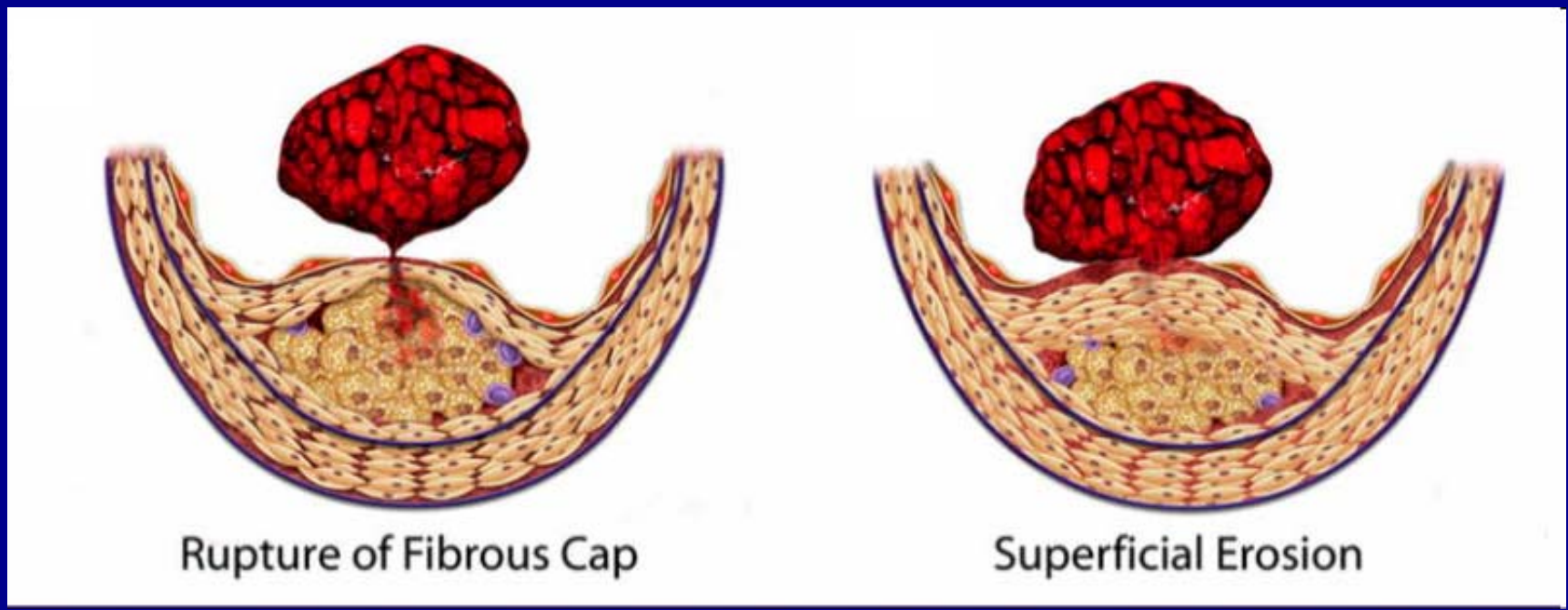


1. Rasheed S et al. PLoS ONE 2008; 2. Parra S et al. Atherosclerosis 2007

HIV infection promotes plaque rupture and development of thrombus leading to clinical event

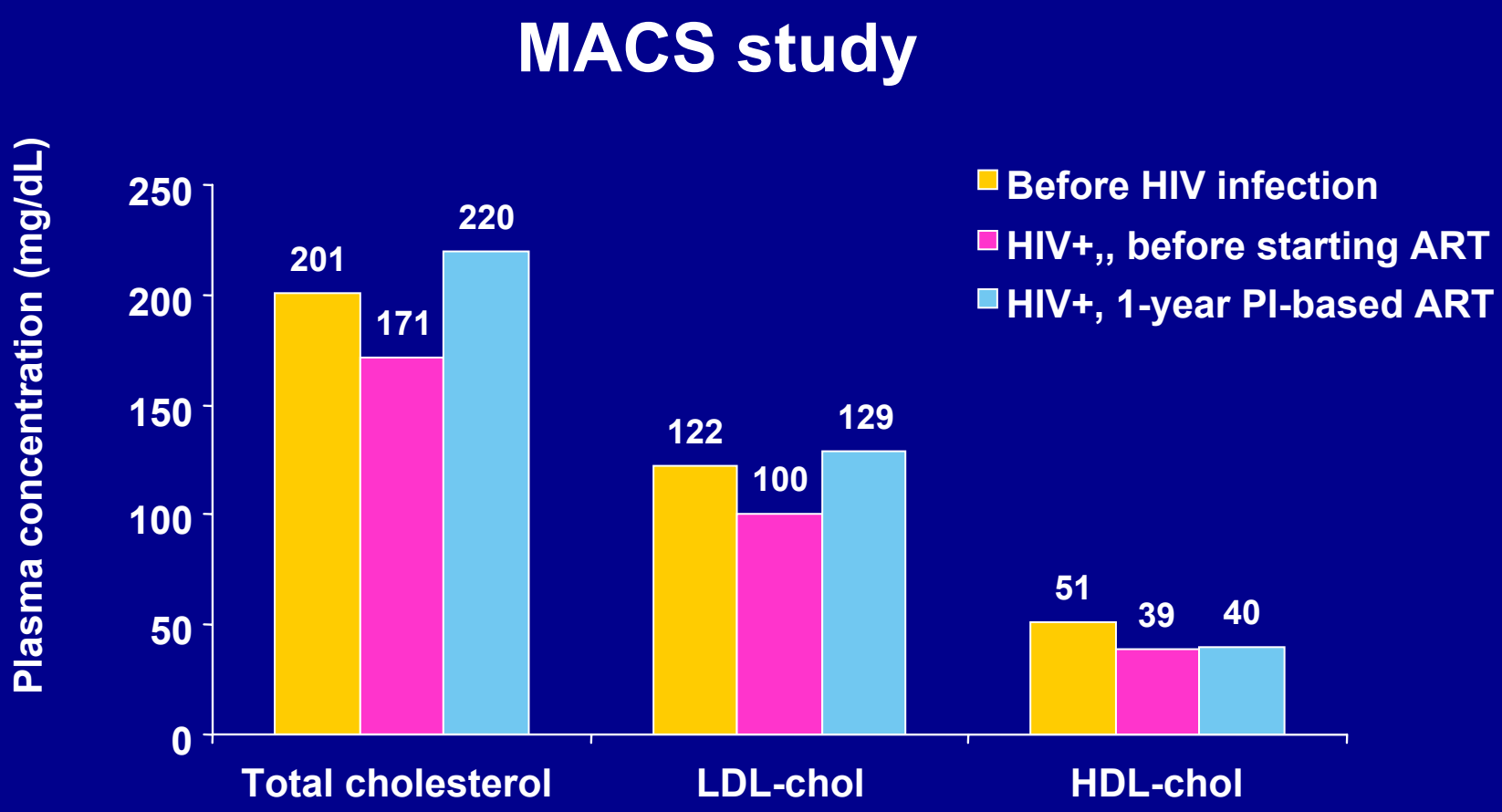
Metalloproteases induction

Endothelial cell apoptosis



1. Lopez-Herrera A et al. Biochim Biophys Acta 2005;
2. Yano M et al. AIDS 2007;

A relative deficit of HDL-cholesterol is characteristic of HIV infection

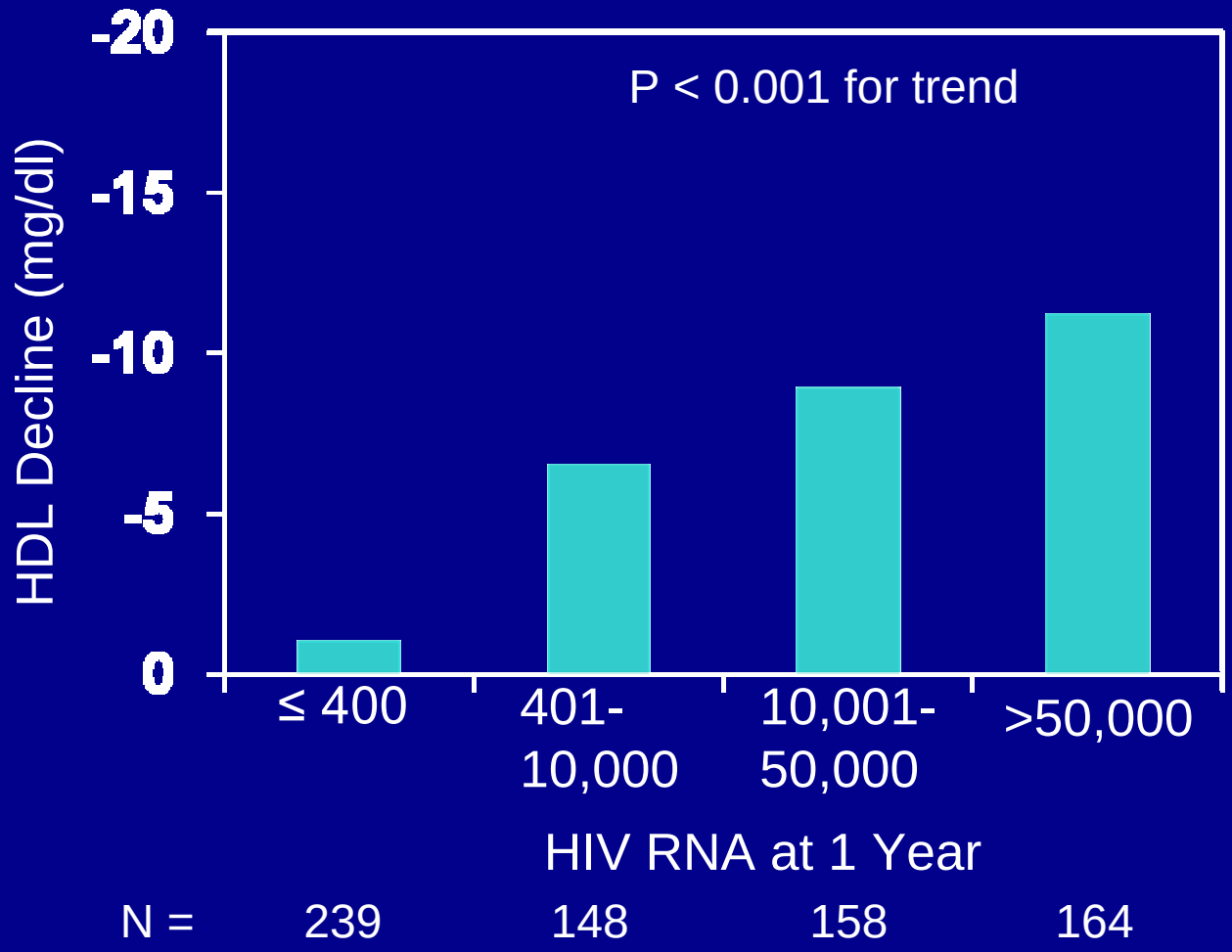


Total cholesterol / HDLc ratio increased

Riddler SA, et al. JAMA 2003

SMART Study: the higher the viral load rebound the higher the HDL-c decrease

DC Patients on ART at Baseline with HIV RNA ≤ 400 copies /mL:
HDL Decline at 1 Year According to HIV RNA Level at 1 Year



Neaton J. Personal communication

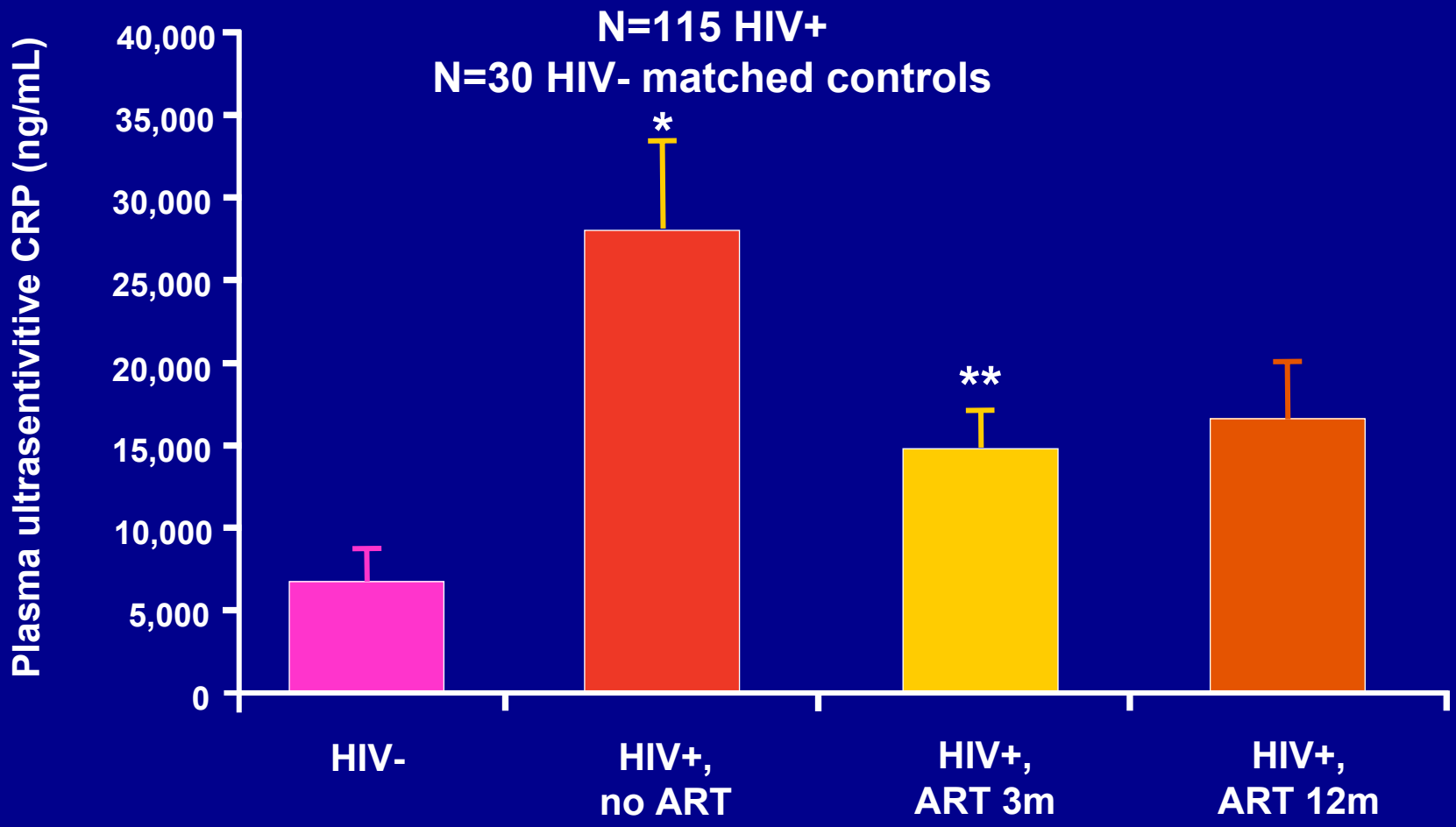
Association between inflammatory and coagulation biomarkers with mortality and CV disease

SMART Study

Biomarker	Global mortality (n=85)		CV disease (n=136)	
	OR	*P*	OR	*P*
Ultrasensitive CRP	3.5	0.004	1.6	0.20
IL-6	12.6	<0.0001	2.8	0.003
Amyloid A	2.3	0.08	1.6	0.12
Amyloid P	1.1	0.90	2.8	0.002
D-dimer	13.3	<0.0001	2.0	0.06

Kuller L et al. CROI 2008

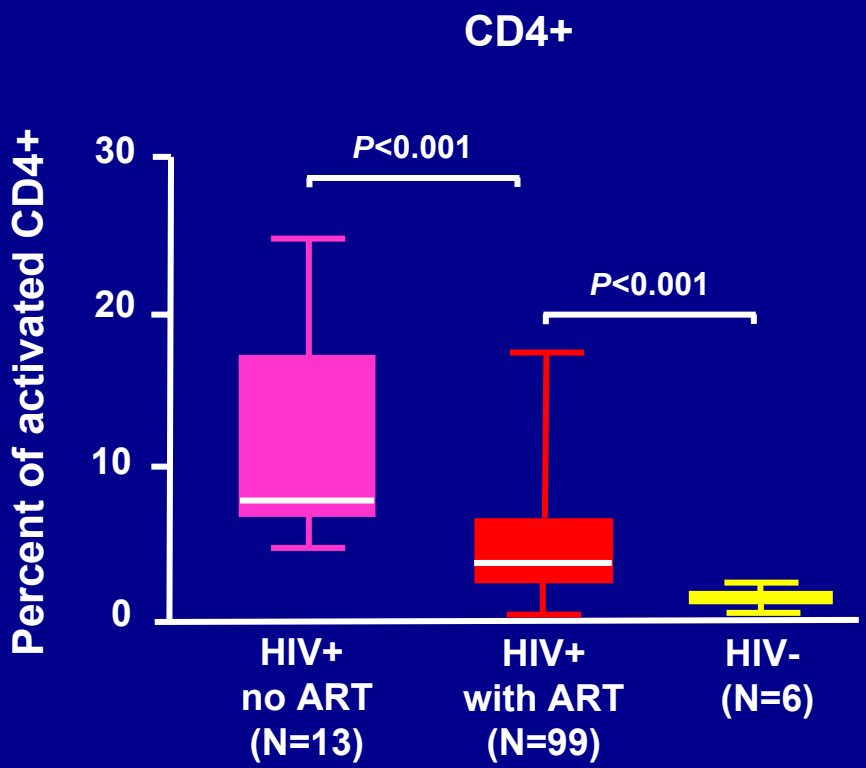
ART decreases inflammation in HIV+ persons, but still higher than HIV-

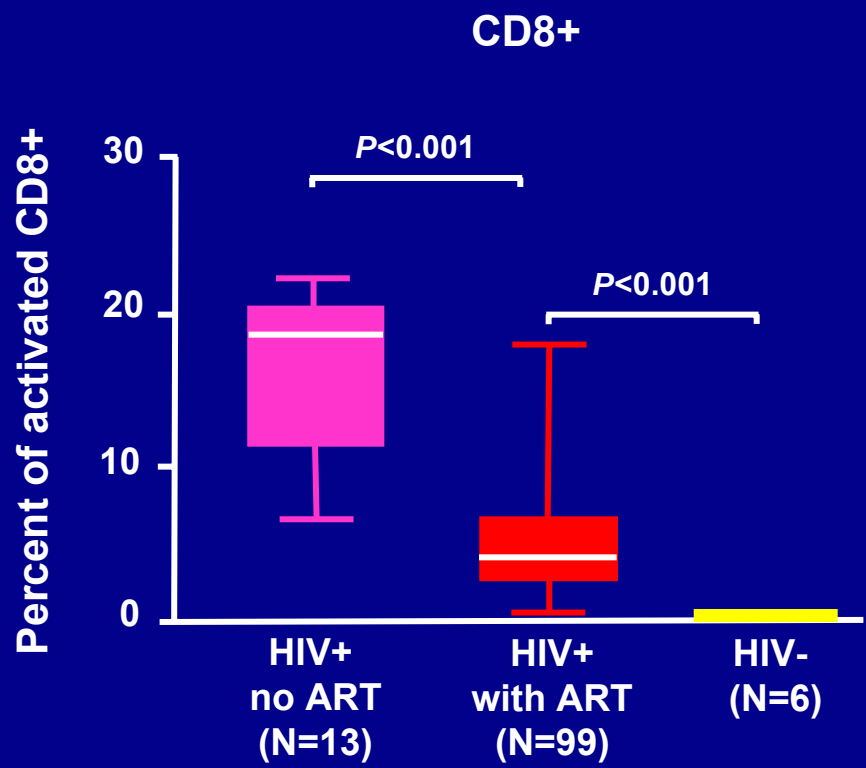


- *P*<0.001 vs VIH-
- *P*<0.001 vs VIH+, sin TAR

Kristoffersen US, et al. 15th CROI 2008

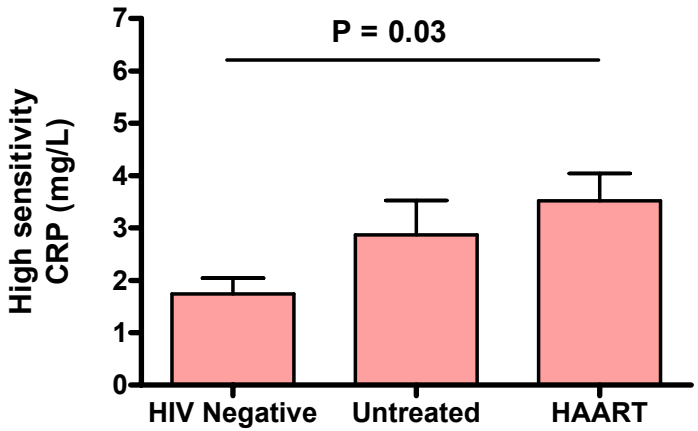
ART decreases immune activation in HIV+ persons, but still higher than HIV-

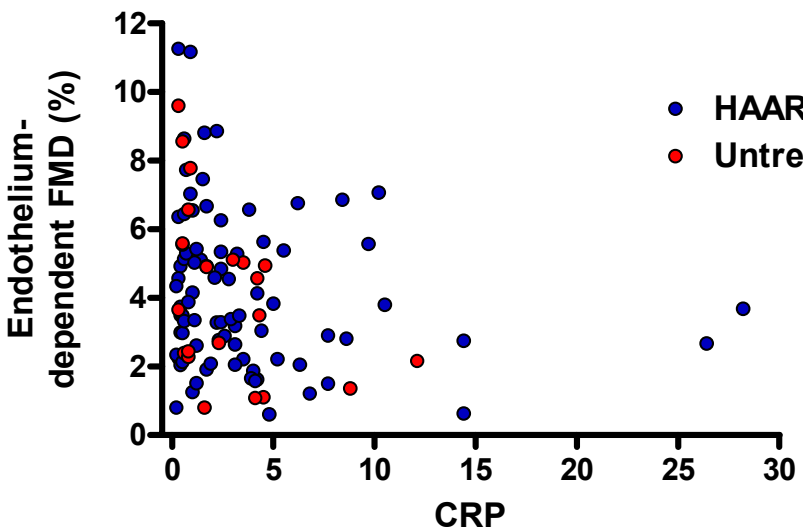


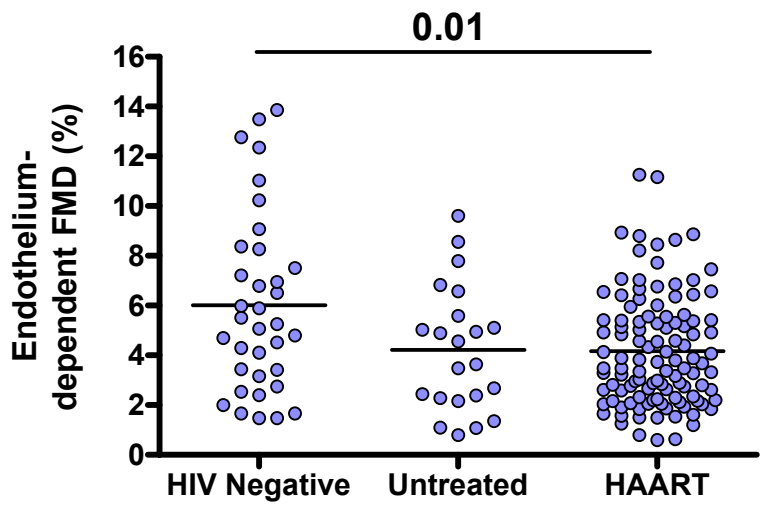


Hunt PW, et al. J Infect Dis 2003

ART decreases inflammation in HIV+ persons, but endothelial function not restored







Hsue P, et al. CROI 2010

Contribution of THERAPY

Higher risk of myocardial infarction with specific antiretrovirals?

Increase in the risk of MI by individual antiretroviral drugs and families

	DAD 2007	DAD 2008	DAD2009
PI (as a family)	16% per year (relative to NNRTI) (10% per year, after adjustment for lipids, BP, and DM)	-	-
LPV/r	-	-	13% per year
IDV	-	-	12% per year
ABC	-	90% recent exposure * 14% per year	68% recent exposure * 7% per year
ddI	-	49% recent exposure * 6% per year	41% recent exposure *

* Recent exposure means current exposure or stopped in the previous 6 months.
# No association found in a subsequent report (IAS 2009)

1. DAD NEJM 2007; 2. DAD Lancet 2008; 3. DAD CROI 2009

Despite its prospective design, some important data are missing in DAD study

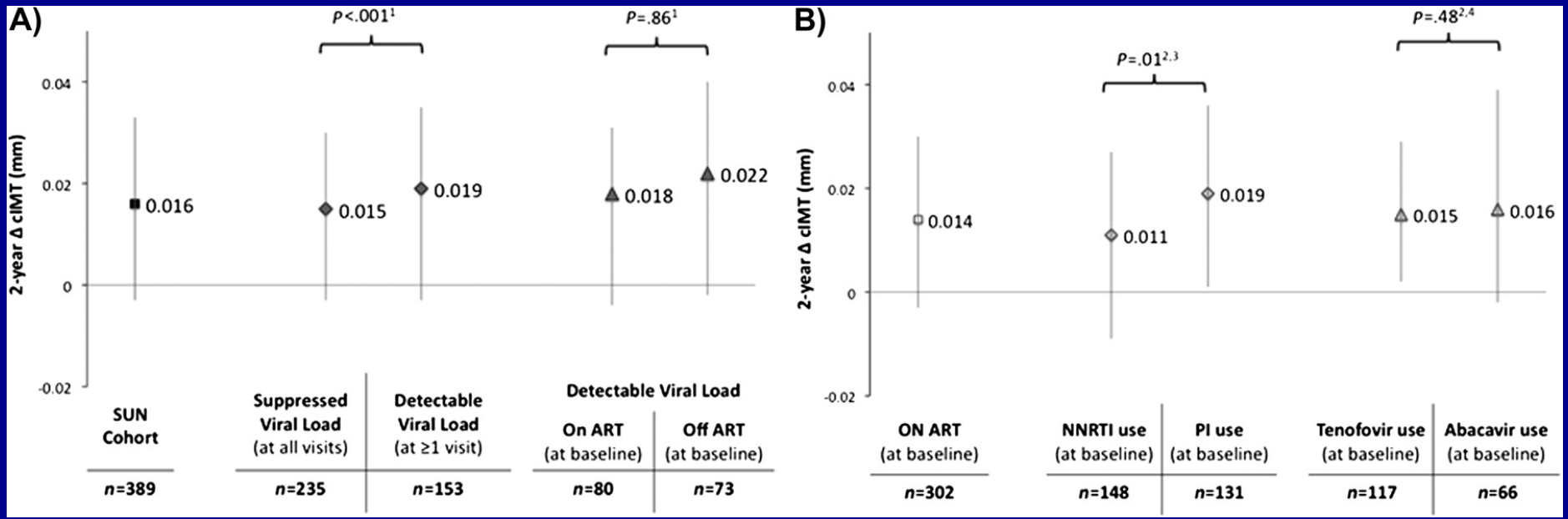
Table 1 Cardiovascular risk factors by duration of combination antiretroviral treatment (CART)*

Risk factor	Percentage patients with missing data†	Duration of CART			
		0 years ($n = 5973$)‡	<1 year ($n = 5292$)‡	1–2 years ($n = 6805$)‡	2–3 years ($n = 9050$)‡
Sex (% male)	0	69.6	74.4	75.0	76.3
Age (years) [median (IQR)§]	0	37.4 (32.8–43.0)	38.1 (33.0–44.4)	38.8 (34.0–45.0)	39.1 (34.7–45.8)
Currently smoke (% yes)	24	62.5	59.4	59.5	58.0
Previous cardiovascular disease (% yes)	0	0.8	1.2	1.2	1.3
Systolic blood pressure (mmHG) [median (IQR)]	34	120 (110–130)	120 (110–130)	120 (110–130)	120 (114–130)
Diabetes (% yes)	0	1.9	2.3	2.4	2.5
Total cholesterol (mmol/L) [median (IQR)]	11	4.6 (3.8–5.3)	4.8 (4.0–5.7)	5.1 (4.3–6.0)	5.2 (4.4–6.2)
HDL cholesterol (mmol/L) [median (IQR)]	40	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.2 (1.0–1.5)	1.1 (0.9–1.4)
Total cholesterol/ HDL ratio [median (IQR)]	40	3.9 (3.1–5.0)	4.2 (3.3–5.3)	4.3 (3.3–5.6)	4.6 (3.5–6.0)
Triglycerides (mmol/L) [median (IQR)]	11	1.3 (0.9–2.1)	1.5 (1.0–2.3)	1.6 (1.0–2.5)	1.8 (1.1–2.9)
Lipodystrophy (% reported)	0	4.6	6.1	12.5	20.6

Law M et al. HIV Med 2006

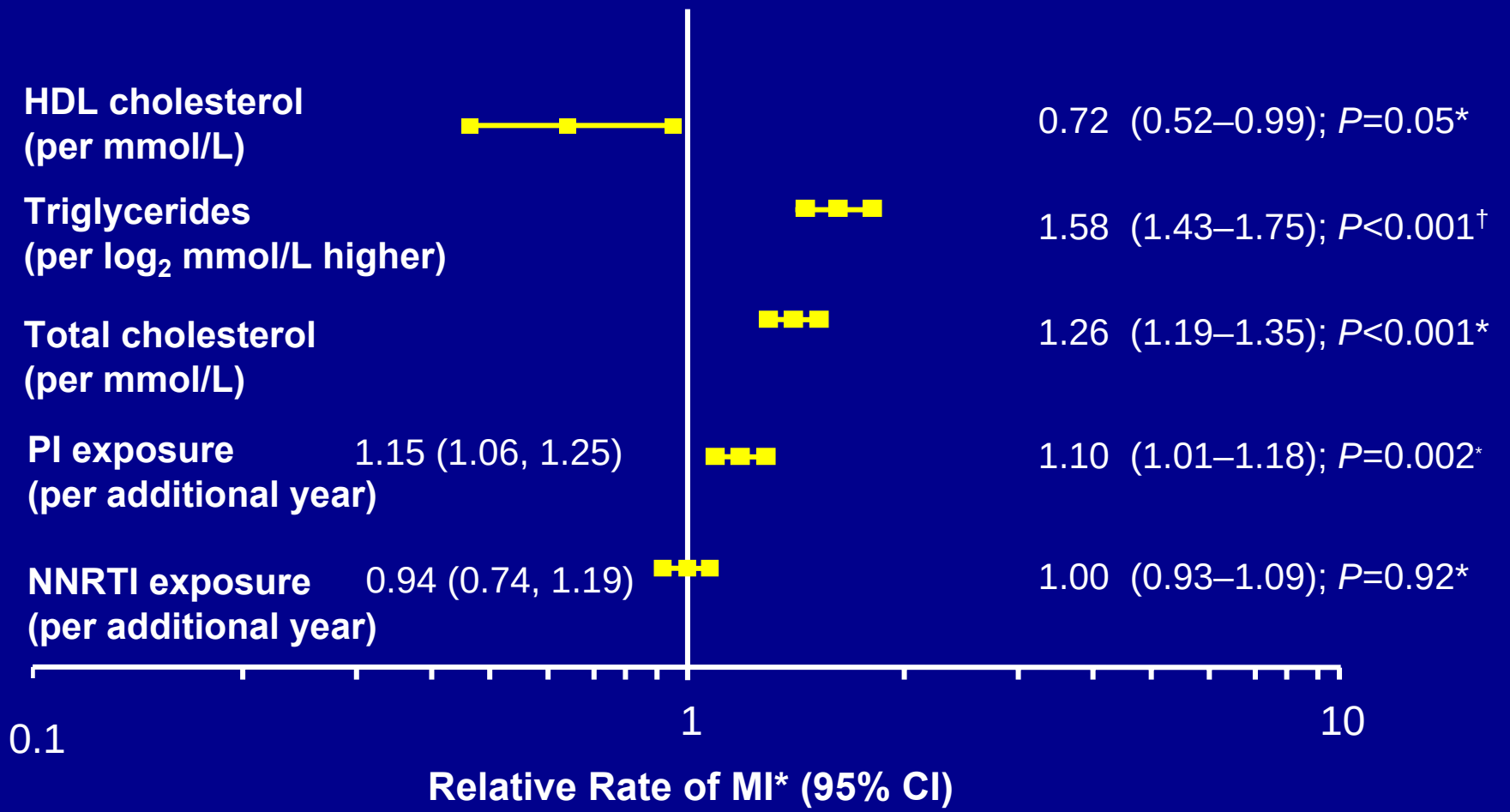
PI-based ART leads to higher ΔcIMT than NNRTI-based ART after 2 years

Two-year carotid artery intima-media thickness (CIMT) progression, human immunodeficiency virus (HIV) RNA viral load and baseline combined antiretroviral therapy (cART) use among Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study) participants (n = 389).



Baker JV et al. Clin Infect Dis 2011

Contribution of dyslipidemia to MI risk



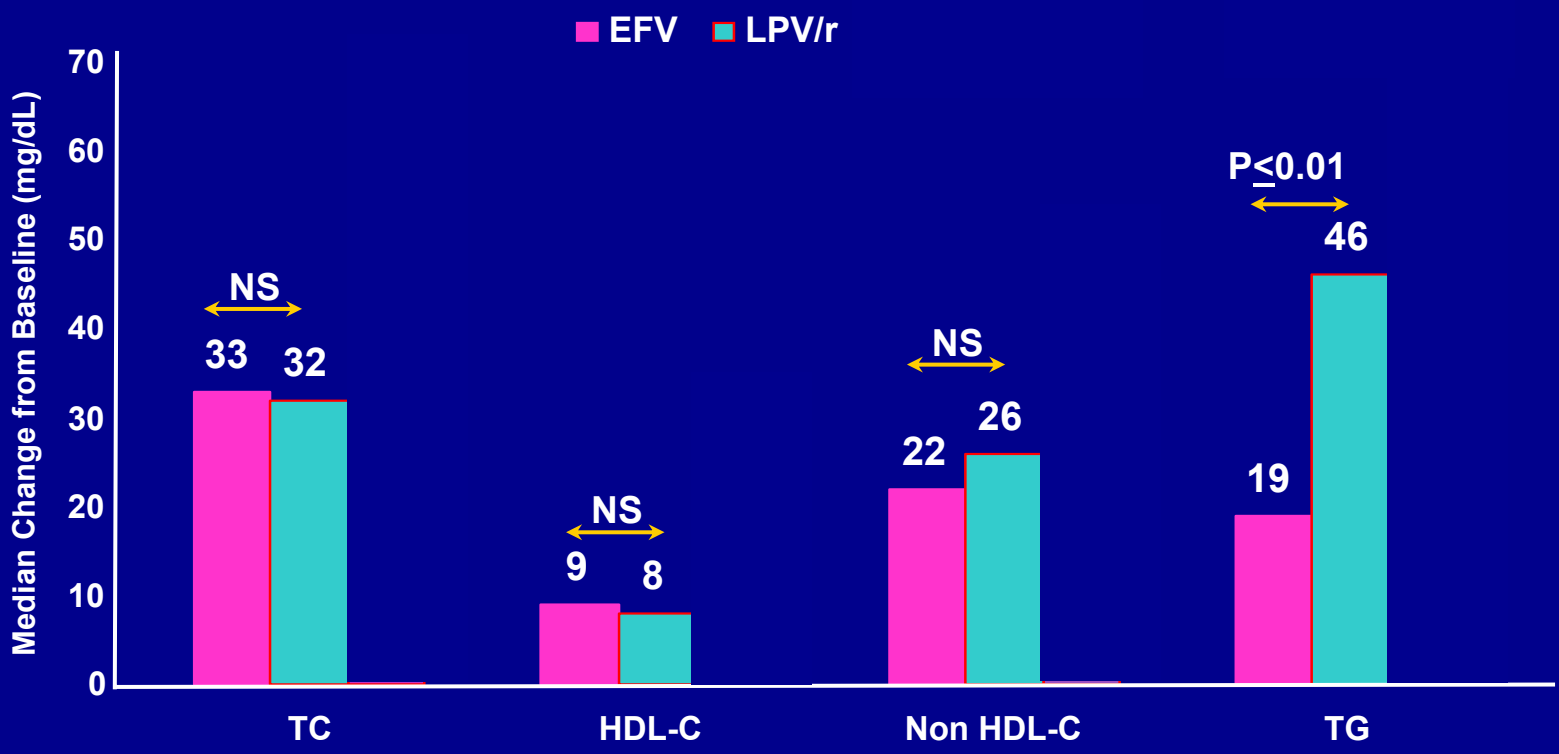
*Adjusted for conventional risk factors (sex, cohort, HIV transmission group, ethnicity, age, BMI, family history of CVD, smoking, previous CVD events, lipids, diabetes, and hypertension).

†Unadjusted model.

Friis-Møller N et al. N Engl J Med 2007

The distinctive lipid effect of PI therapy is an increase in triglycerides

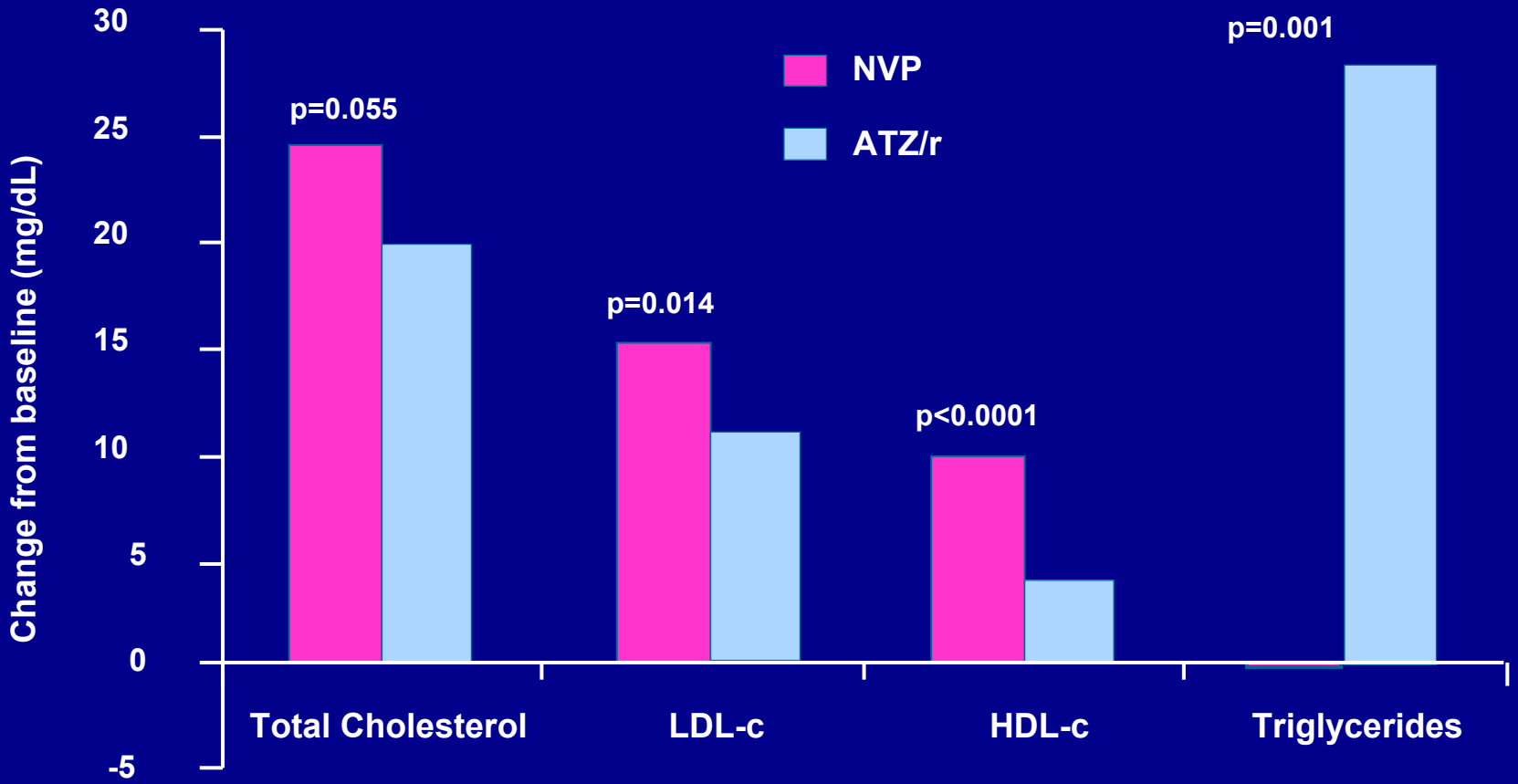
ACTG 5142 study



Haubrich R et al., 14th CROI, Los Angeles 2007, #38

The distinctive lipid effect of PI therapy is an increase in triglycerides

ARTEN study



Podzamcer et al. 11th IWADRCHIV 2009, Philadelphia, USA, poster P29

Podzamczer et al. EACS 2009, Cologne, Germany, oral presentation PS10/3

Current PIs do not induce insulin resistance in healthy volunteers

Studies on healthy adult volunteers

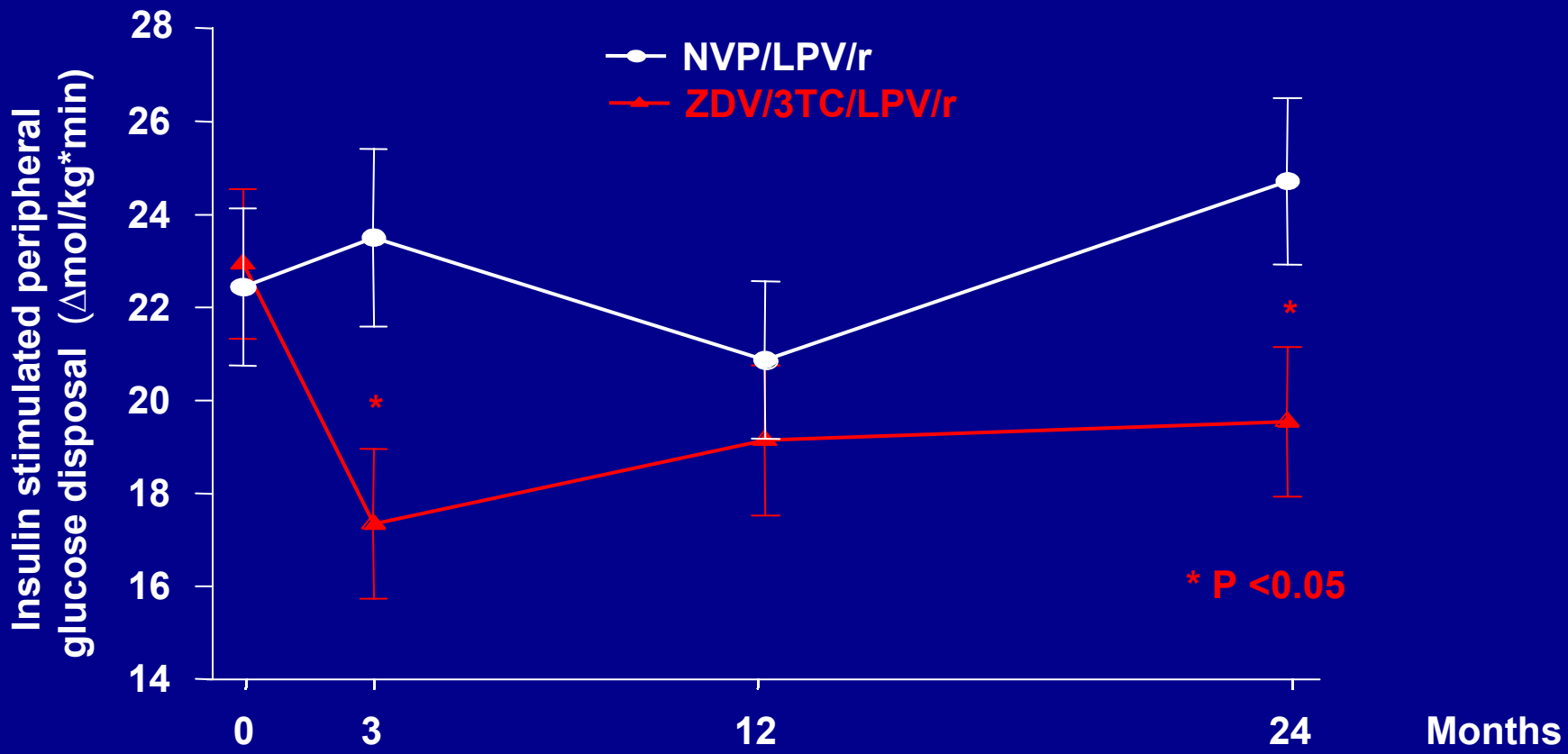
PI tested	N	Dose	HIV status	Method	Tx	Change in insulin sensitivity/ glucose disposal	P-value
IDV [1]	6	1200 mg	HIV -	Clamp	Single dose	- 34%	<0.001 *
LPV/r [2]	20	400/100 mg BID	HIV -	Clamp	5 days	- 24%	0.008 *
ATV [2]	20	400 mg QD	HIV -	Clamp	5 days	<- 1%	NS *
LPV/r [3]	25	400/100 mg BID	HIV -	Clamp	10 days	- 25%	<0.001 †
ATV/r [3]	25	300/100 mg QD	HIV -	Clamp	10 days	- 10%	NS †
LPV/r [4]	6	533/133 mg BID	HIV -	Clamp	4 weeks	- 3%	NS
ATV [5]	9	400 mg QD	HIV -	Clamp	4 weeks	- 9%	NS
LPV/r [5]	9	400/100 mg BID	HIV -	Clamp	4 weeks	- 7%	NS

*Significance relative to placebo; †significance relative to baseline.

1. Noor MA, et al. AIDS 2002; 2. Noor MA, et al. AIDS 2004; 3. Noor MA, et al. AIDS 2006; 4. Lee GA, et al. Clin Infect Dis 2006; 5. Dube M, et al. International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 2007 (Abstract 17)

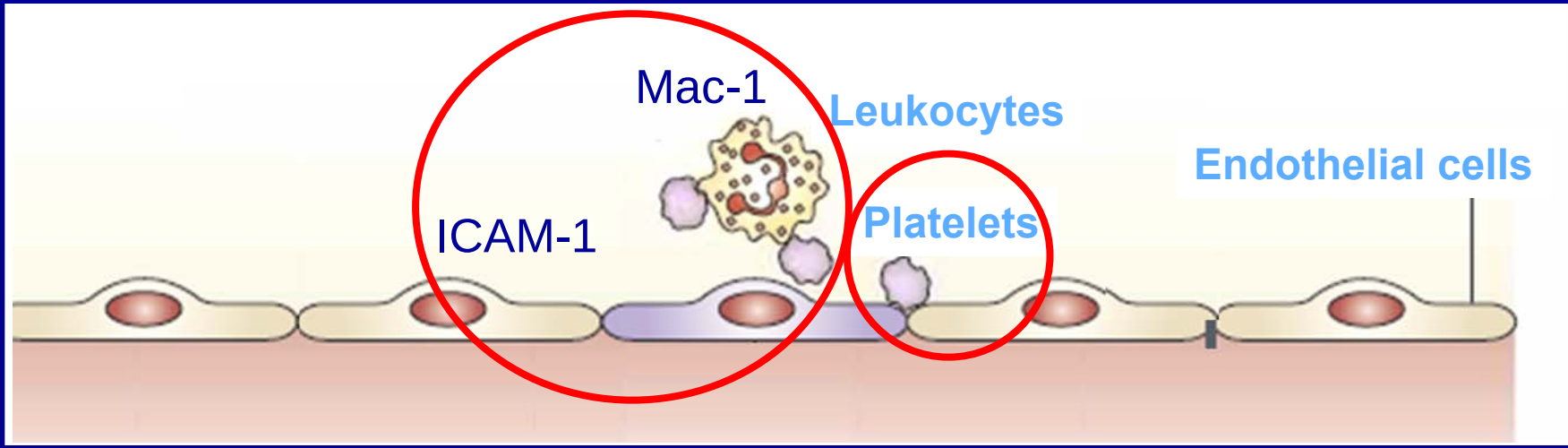
NRTI (but not PI) induce insulin resistance in HIV+ patients

MEDICLAS study



Van Vonderen M et al. 9th Intl Workshop on AE's & Lipodystrophy in HIV, Sydney 2007: abstract O-15

The association between ABC and MI remains controversial



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

The association between ABC and MI remains controversial: 2011 FDA meta-analysis

	ABC	Non-ABC	(95% CI)[1]	MH IR (95% CI)[2]
# Subjects	5028	4840		
Overall # MI events reported	**24/5028**	**22/4840**	**0.008% (-0.26%,-.27%)**	**1.02 (0.56,1.84)**
GSK	6/2341	9/2367	-0.11% (-0.43%,0.21%)	0.70 (0.25,2.00)
NIH	12/1985	9/1610	0.03% (-0.45%,0.51%)	1.06 (0.43,2.61)
Academic	6/702	4/863	0.31% (-0.53%,1.16%)	1.60 (0.46,5.62)
Stratified odds ratio sensitivity analysis excluding 8 trials with no reported MI in either treatment group similarly found no statistically significant association between MI and ABC use (OR 1.06; 95%CI 0.57-2.00)				

[1] Mantel-Haenszel Risk Difference

[2] Mantel-Haenszel Odds Ratio. This approach does not include studies with 0 events in both arms.

Ding, X et al. 18th CROI 2011. 27 Feb-2 March 2011. Abstract 808

Management

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The European AIDS Clinical Society (EACS) Guidelines are freely downloadable from www.europeanaidsclinicalsociety.org.
A declaration of potential conflict of interest of the panel members can be found at the same address.

English version

EACS
European AIDS Clinical Society

Guidelines

Version 6.0 - October 2011

Recommendations for initiation of ART in HIV-positive persons without prior ART exposure [(i)]

Recommendations are graded while taking into account both the degree of progression of HIV disease and the presence of or high risk for developing various types of (co-morbid) conditions

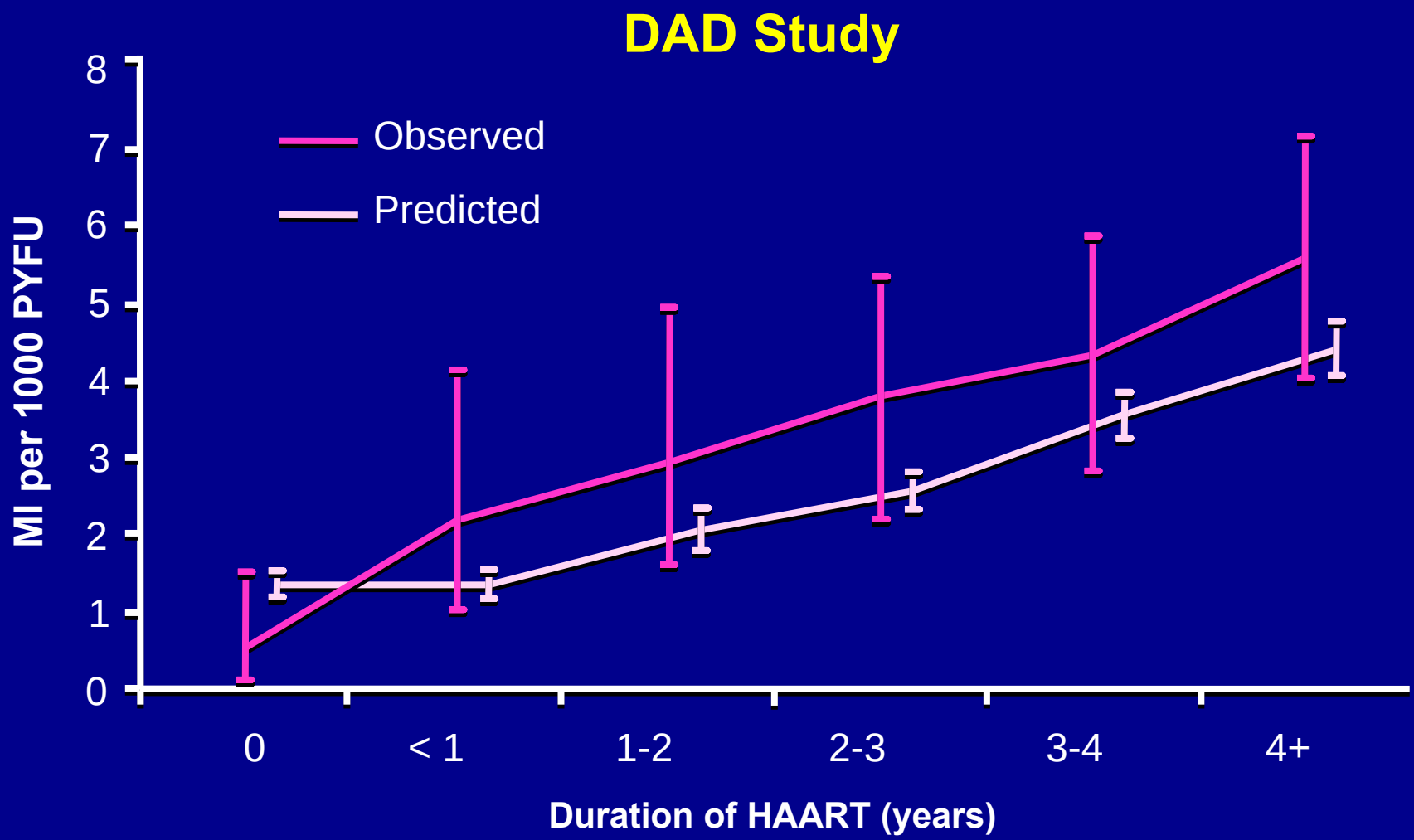
Condition	Current CD4+ lymphocyte count [(ii,iii)]	
	350-500	>500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
Autoimmune disease – otherwise unexplained	C	C
High risk for CVD (>20% estimated 10 yr risk) or history of CVD	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R [(iv)]	D
HCV for which anti-HCV treatment is being considered or given	R [(v)]	D [(vi)]
HCV for which anti-HCV treatment not feasible	R	C

http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-6.pdf

	Assessment	At HIV diagnosis	Prior to starting cART	Follow up frequency	Comment	See page
COINFECTIONS						
STIs	• Syphilis serology	+		Annual/as indicated	Consider more frequent screening if at risk	
	• STI screen	+		Annual/as indicated	Screen if at risk	
Viral Hepatitis	• Hep A serology	+			Screen at risk, vaccinate if non-immune	80
	• Hep C screen	+		Annual/as indicated	Annual Screen if ongoing risk. Measure HCV-RNA if HCV Ab+ve or if acute infection suspected. If HCV-RNA +ve	103
	• Hep B screen	+	+		Vaccinate if non-immune. Annual screen in susceptible patients. If Hep B sAg +ve	97
Tuberculosis	• CXR	+			Consider routine CXR in patients from high prevalence TB populations	
	• PPD if CD4 count >400	+		Re-screen if exposure		
	• IGRA in selected high risk populations (if available)	+				
Others	• Varicella zoster virus serology	+			Offer vaccination where indicated	80
	• Measles/Rubella serology	+			Offer vaccination where indicated	80
	• Toxoplasma serology	+				
	• CMV serology	+				
	• Leishmania serology	+/-			Screen according to travel history/origin	
	• Tropical parasites: e.g. schistosomiasis, strongyloides serology	+/-			Screen according to travel history/origin	
NON-INFECTIOUS CO-MORBIDITIES						
Haematology	• FBC	+	+	3-12 m		
	• Haemoglobinopathies	+			Screen at risk patients	
	• G6PD	+			Screen at risk patients	
Body composition	• Body-mass index	+	+	Annual		Online table: Lifestyle interventions
Cardiovascular disease	• Risk assessment (Framingham score [iii])	+	+	Annual	Should be performed in all men > 40 and women > 50 years without CVD	48
	• ECG	+	+/-		Consider baseline ECG prior to starting PIs associated with potential conduction problems	
Hypertension	• Blood pressure	+	+	Annual		50
Lipids	• TC, HDL-c, LDL-c, TG [iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	56

http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-6.pdf

Risk of myocardial infarction in HIV-infected patients can be estimated with the Framingham score



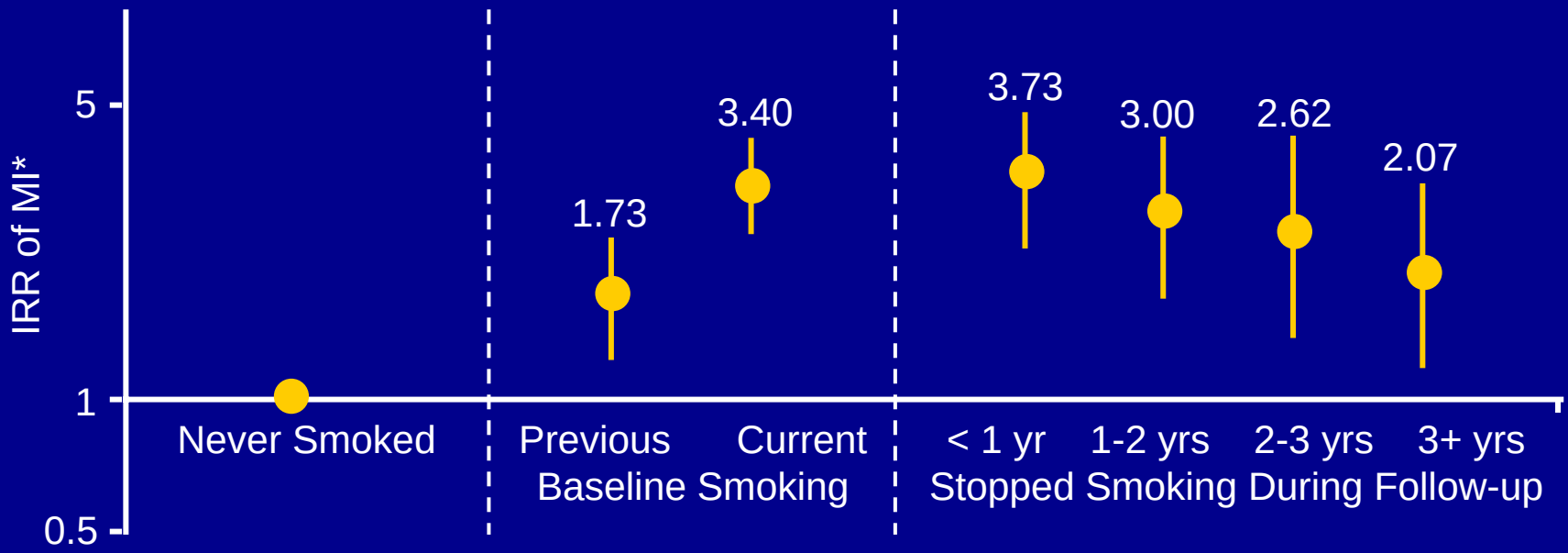
Framingham score: gender, smoking, age, systolic BP, total and HDL cholesterol

Law MG et al. HIV Med 2006; 7: 218-230

Smoking cessation decreases risk of CVD in HIV-infected patients

D:A:D Study

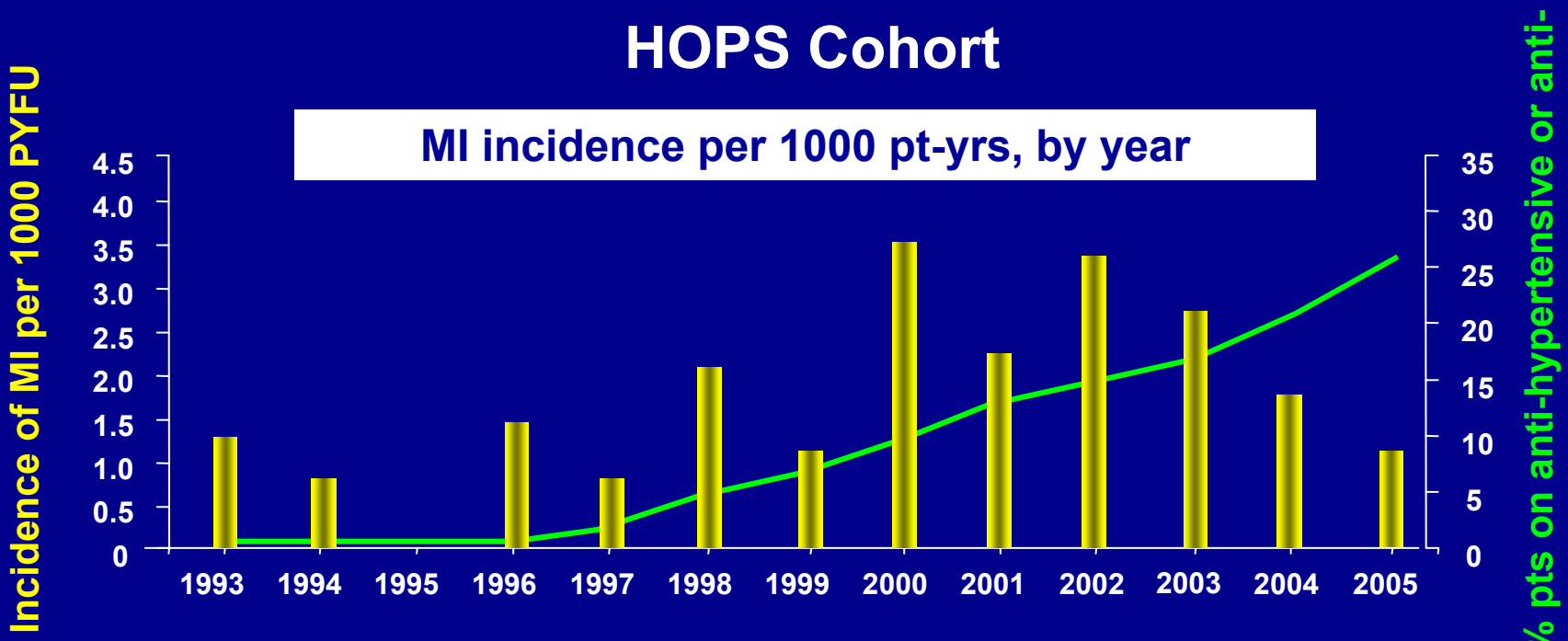
- Cessation of tobacco smoking reduced risk of MI, coronary heart disease, and CVD in HIV-infected patients
  - No association of time since smoking cessation and mortality risk



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

Petoumenos K, et al. CROI 2010. Abstract 124.

The incidence of myocardial infarction can be satisfactorily modified with intervention



Effect	HR_{adj}	95% CI	P-value
Lipid-lowering agents	0.34	0.14–0.85	0.021
Age >40 y	2.38	0.88–6.43	0.087
Diabetes	2.45	0.99–6.05	0.052
Smoking	2.22	0.98–5.05	0.057

Lichtenstein K et al. CROI 2006. Abstract 735.

Conclusions

- **Higher risk of CVD in HIV + than HIV – persons:**
  - Rationale for CVD prevention in clinical practice
- **Traditional risk factors account for a substantial portion of CV risk in HIV + persons:**
  - Rationale for early and aggressive intervention
- **Uncontrolled HIV and other concurrent co-infections further increase the risk for CV disease:**
  - Rationale for early and continuous ART and for HCV and other co-infections
- **Some antiretrovirals may increase further CV risk through lipid impact but effective ART decreases HIV-associated CV risk:**
  - From a CV perspective, much better to treat that not to treat
  - Choosing/switching ART due to CV disease concerns only justified if both CV risk estimate and plasma cholesterol are high

5th International Symposium on Neuropsychiatry and HIV

Neuropsychiatry HIV

Practical focus on the diagnosis and treatment of the neuropsychiatric and neuropsychological aspects of HIV-infected patients.

Barcelona, May 24th and 25th 2012

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Thursday May 24th 2012

09:00h-9:15h.	Opening
09:15h-10:15h.	**Anxiety Disorders**. Milton Wainberg
10:15h-11:15h.	**Drug-drug Interactions** (to be announced)
11:15h-11:45h.	Coffee Break
11:45h-12:15h.	**Oral Communications session**
12:45h-13:45h.	**Clinical Guidelines: Cognitive Impairment**. Paola Cinque
13:45h-15:00h.	Lunch time
15:00h-16:00h.	**Update on ARV Therapy and Neurocognitive impairment.** Prof. Scott Letendre
16:00h-17:00h.	**Clinical Case study session**

Friday May 25th 2012

09:00h-10:00h.	**Non HIV associated neurocognitive disorder** (to be announced)
10:00h-11:00h.	**Sexual Dysfunction** (to be announced)
11:00h-11:30h.	Coffee Break
11:30h-13:00h.	**Workshops**
	Workshop 1: **Neuropsychological Assessment.** José A. Muñoz Moreno
	Workshop 2: **Psychotherapy** (to be announced)
13:00h-13.30h.	Closing

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AIDS Spanish National Plan

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