6th Infectivology Today®

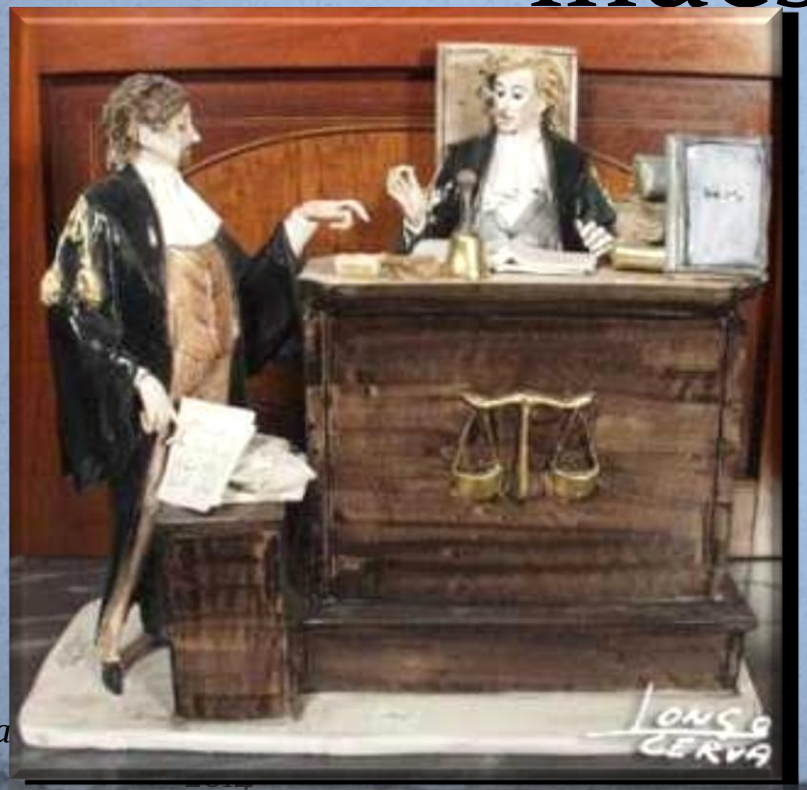
Evitare i Pis nelle terapie di prima linea per gli effetti indesiderati?

Paolo Maggi

Clinica delle Malattie Infettive
Università degli Studi di Bari

Paestum (Sa) 15- 16 -17 maggio 2014

Evitare i Pis nelle terapie di prima linea per gli effetti indesiderati?



No, signori della corte!

frequent/severe side effects[i] - 2/2

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genitourinary	Nervous	Body fat	Metabolic	Other
PI										
IDV	**Dry skin** Nail dystrophy	Nausea and diarrhoea[ii]	Jaundice	**IHD**		**Nephrolithiasis**		**↑abdominal fat**	**Dyslipidaemia** Diabetes mellitus	
SQV									Dyslipidaemia	
LPV				**IHD**					**Dyslipidaemia**	
FPV	Rash			**IHD**					**Dyslipidaemia**	
ATV			Jaundice			Nephrolithiasis			Dyslipidaemia	
DRV									Dyslipidaemia	
TPV			**Hepatitis**				**Intracranial haemorrhage**		**Dyslipidaemia**	
Fusion inhibitors										
ENF	**Injection site reactions**									Hypersensitivity, ↑risk for pneumonia
Integrase inhibitors										
RAL		Nausea			Myopathy		Headache			
CCR5 inhibitors										
MVC			Hepatitis	**IHD**						↑risk for infections

Early Case Reports in 1998

Author	Age	Sex	Event	PI	CVRF	CT (mg/dL)	TG (mg/dL)
Henry[1]	26	M	Angina RCA thrombosis	RTV + SQV	Smoking		
Henry[1]	37	M	Angina LAD occlusion	SQV	Diabetes	480	1945
Behrens[1]	60	M	Anterior MI	SQV	Smoking	285	–
Behrens[1]	58	M	Femoral occlusion	IDV	–	285	273
Gallet[1]	33	M	Inferior MI RCA occlusion	RTV then NFV	Smoking	308	695
Gallet[1]	32	M	Anterior MI LAD stenosis	IDV	Smoking	176	114
Gallet[1]	54	M	Angina	RTV + SQV	–	636	1962
Vittecoq[1]	36	M	Anterior MI	IDV	Smoking	–	361
Vittecoq[1]	40	M	Transient Ischemic attacks	IDV	Smoking	281	695
Vittecoq[1]	47	M	Anterior MI	IDV	Heredity	296	–
Jütte[2]	50	M	MI	IDV	Smoking	263	640
Jütte[2]	40	M	MI RCA&Cx occlusion	NFV	Smoking Heredity	294	199
Jütte[2]	35	M	MI RCA occlusion	RTV	Smoking Heredity	301	548

[1]*Lancet* 1998;351.
[2]Jütte. *AIDS* 1999;13:1796.

LAD, Left Anterior Descending. Cx, Circumflex. RCA, Right Coronary Artery. MI, Myocardial Infarction

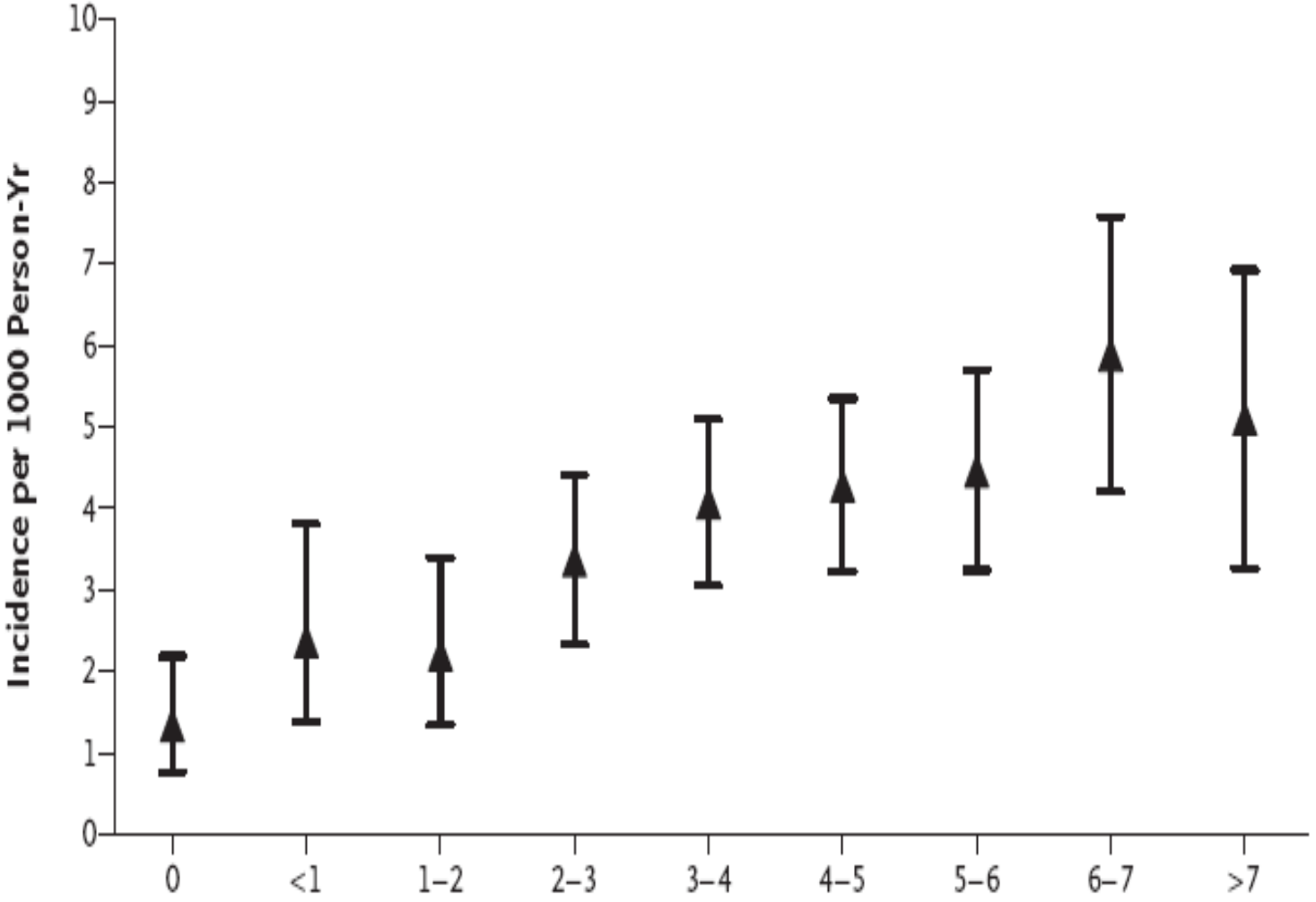
Protease inhibitors:

The smoking gun ?

Studi prospettici:
Data Collection on Adverse events of Anti-HIV Drugs

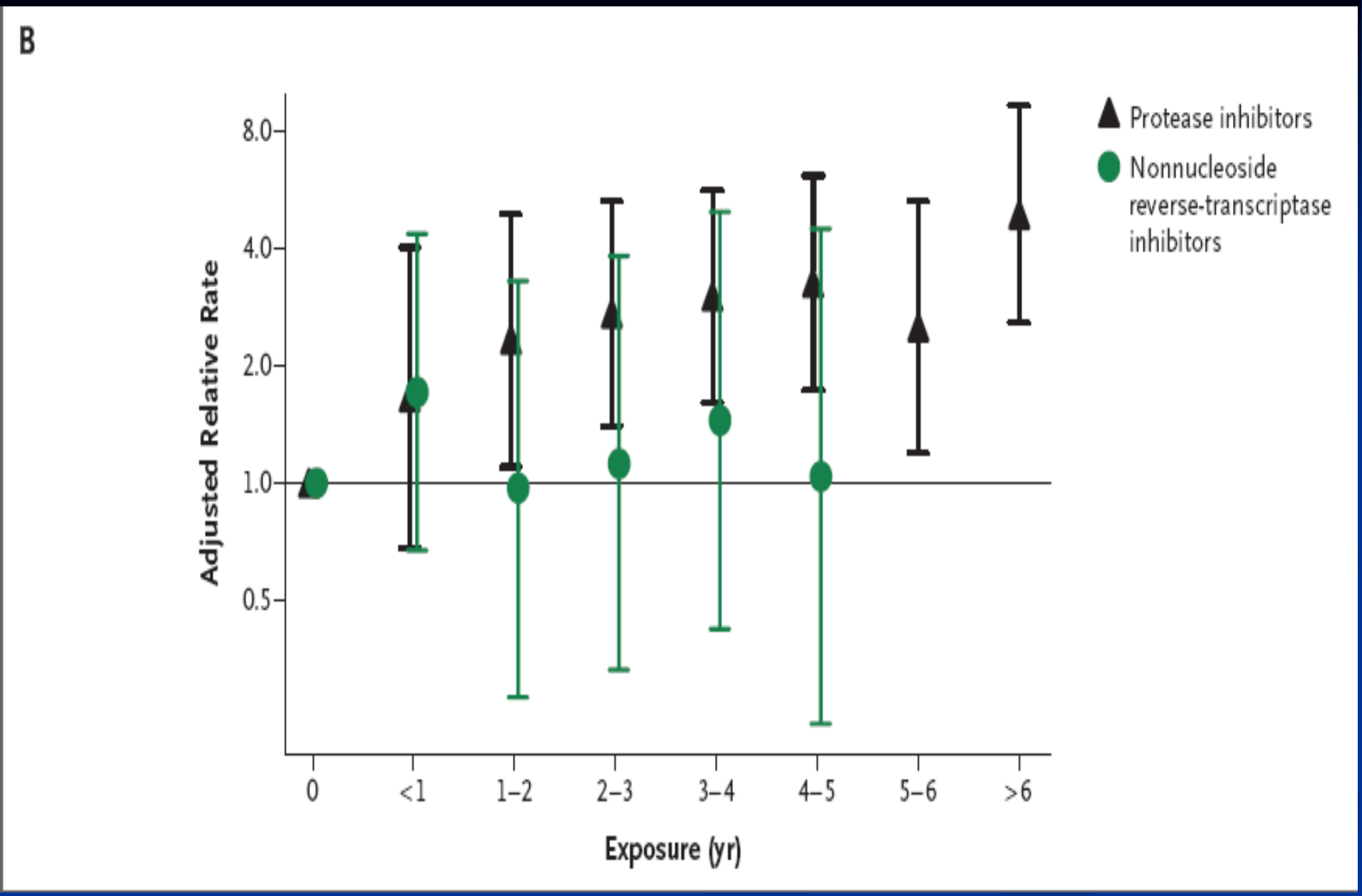
DAD Study

- Prospective multinational cohort study initiated in 1999 (Europe, USA, Australia)
- 11 cohorts; 188 clinics; 21 countries
- 23468 patients
- 36145 person years of follow up



	0	<1	1–2	2–3	3–4	4–5	5–6	6–7	>7	Total
No. of Events	16	17	20	41	61	62	51	47	30	345
No. of Person-Yr	11,815	7105	9027	12,098	14,892	14,394	11,351	7935	5853	94,469

The DAD study group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; 356: 1723-1735.



The DAD study group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; 356: 1723-1735.

AIDS 2004, 18:1023-1028

Maggi P, Lillo A, Perilli F, Maserati R, Chirianni A

on behalf of the PREVALEAT group.

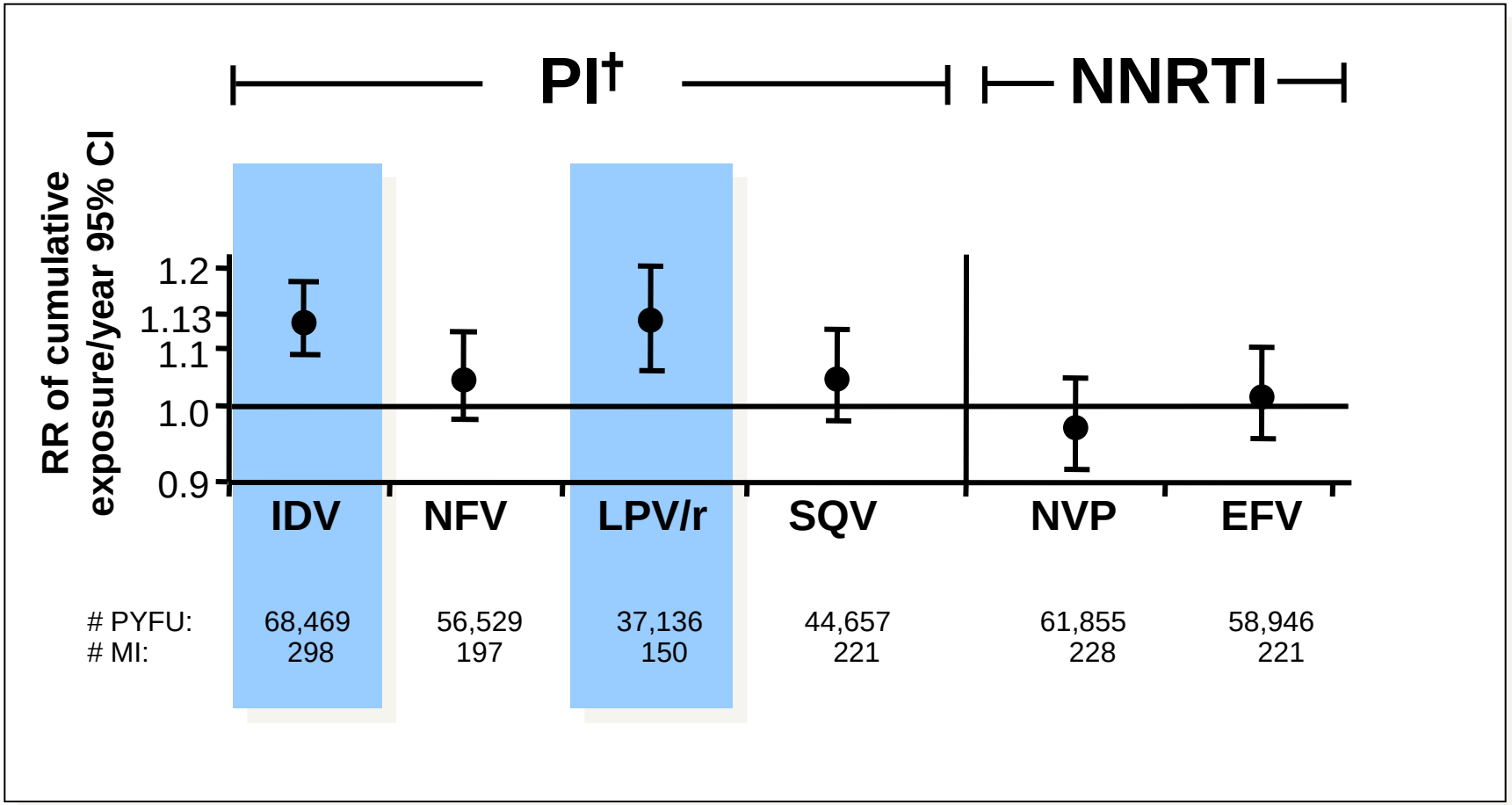
Colour-doppler ultrasonography of carotid vessels in patients treated with antiretroviral therapy: a comparative study

Results /2

Comparison of ultrasonographic findings

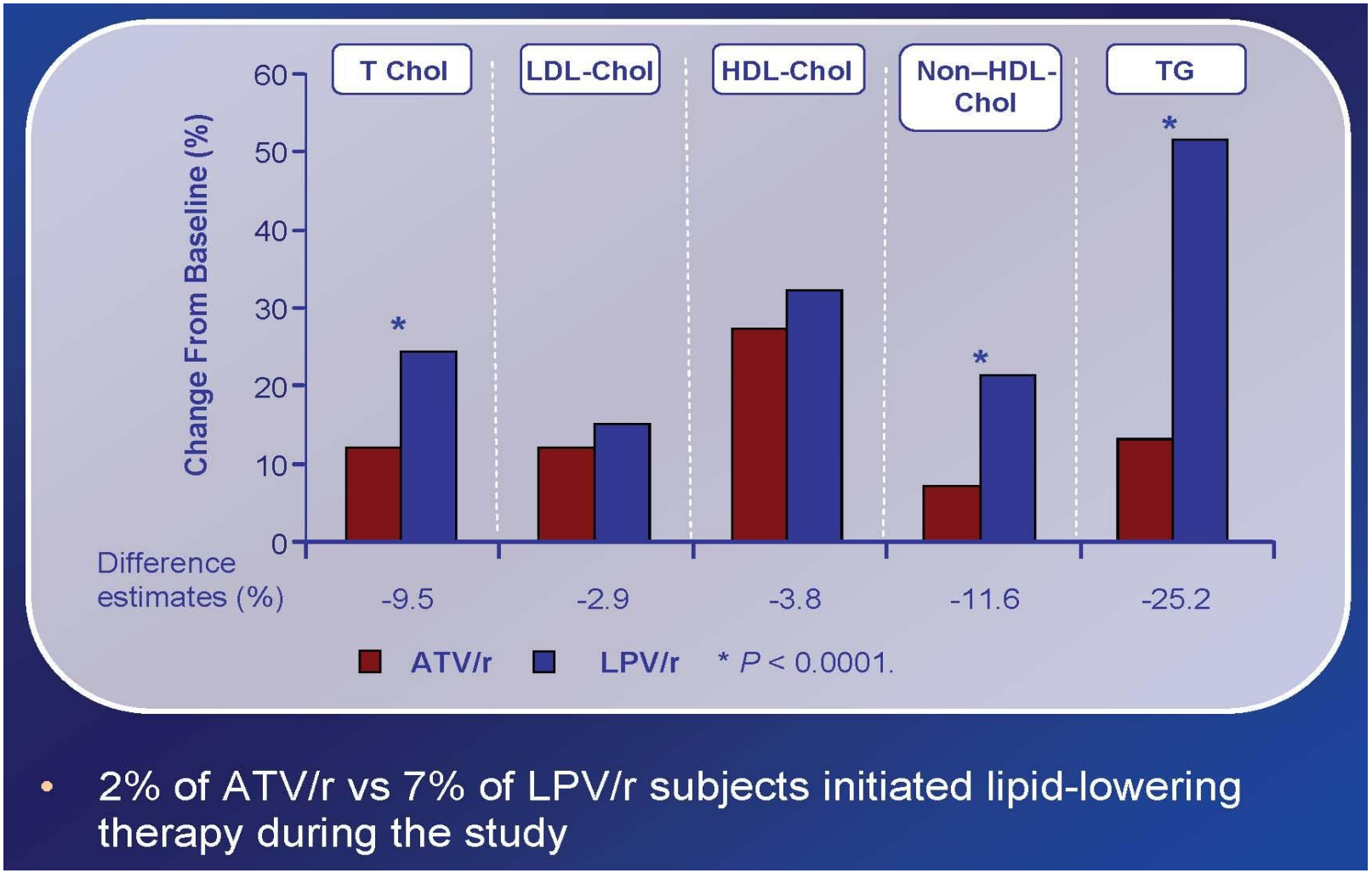
	PI	NNRTI	2NRTI/Naïve
	105	**125**	**63**
Acquired lesions	55 **(52.4 %)**	19 **(15.2 %)**	9 **(14.3 %)**
IMT	25	10	3
IMT+*plaques*	24	6	4
plaques	6	3	2
Total plaques	30 (28.5 %)	9 (7.2%)	6 (9.5%)
Normal findings	50 (47.6%)	106 (84.8 %)	54 (85.7 %)
Median IMT value (mm)			
right carotids	1.2 (1.01-2.47)	1.31 (1.01-2.33)	1.2 4 (1.02-1.4)
left carotids	1.3 (1.01-3.0)	1.36 (1.01-2.08)	1.4 (1.1-3.5)
Percentage of stenosis			
right carotids	42.9% (15-54)	35% (25-66)	30% (20-40)
left carotids	41.9% (15-70)	38% (25-52)	46.7 (one patient)

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

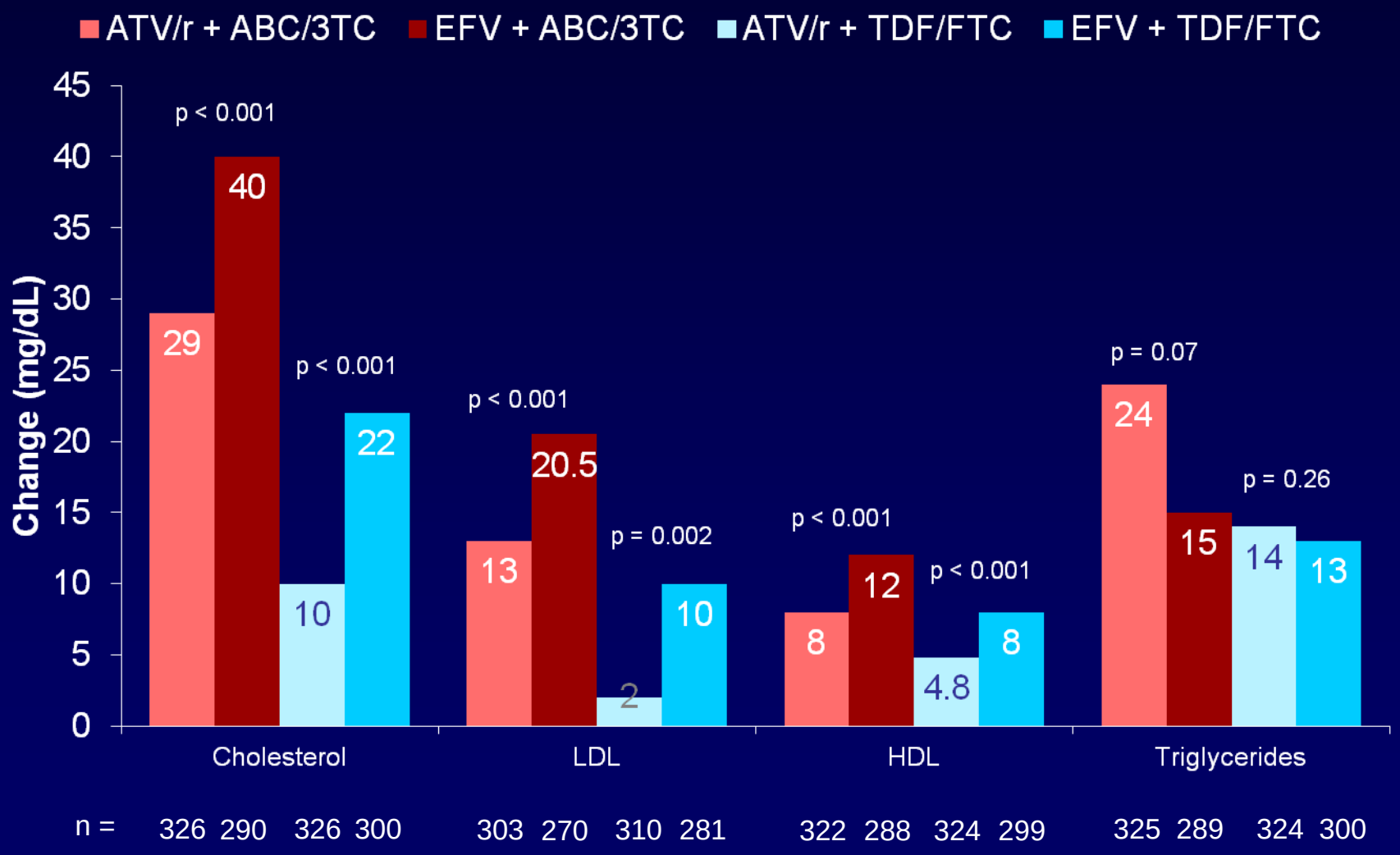
CASTLE:
Change in fasting lipids over 48 weeks



- 2% of ATV/r vs 7% of LPV/r subjects initiated lipid-lowering therapy during the study

Molina J-M et al. Lancet 2008; 372:646-55

ACTG 5202: median change in fasting lipids (mg/dL) in overall population at 48 weeks



Daar et al. CROI 2010, pres. 59LB.

Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events

(D:A:D Study)

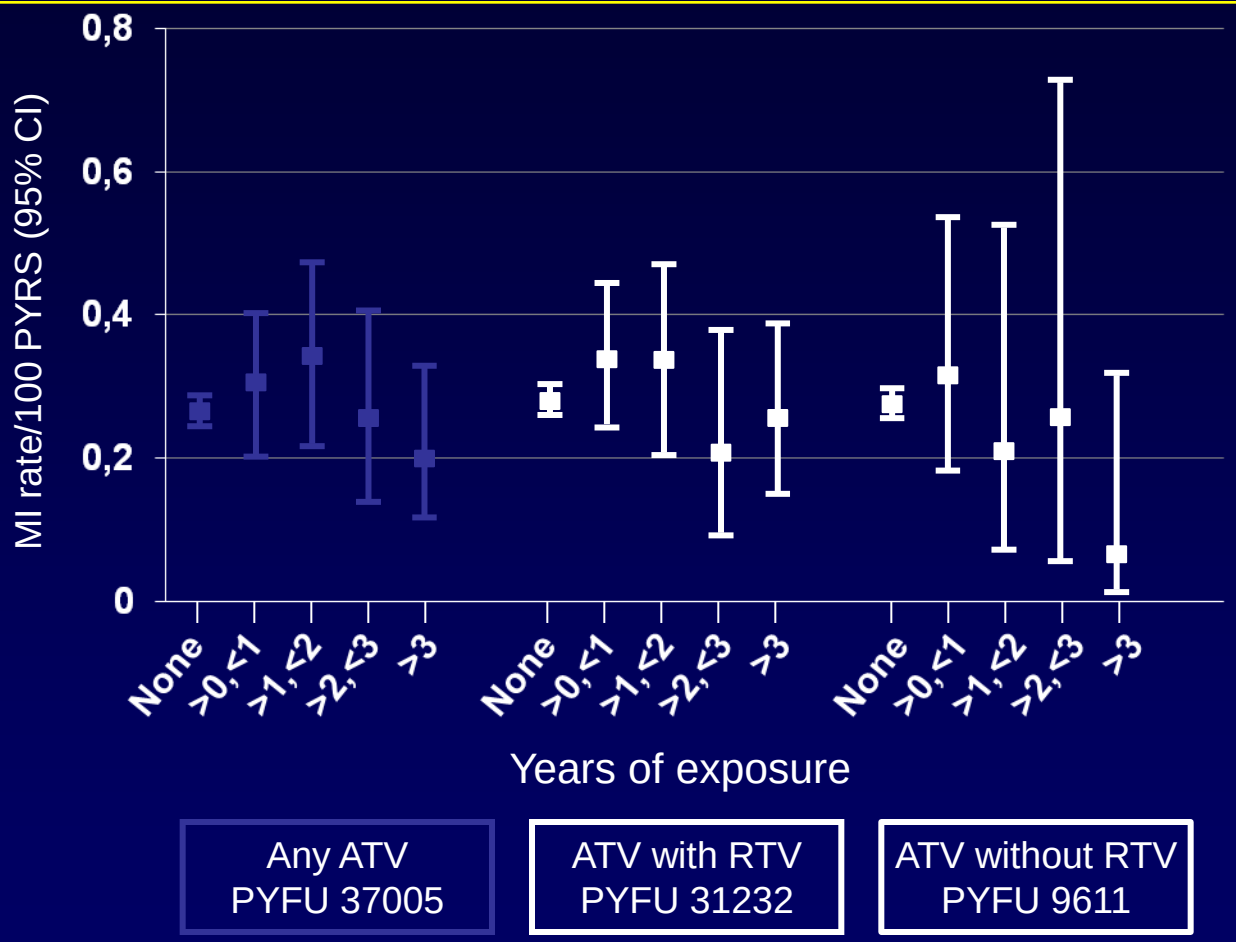
Table 2. Rates of MI and stroke according to the cumulative duration of exposure (years) to atazanavir (ATV), ATV boosted with ritonavir (ATV-RT) and ATV unboosted.

	Events	PYFU[a]	Rate (/100 PYFU)	95% CI
Myocardial infarction				
Any ATV (years)				
None	740	264901	0.279	0.259, 0.299
>0, ≤1	41	13323	0.308	0.214, 0.402
>1, ≤2	29	8307	0.349	0.222, 0.476
>2, ≤3	15	5974	0.251	0.141, 0.414
>3	19	9401	0.202	0.122, 0.316
ATV-RT (years)				
None	751	270676	0.277	0.258, 0.297
>0, ≤1	41	12039	0.341	0.236, 0.445
>1, ≤2	24	7110	0.338	0.203, 0.473
>2, ≤3	10	4863	0.206	0.099, 0.378
>3	18	7220	0.249	0.148, 0.394
ATV unboosted (years)				
None	821	292295	0.281	0.262, 0.300
>0, ≤1	15	4686	0.320	0.179, 0.528
>1, ≤2	4	1967	0.203	0.055, 0.521
>2, ≤3	3	1227	0.244	0.050, 0.715
>3	1	1731	0.058	0.001, 0.322

(d'Arminio Monforte A et al., AIDS 2013)

D:A:D: MI rate

stratified by cumulative exposure to any ATV, ATV with ritonavir, and ATV without ritonavir



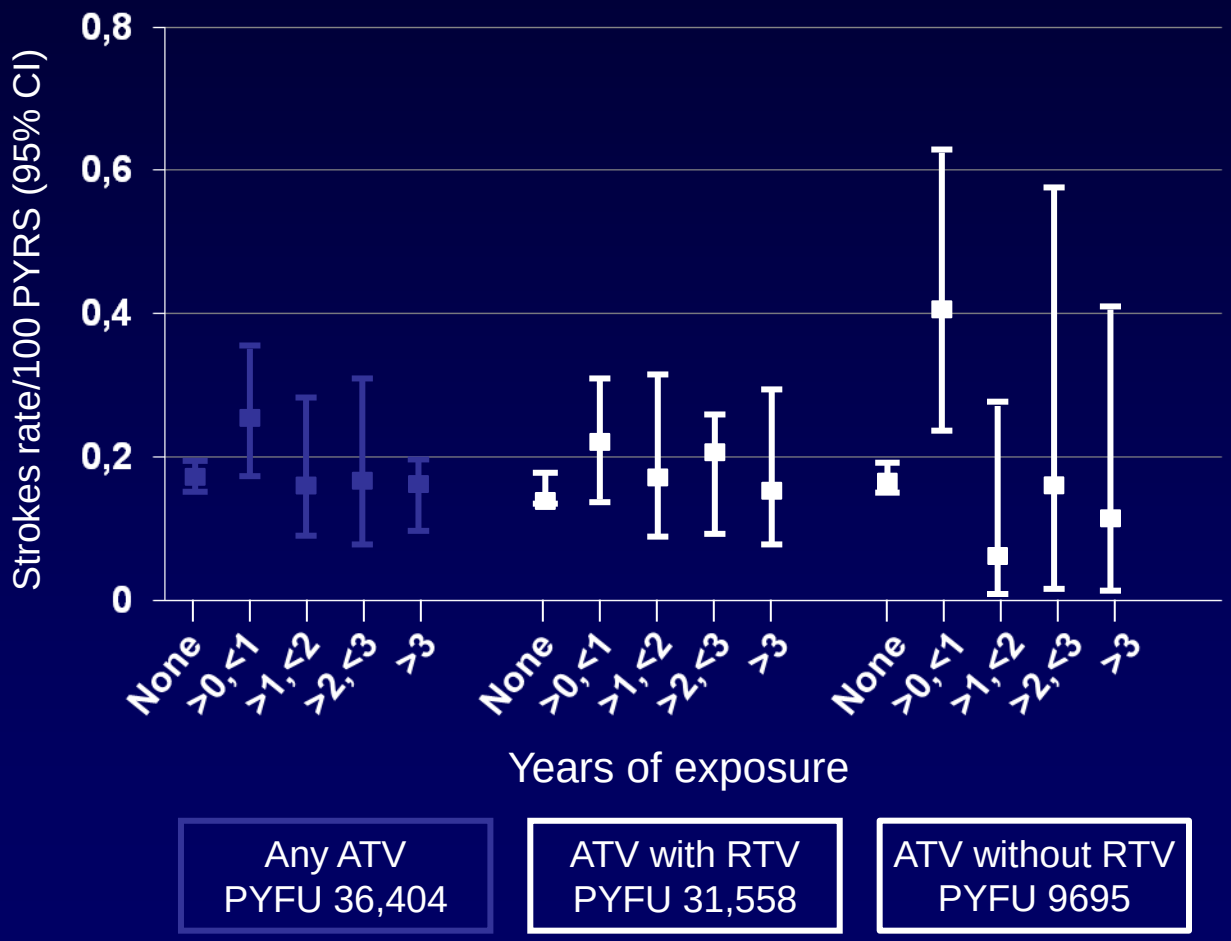
- The rate of MI varied from 2.80 (95% CI: 2.6, 23.0)/1000 PYFU in those with no exposure to ATV to 2.0 (1.2, 3.2)/1000 PYFU in those with >3 years exposure

Monforte et al. CROI 2012, poster 823.

PYFU, person-years of follow-up

D:A:D: strokes rate

stratified by cumulative exposure to any ATV, ATV/r, and ATV without ritonavir



- The rate of stroke was
  - 1.7 (95% CI: 1.6, 1.9)/1000 PYFU in those with no exposure to ATV
  - 1.7 (1.0, 2.7)/1000 PYFU in those with >3 years exposure
- Longer exposure to ATV was not associated with an increased risk of MI or stroke either in univariate or in multivariate analyses

Monforte et al. CROI 2012, poster 823.

PYFU, person-years of follow-up

New approaches?

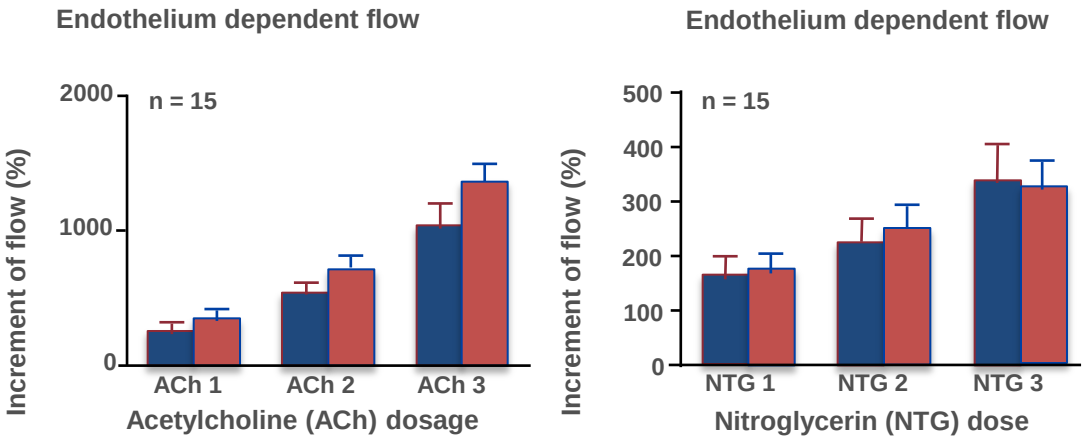
Heme oxygenase–carbon monoxide signalling pathway in atherosclerosis: anti-atherogenic actions of bilirubin and carbon monoxide?

Richard C.M. Siow, Hideyo Sato[1], Giovanni E. Mann*

Vascular Biology Research Centre, School of Biomedical Sciences, King's College London, Campden Hill Road, London W8 7AH, UK

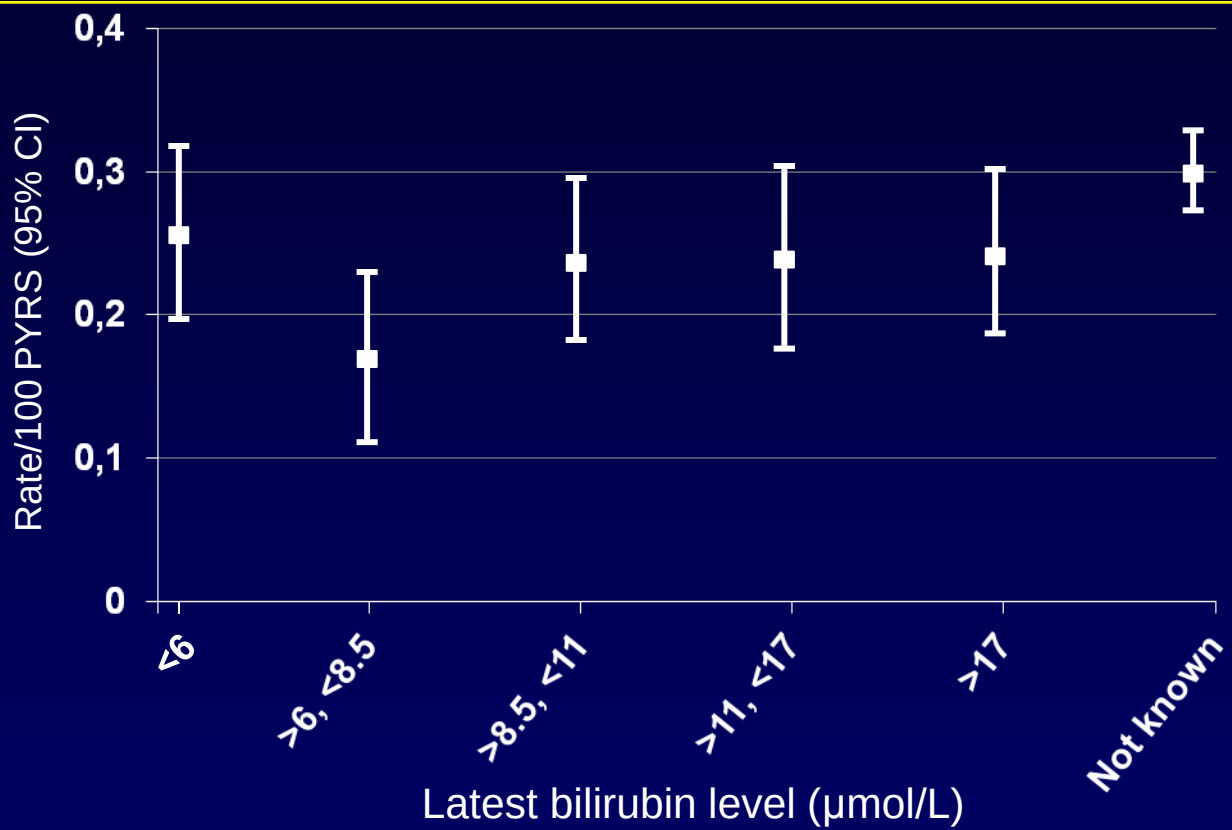
Siow C.M. et al., Cardiovascular Research 1999; 41:385-394

The bilirubin-increasing drug ATV improves endothelial function in patients with Type 2 Diabetes Mellitus (T2DM)



Dekker D et al.Arterioscler Thromb Vasc Biol 2011; 31:458–463

D:A:D: MI event rate stratified by latest bilirubin level

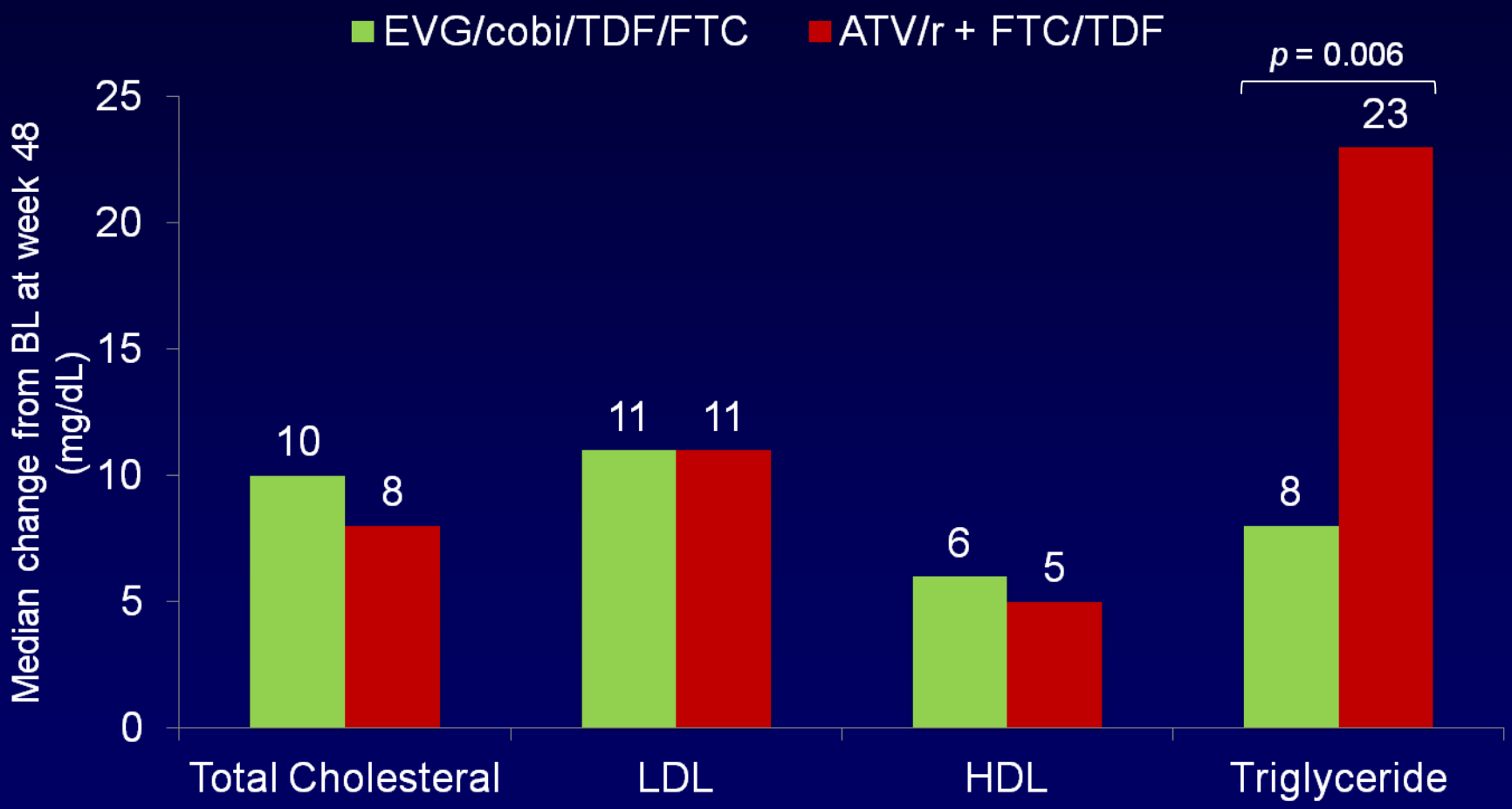


- Further adjustment for the latest bilirubin level, in the subgroup of cohorts that provide these data, had no impact on the size of the association with either MI or stroke

Monforte et al. CROI 2012, poster 823.

PYFU, person-years of follow-up

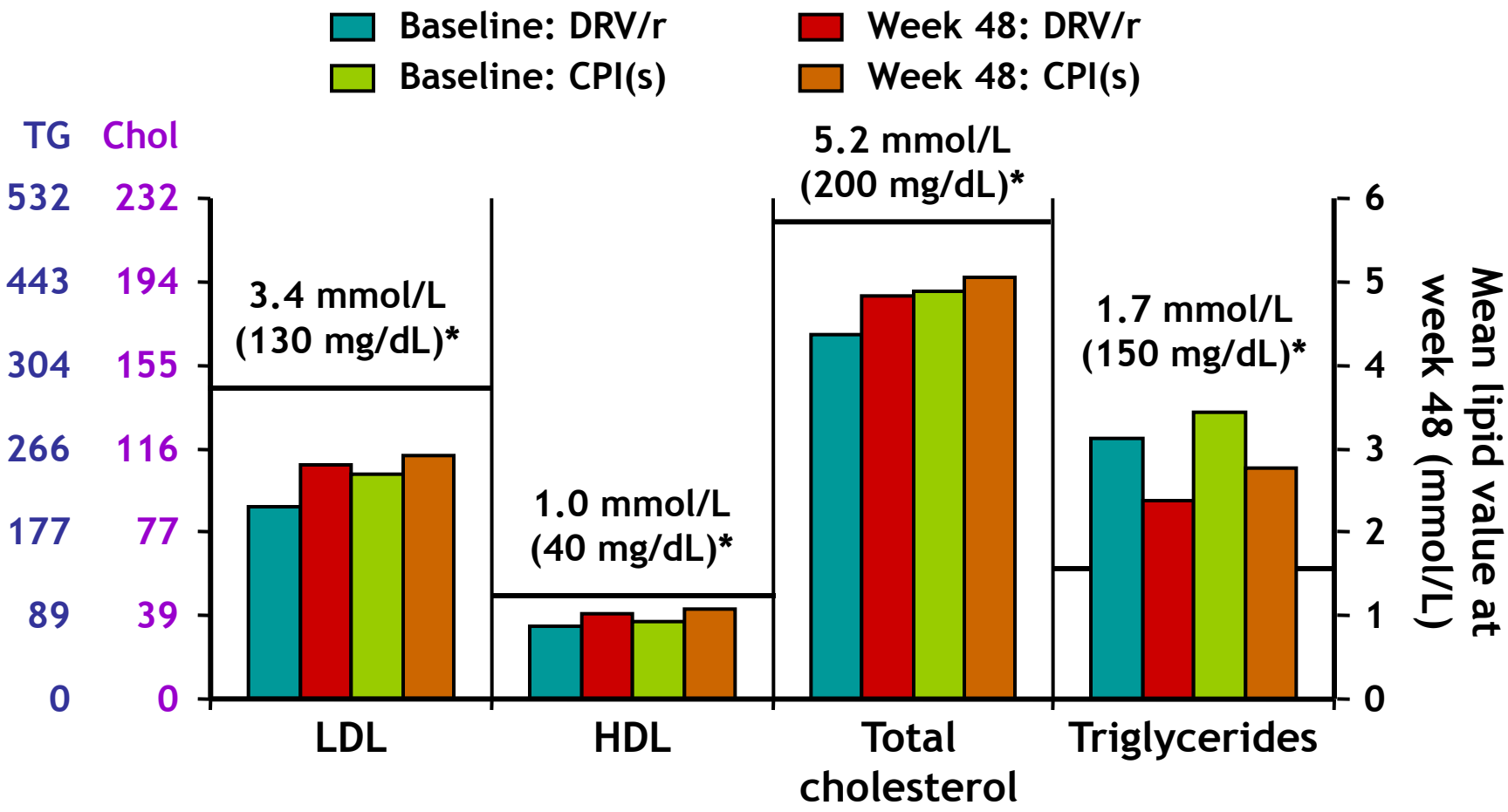
Study 103: change from baseline in fasting lipids at week 48



DeJesus et al. CROI 2012, poster 627.

EVG/cobi/TDF/FTC fixed dose combination is an investigational compound, currently not approved for HIV treatment

POWER 1&2 (DRV/r reg.): Lipid levels at week 48

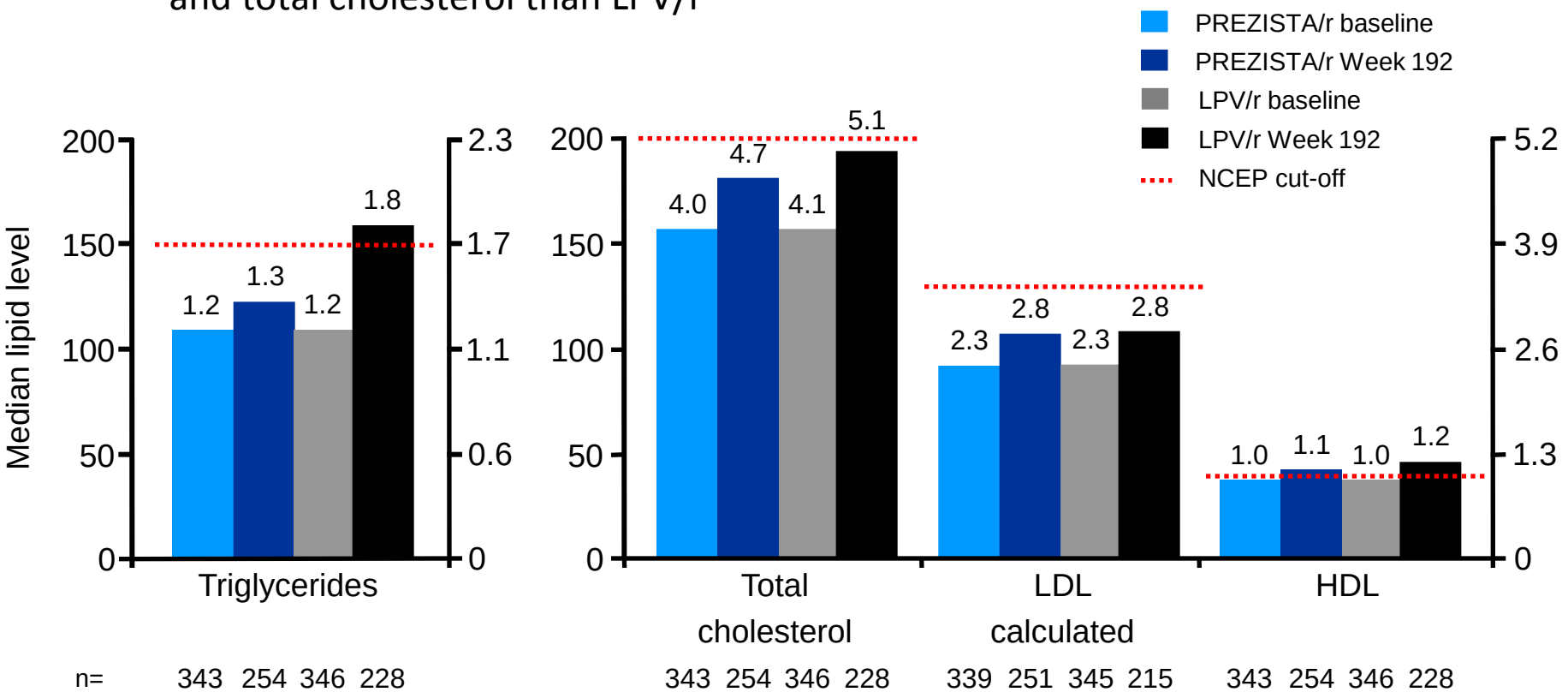


*Normal lipid levels taken from the NCEP

Clotet et al. Lancet 2007; 369:1169-78

ARTEMIS:
Median lipid levels at baseline and Week 192

- PREZISTA/r was associated with smaller median increases in triglycerides and total cholesterol than LPV/r



Left axis mg/dL; right axis mmol/L

NCEP = National Cholesterol Education Program; LDL = low-density lipoprotein; HDL = high-density lipoprotein

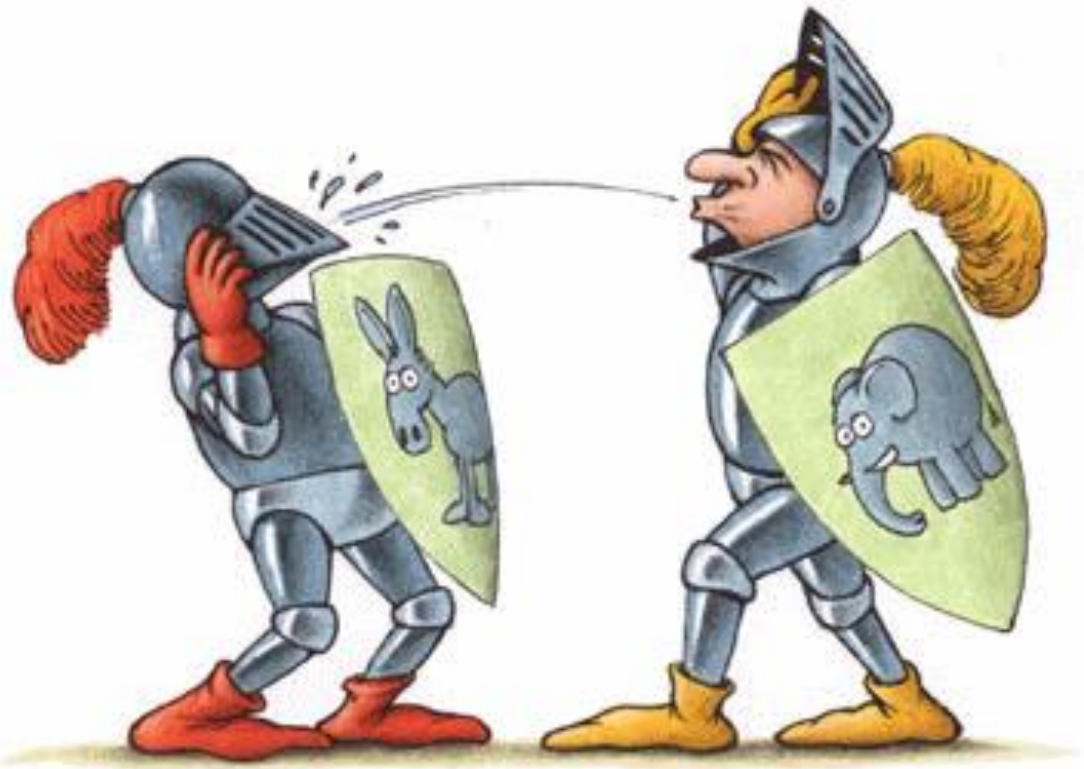
ODIN: laboratory abnormalities

Treatment-emergent grade 2–4 lipid and liver-related laboratory abnormalities (≥2% incidence), n (%)*	Once-daily DRV/r 800/100mg (N=294)	Twice-daily DRV/r 600/100mg (N=296)	P value
Triglycerides	15 (5.2)	31 (11.0)	<0.014
Total cholesterol*	29 (10.1)	58 (20.6)	<0.0007
LDLc cholesterol*	28 (9.8)	47 (16.7)	<0.019
ALT	5 (1.7)	10 (3.5)	0.20
AST	6 (2.1)	10 (3.5)	0.32
Non-graded lipid-related laboratory abnormalities, n (%)			
HDL below the lower normal limit	57 (19.9)	52 (18.4)	0.67

*Based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events 2004, which does not have a grade 1 classification for triglycerides and grade 4 for total cholesterol and LDL

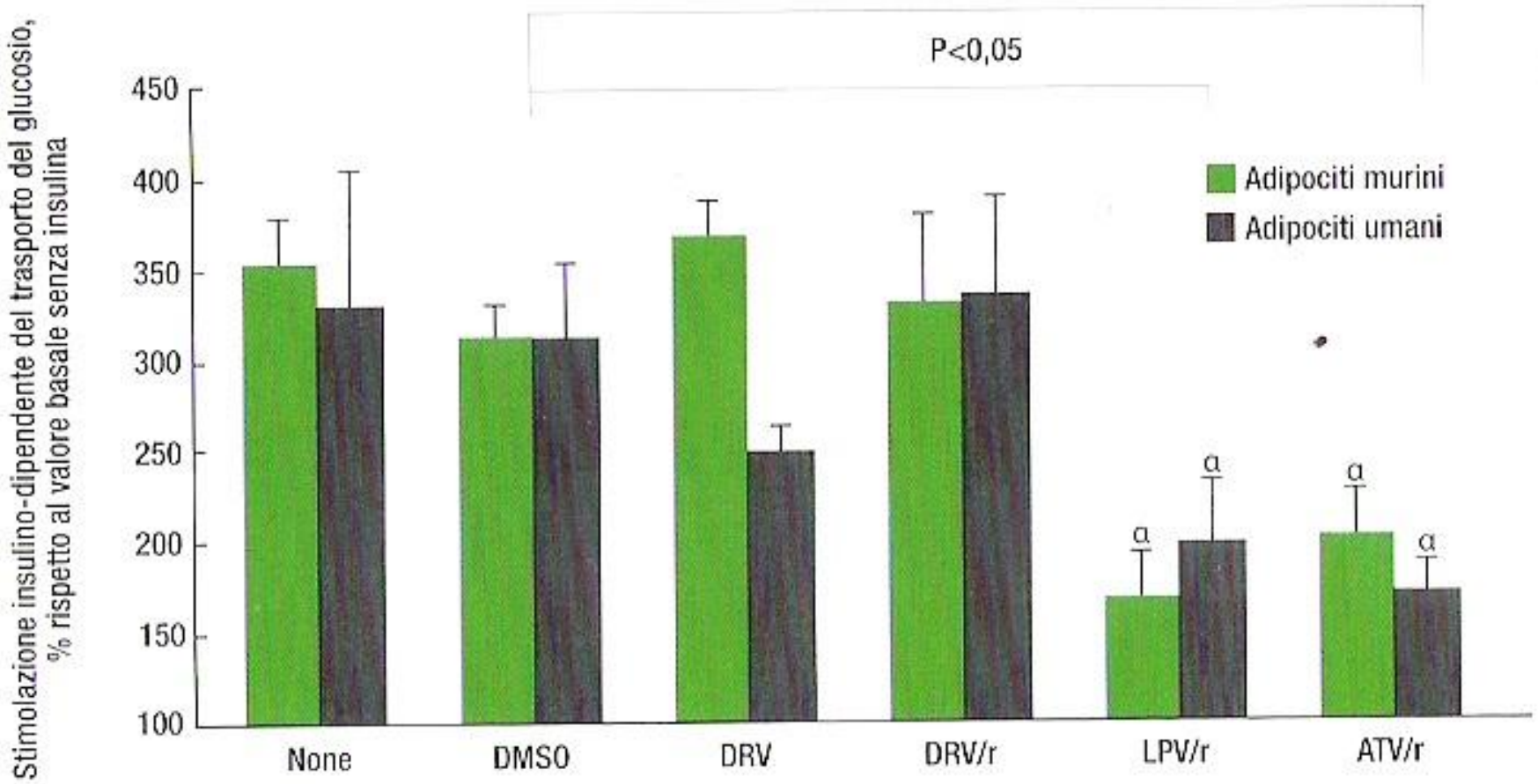
LDLc = low-density lipoprotein (calculated); ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL = high=density lipoprotein

CROI 2010, Cahn. P. ET AL.



www.HelloCrazy.com

Effetto degli IP sulla via del segnale insulinico



Bibliografia:

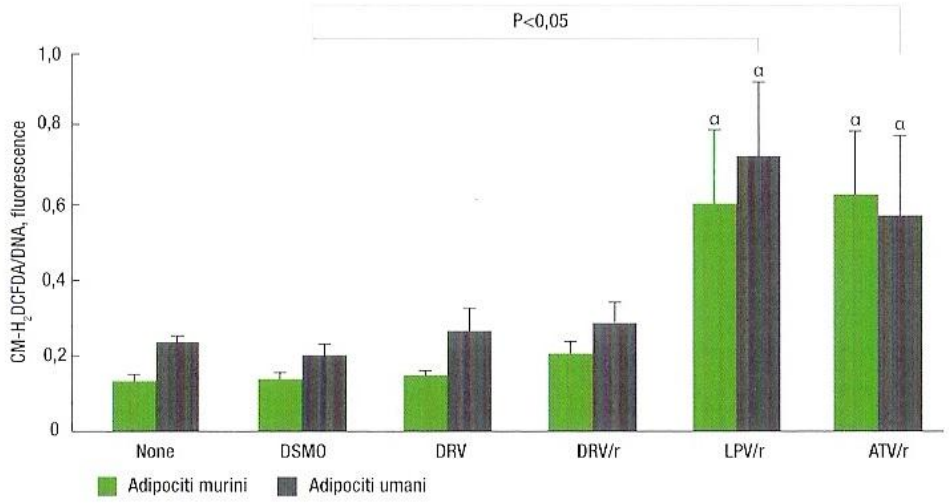
1. Capel E, *et al*. Effects of ritonavir-boosted darunavir, atazanavir and lopinavir on adipose functions and insulin sensitivity in murine and human adipocytes. *Antivir Ther*. 2011 Nov 28 [in press].

2. Pérez-Matute P, *et al*. Minimal effects of Darunavir on adipocyte differentiation and metabolism in 3T3-L1 cells. *J Infect Chemother*. Published online 14 January 2012.

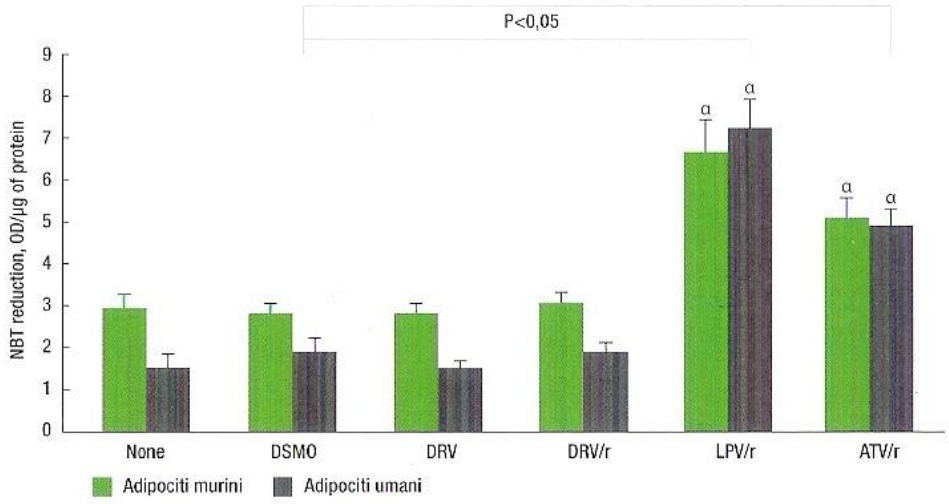
3. Le Moal G, *et al*. Lopinavir to atazanavir or darunavir switch in HIV-1-infected patients with dyslipidemia: an observational study. *Journal of the International AIDS Society* 2010, 13 (Suppl4): P46.

4. Vigouroux C, *et al*. Molecular mechanisms of human lipodystrophies: From adipocyte lipid droplet to oxidative stress and lipotoxicity. *The International Journal of Biochemistry & Cell Biology* 43 (2011): 862-876.

Effetti degli IP sulla funzionalità mitocondriale e sulla produzione di ROS



Effetti degli IP sulla funzionalità mitocondriale e sulla produzione di ROS



Istogramma tratto da Figura 2(E, F) Capel, *et al*

Murphy RL, Berzins B, Zala C, et al.
AIDS. 2010 Mar 27;24(6):885-90.

Change to atazanavir/ritonavir treatment improves lipids but not endothelial function in patients on stable antiretroviral therapy

Journal of the International AIDS Society 2012, 15(Suppl 4):18202

Metabolic effects of atazanavir/ritonavir vs darunavir/ritonavir in combination with tenofovir/emtricitabine in antiretroviral-naı ve patients (ATADAR Study)

Martinez, et al

Purpose of the study

We investigated whether both regimens might differ regarding plasma lipids, insulin resistance (HOMA-IR), and estimated glomerular filtration rate (MDRD).

Methods

Multicentre, randomized, clinical trial (ATADAR Study, NCT01274780). Primary end-point: 24-week change in total cholesterol. Secondary end-points: changes in lipids other than total cholesterol, HOMA-IR, and MDRD; clinical tolerability; and efficacy. We assumed that patients assigned to DRV/r would have an increase in plasma total cholesterolB21 mg/dL, which was the difference between lopinavir/r and ATV/r in CASTLE study. Fasting plasma lipids, glucose, insulin, and creatinine were measured at baseline, and 4, 12, and 24 weeks. Analyses were by intent-to-treat.

Summary of results

180 patients were randomized (ATV/r91, DRV/r89).

At 24 weeks, total cholesterol (mean, SD) changed 7.26 (26.76) mg/dL with ATV/r and 11.47 (25.85) mg/dL with DRV/r (estimated difference ATV/r minus DRV/r 4.21 (95% CI12.11 to 3.69), P0.2944), thus confirming our primary hypothesis. Changes (mean, SD) in triglycerides were roughly similar: 16.29 (61.76) mg/dL with ATV/r and 18.40 (64.24) mg/dL with DRV/r (P0.8261), but there were trends to more favourable changes in LDL (2.14 [21.45] vs 3.14 [21.97] mg/dL, P0.1160) and HDL cholesterol (5.50 [10.36] vs 3.88 [8.42] mg/dL, P0.2625), and total-to-HDL cholesterol ratio (1.16 [6.38] vs 0.14 [0.86], P0.0652) with ATV/r than with DRV/r. There were small, non-significant decreases in HOMA-IR (ATV/r 0.17 [2.48] vs DRV/r 0.70 [3.38], P0.3785) and MDRD (ATV/r 7 [22] vs DRV/r 6 [15] mL/min/1.73 m2, P0.6652). 6 ATV/r and 3 DRV/r patients had their study drugs discontinued because of adverse effects (P0.4967). 7 additional patients in each arm had confirmed HIV RNA 50 copies.

Conclusions

There were trends to more favourable changes in LDL and HDL cholesterol and particularly total-to-HDL cholesterol ratio at 24 weeks with ATV/r than with DRV/r.

#745

LDL Particles and Lipoprotein-Phospholipase A2 in Naive HIV+ Patients Randomized To DRV/r vs ATV/r

Maria Saumoy

LDL e LPA2 DRV vs ATV: ATV aumenta i trigliceridi e LDL aterogeniche (gli altri non cambiano)

CROI 2014
Conference on Retroviruses and Opportunistic Infections

#802

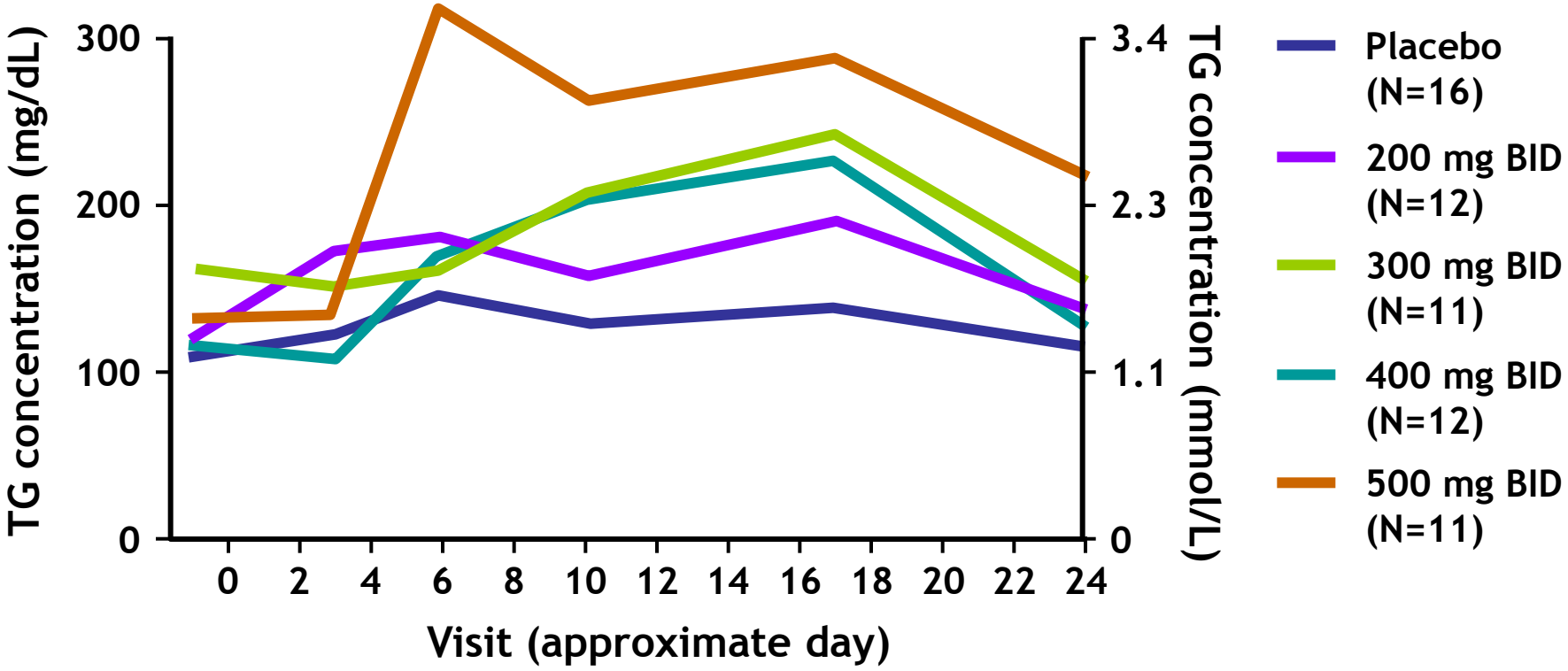
Low Pre-ART CD4+ T Cells, Female Sex, and Atazanavir Use Increase Obesity Risk After Starting ART

Benjamin Atkinson

CROI 2014
Conference on Retroviruses and Opportunistic Infections

Effect of ritonavir on triglycerides is dose-dependent

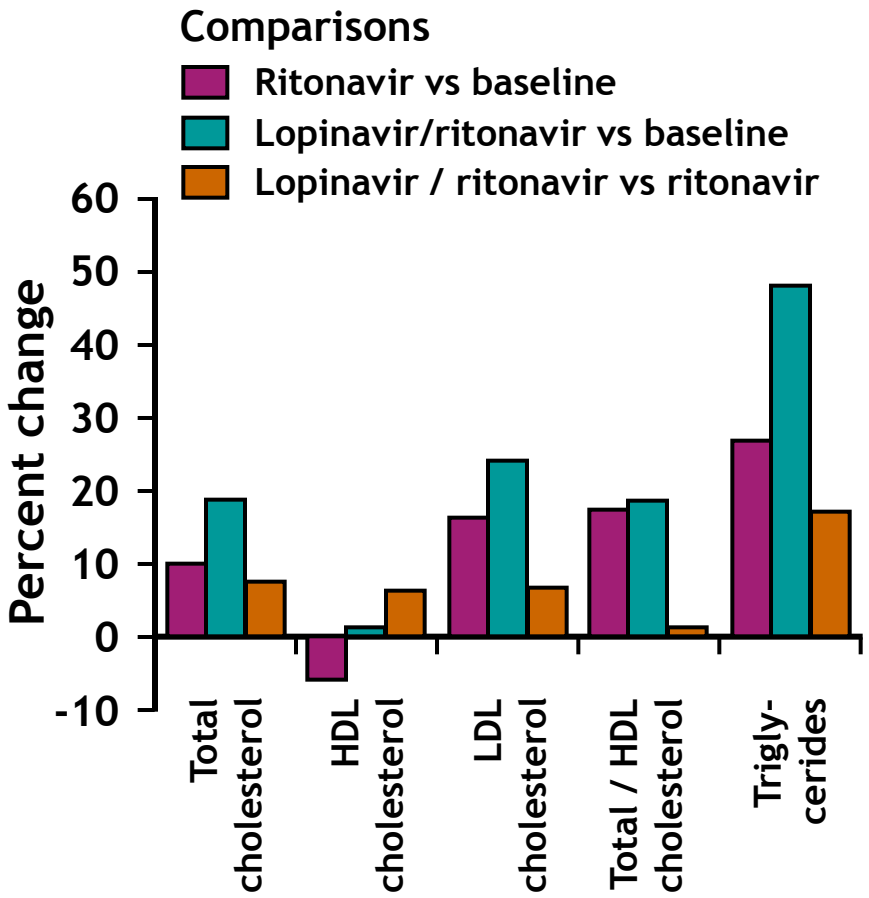
Impact of RTV (200-500 mg BID) vs placebo on TG production in HIV-infected subjects



Hsu et al. Antimicrob Agents Chemother 1997;41:898-905

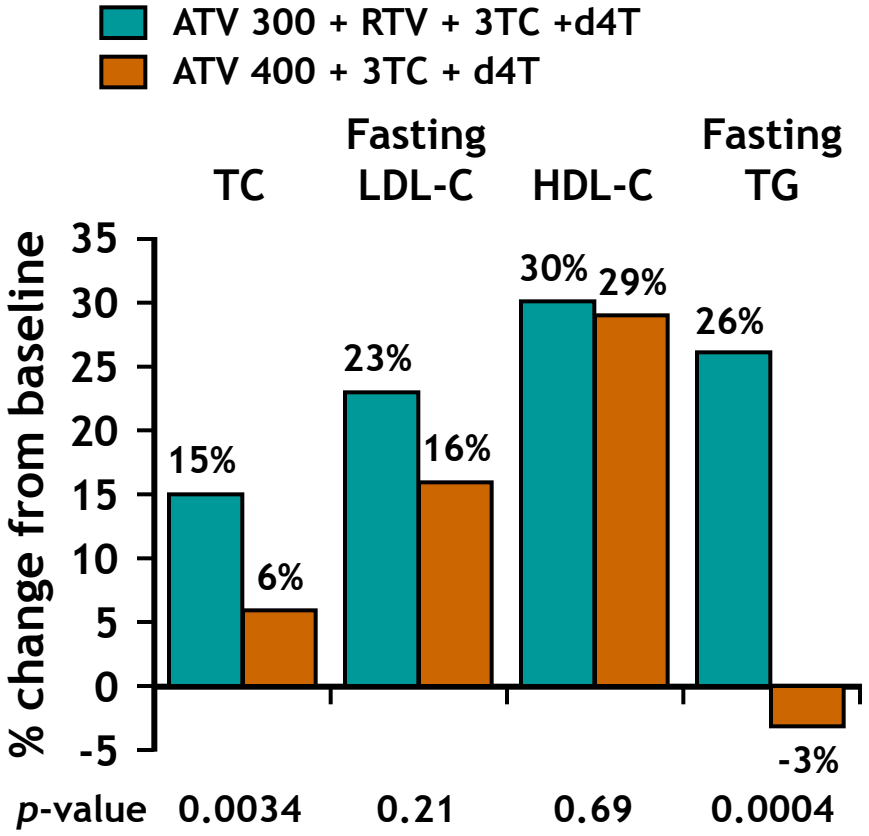
Low-dose ritonavir also matters…

RTV 100mg BID (N=20) or LPV/RTV 400/100 mg BID (N=20) x 14 days healthy volunteers



Shafran SD et al. HIV Med. 2005;6:421-25

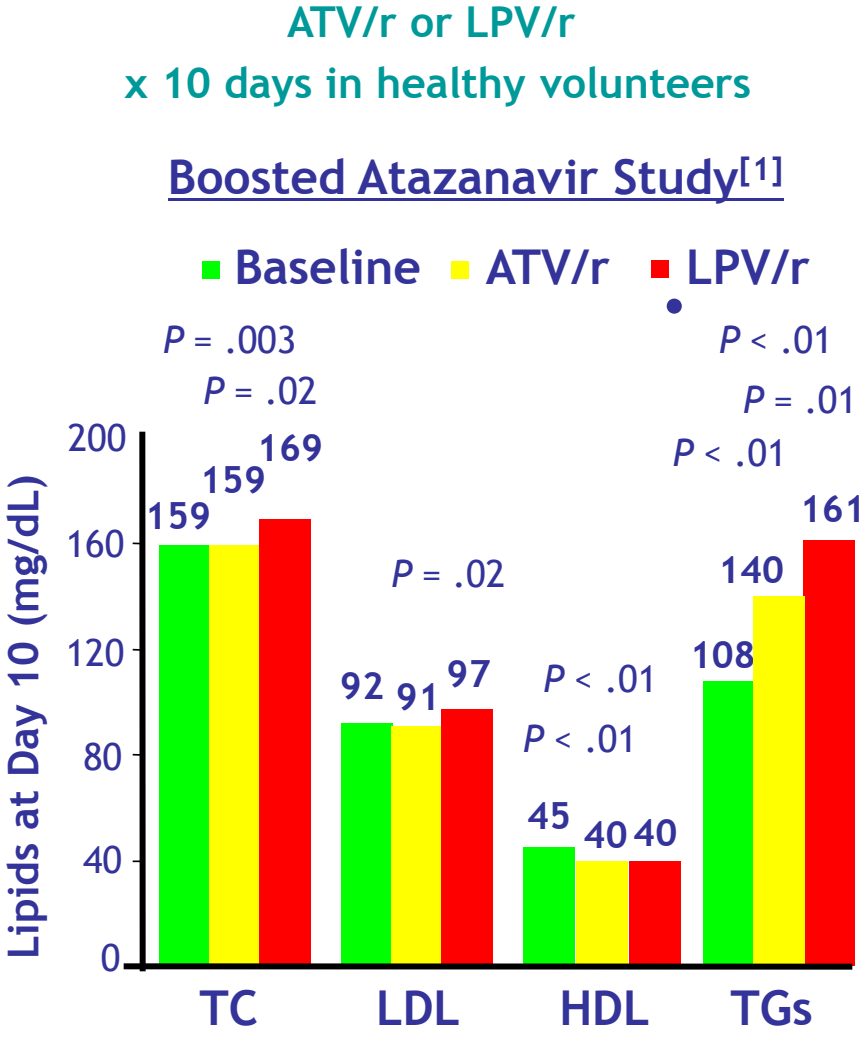
BMS 089 Study 48 weeks
Antiretroviral-naïve HIV-infected patients



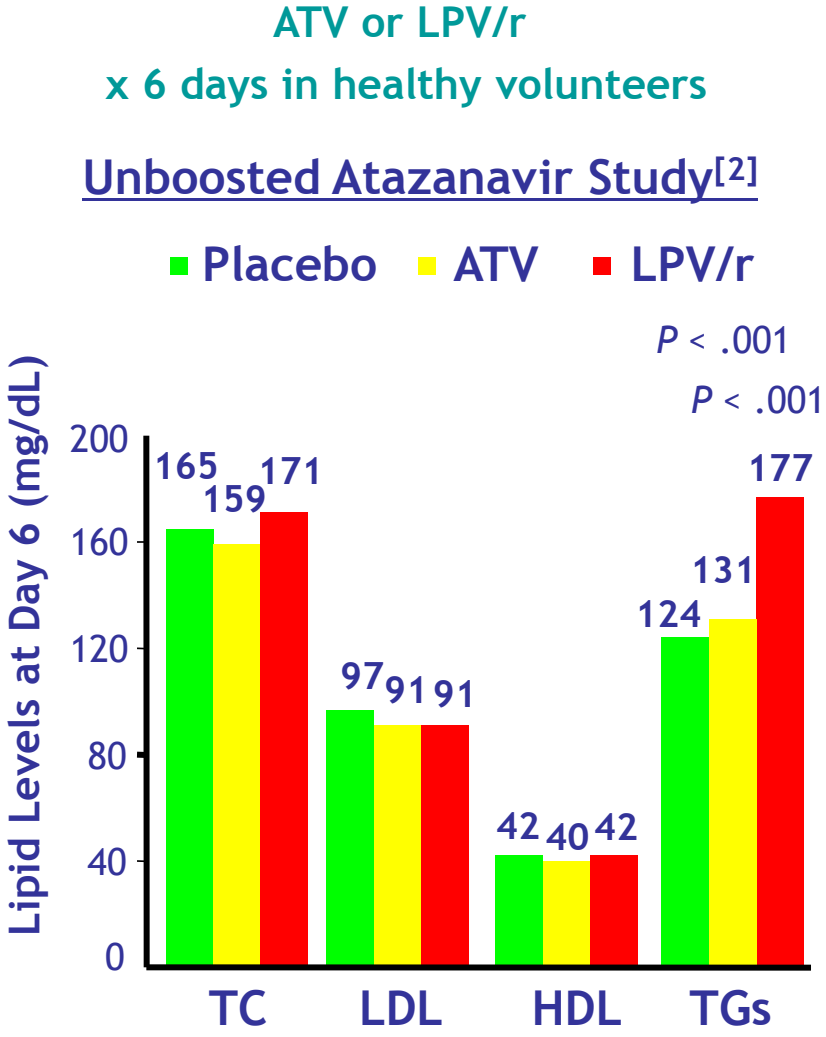
Malan N *et al.* 13th CROI 2006, abs 107LB

Low-dose ritonavir also matters…

ATV/r or LPV/r
x 10 days in healthy volunteers

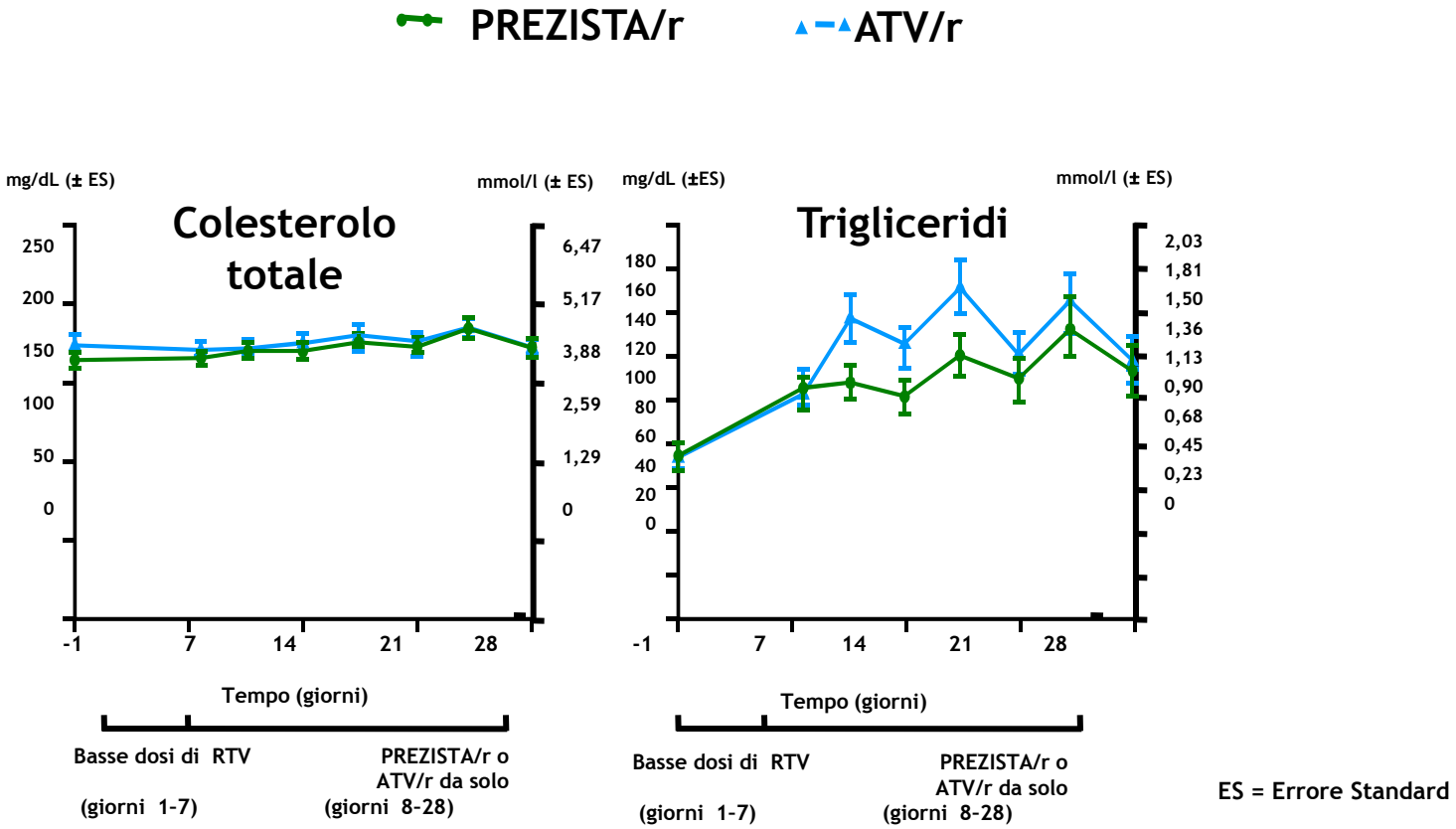


ATV or LPV/r
x 6 days in healthy volunteers



1. Noor MA et al. Lipodystrophy Workshop 2005. Abs 16. 2. Noor MA et al. AIDS 2004

Low-dose ritonavir also matters…



ATV/r or DRV/r 800/100
x 28 days in healthy volunteers

Tomaka F et al. 9th ADRL 2007. Abs P57

Sustained Virologic Efficacy of Atazanavir (ATV) vs Atazanavir/Ritonavir (ATV/r), each in Combination With Abacavir/Lamivudine (ABC/3TC) over 120 Weeks: The ARIES Trial

Squires K, DeJesus E, Bellos N, et al.

ICAAC 2010

Poster H-204

Week 120 – Statistical Analysis of Fasting Lipid Data

ICAAC 2010

Squires K, et al.
Poster H-204

	Baseline ABC/3TC+ ATV, ATV/r	Change from BL to Week 36 ABC/3TC+ ATV, ATV/r	Change from Week 36 to Week 120 ABC/3TC + ATV, ATV/r	Change from BL to Week 120 ABC/3TC + ATV, ATV/r
Cholesterol (median)	**152, 153**	**31, 30**	**-15, 7**	**21, 33**
***p* value**	0.7626	0.4138	<0.0001	0.0001
Triglyceride (median)	**127, 123**	**27, 34**	**-38, -19**	**-11, 19**
***p* value**	0.7550	0.7005	0.0007	<0.0001
HDL (median)	**37, 39**	**10, 8**	**3, 4**	**13, 12**
***p* value**	0.8641	0.7269	0.5376	0.7659
LDL (median)	**88, 85**	**13, 10**	**-6, 5**	**5, 14.5**
***p* value**	0.9662	0.2490	0.0001	0.0168
Ratio (Chol/HDL) (median)	**4.15, 4.10**	**-0.14, -0.14**	**-0.54, -0.18**	**-0.68, -0.30**
***p* value**	0.9207	0.3532	0.0001	0.0051

#746

Darunavir or Atazanavir vs Raltegravir Lipid Changes Are Unlinked To Ritonavir Exposure: ACTG 5257

Ighovwerha Ofotokun

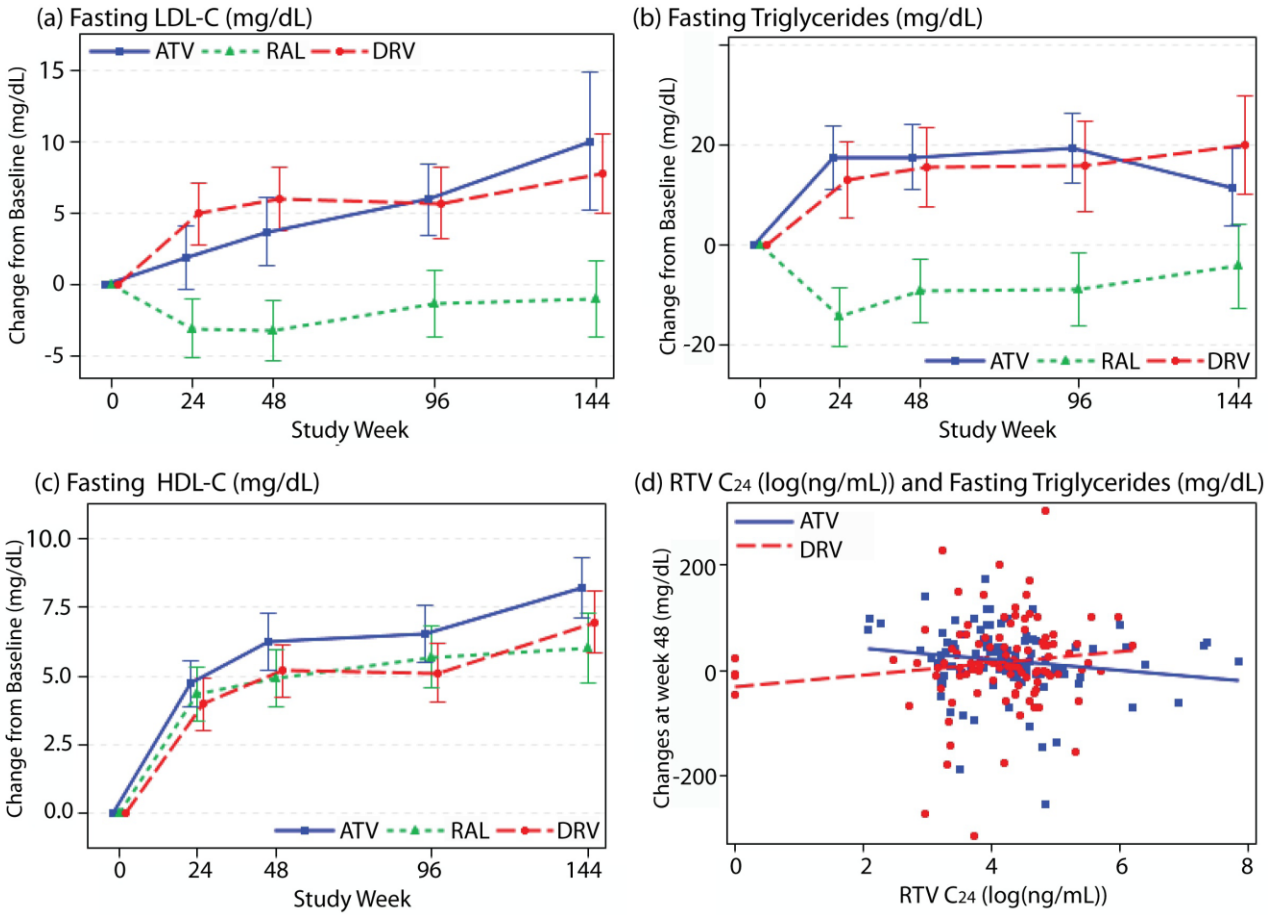
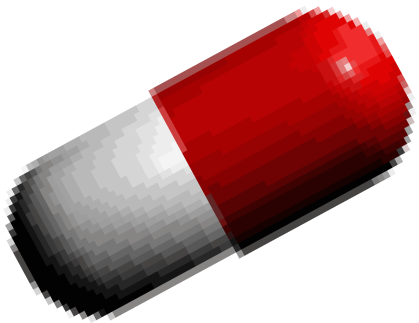


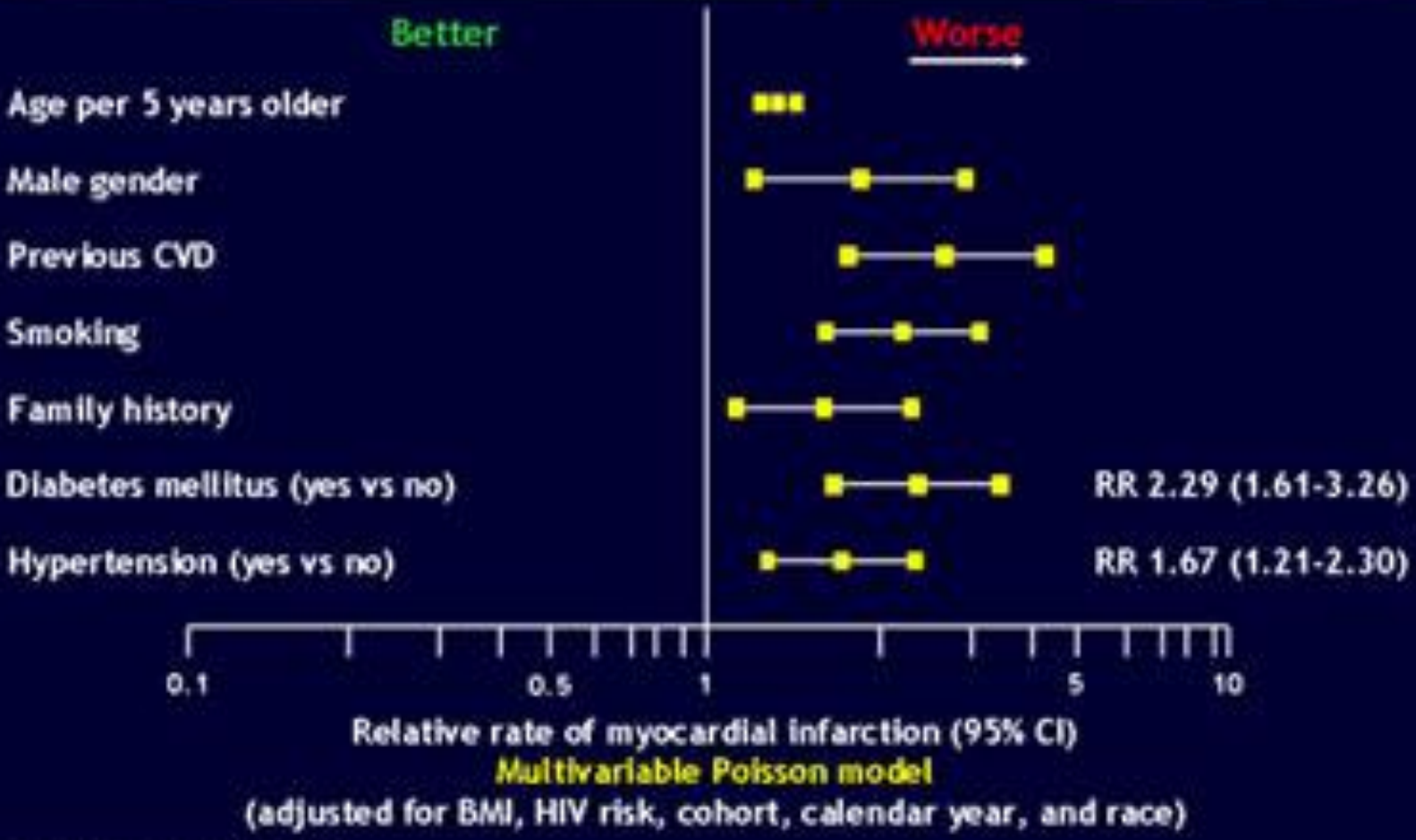
Figure 1: Panels a-c: Mean of Changes from Baseline in Fasting Lipid Profile (mg/dL) over Time; panel d: C_{24} (log(ng/mL)) and Fasting Triglycerides: Change from Baseline to Week 48

CROI 2014
Conference on Retroviruses and Opportunistic Infections

L'infettivologo è farmacocentrico!



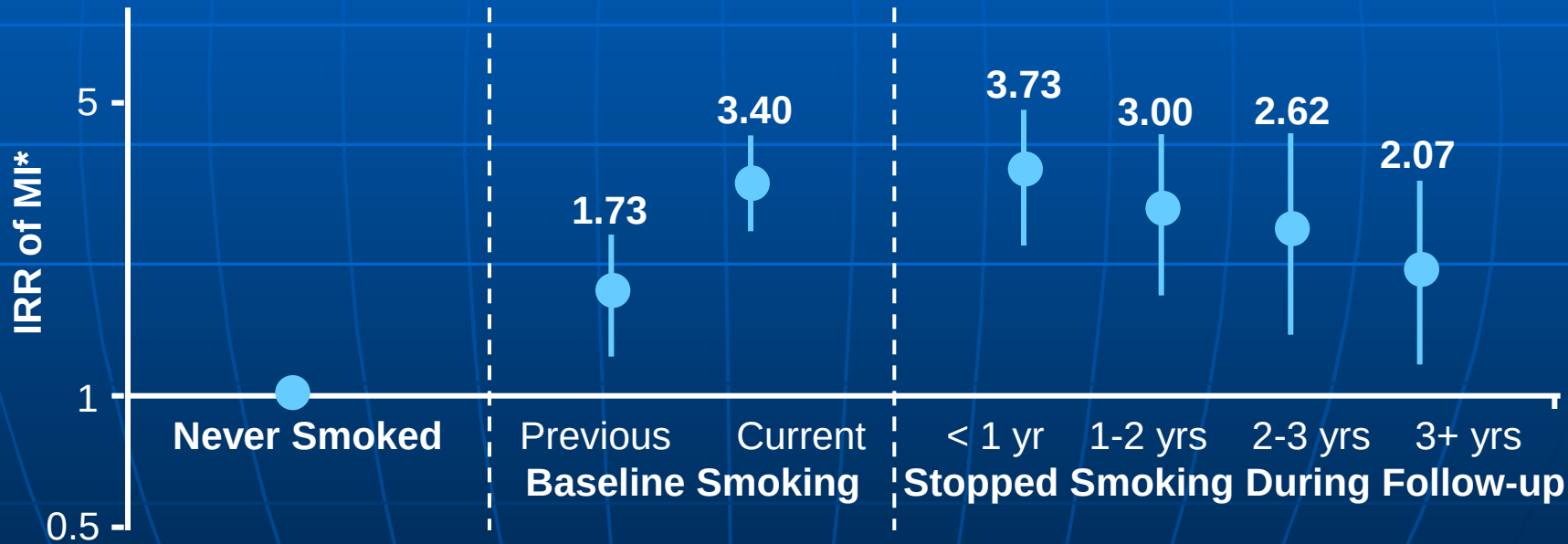
Risk Factors for CHD in an HIV+ Population



Copenhagen HIV program (D:A:D)
Lundgren JD et al. Presented at: 12th Annual Conference on Retroviruses and Opportunistic Infections; February 23, 2005; Boston, MA. Abstract 62.

D:A:D Study: Smoking Cessation Reduces Risk of CVD in HIV-Infected Patients

- 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.

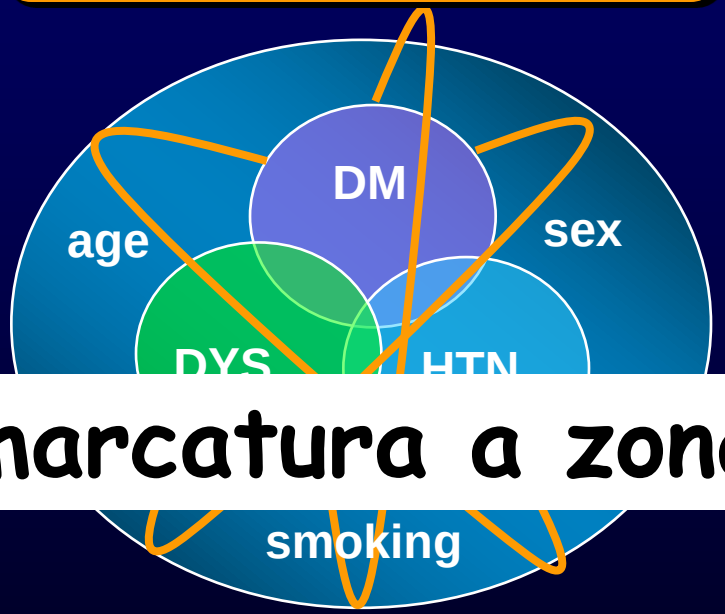
Petoumenos K, et al. CROI 2010. Abstract 124. Reproduced with permission.

Evolution in Understanding of CVD

Traditional Cardiovascular Disease Perspective

New Cardiovascular Risk Perspective

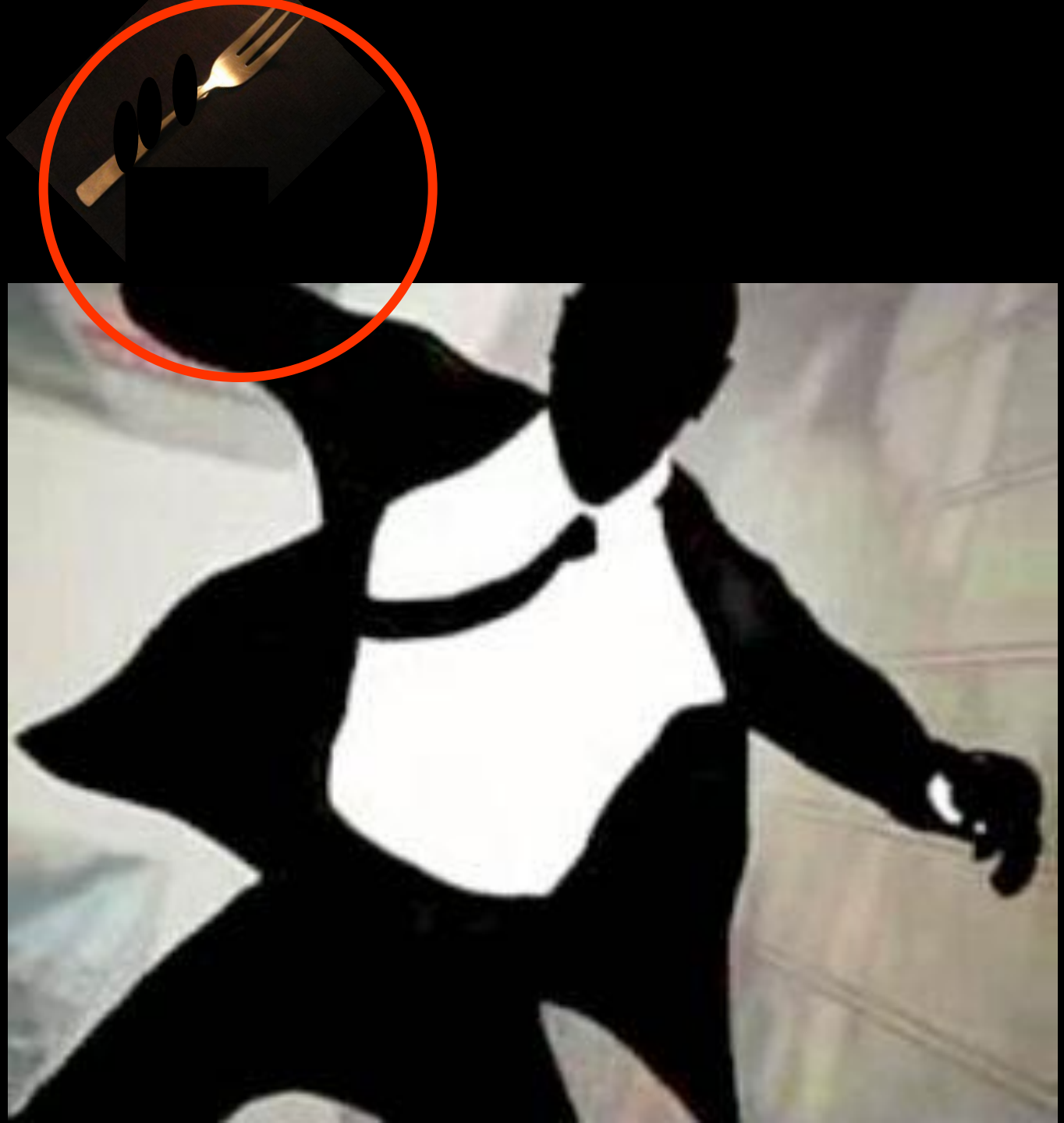
Marcatura a uomo….



O marcatura a zona?

Multiple Independent Risk Factors (Silo Approach)

Cardiovascular Disease Risk Factors (Global Approach)



ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D.

Engl J Med
1999;
340: 115-126

ATHEROSCLEROSIS is an inflammatory disease. Because high plasma concentrations of

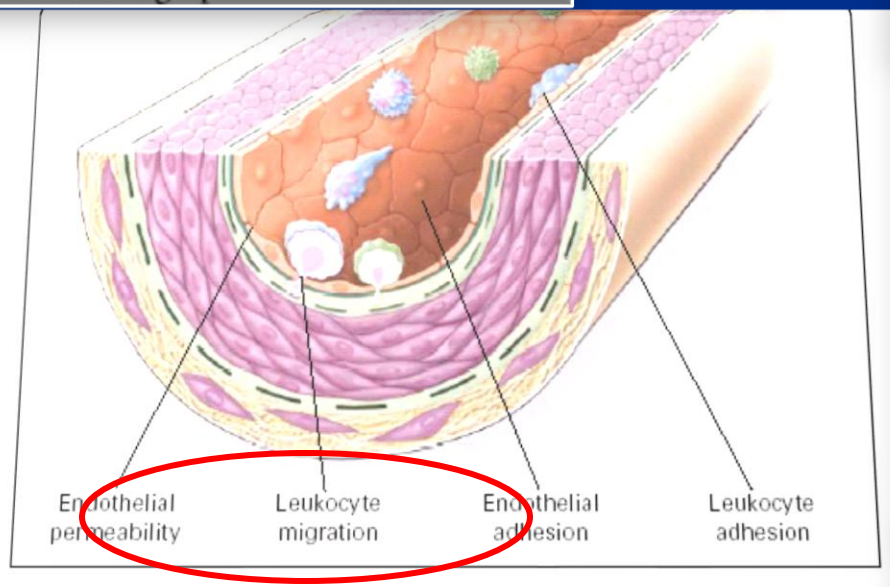
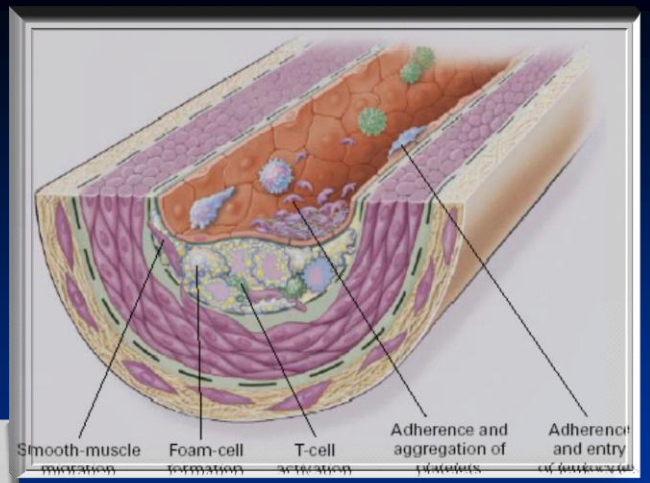
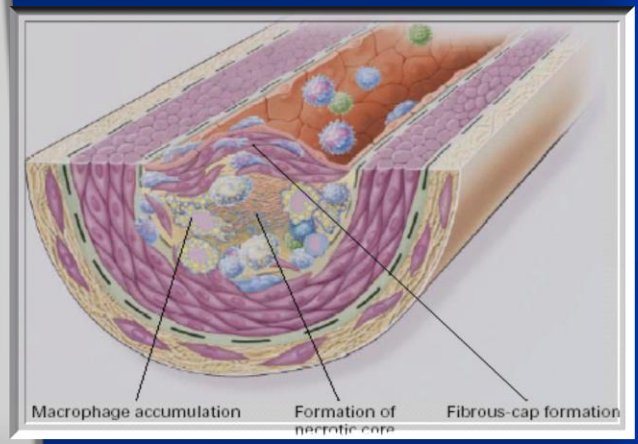
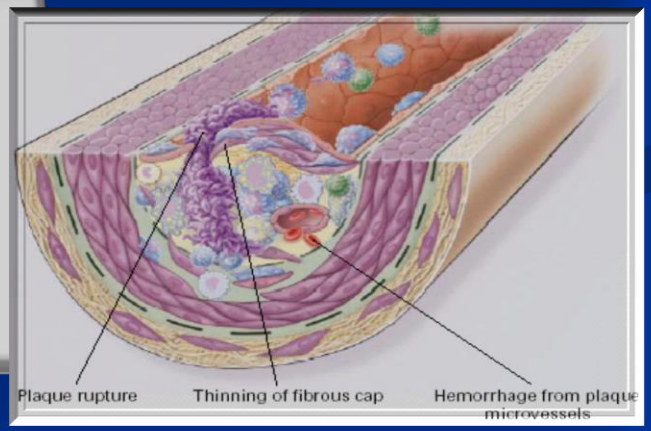


Figure 1. Endothelial Dysfunction in Atherosclerosis.

The earliest changes that precede the formation of lesions of atherosclerosis take place in the endothelium. These changes include increased endothelial permeability to lipoproteins and other plasma constituents, which is mediated by nitric oxide, prostacyclin, platelet-derived growth factor, angiotensin II, and endothelin; up-regulation of leukocyte adhesion molecules, including L-selectin, integrins, and platelet–endothelial-cell adhesion molecule 1, and the up-regulation of endothelial adhesion molecules, which include E-selectin, P-selectin, intercellular adhesion molecule 1, and vascular-cell adhesion molecule 1; and migration of leukocytes into the artery wall, which is mediated by oxidized low-density lipoprotein, monocyte chemotactic protein 1, interleukin-8, platelet-derived growth factor, macrophage colony-stimulating factor, and osteopontin.



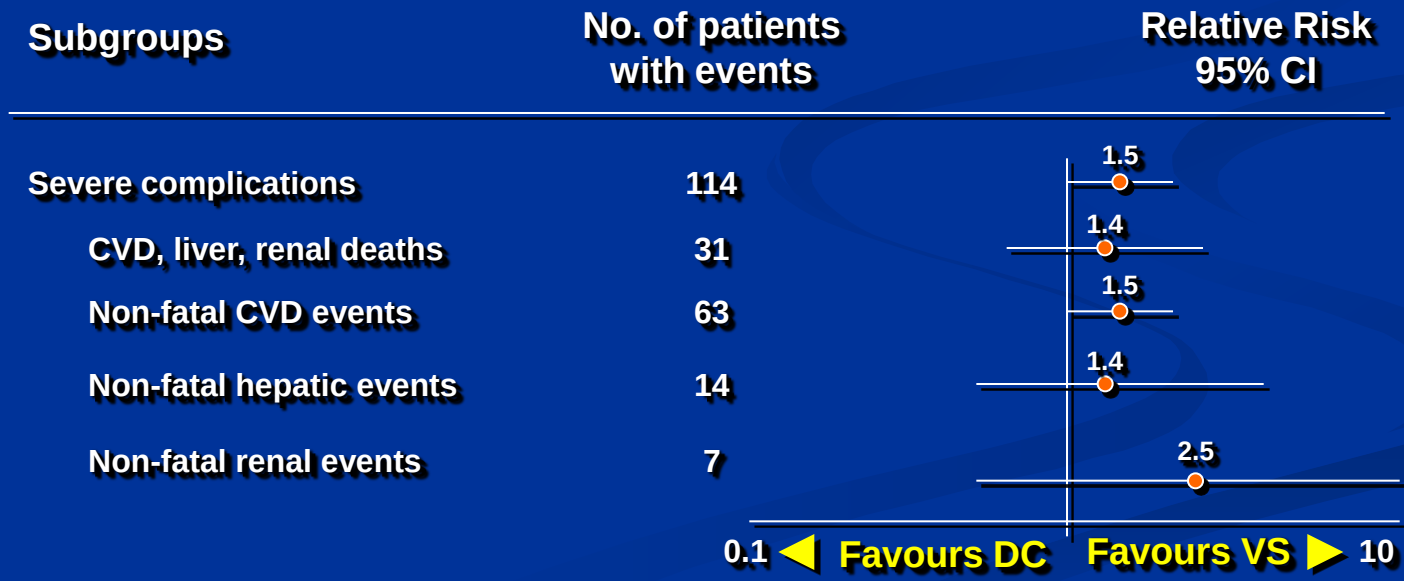




SMART Study: Short-term CD4+ guided episodic use of ART is inferior to continuous therapy

- CD4+ guided drug conservation (DC) strategy was associated with significantly greater disease progression or death compared with continuous viral suppression (VS): RR 2.5 (95% CI: 1.8–3.6; $p<0.001$)
- Includes increased CVD-, liver- and renal-related deaths and non-fatal CVD events

Severe complications endpoint and components



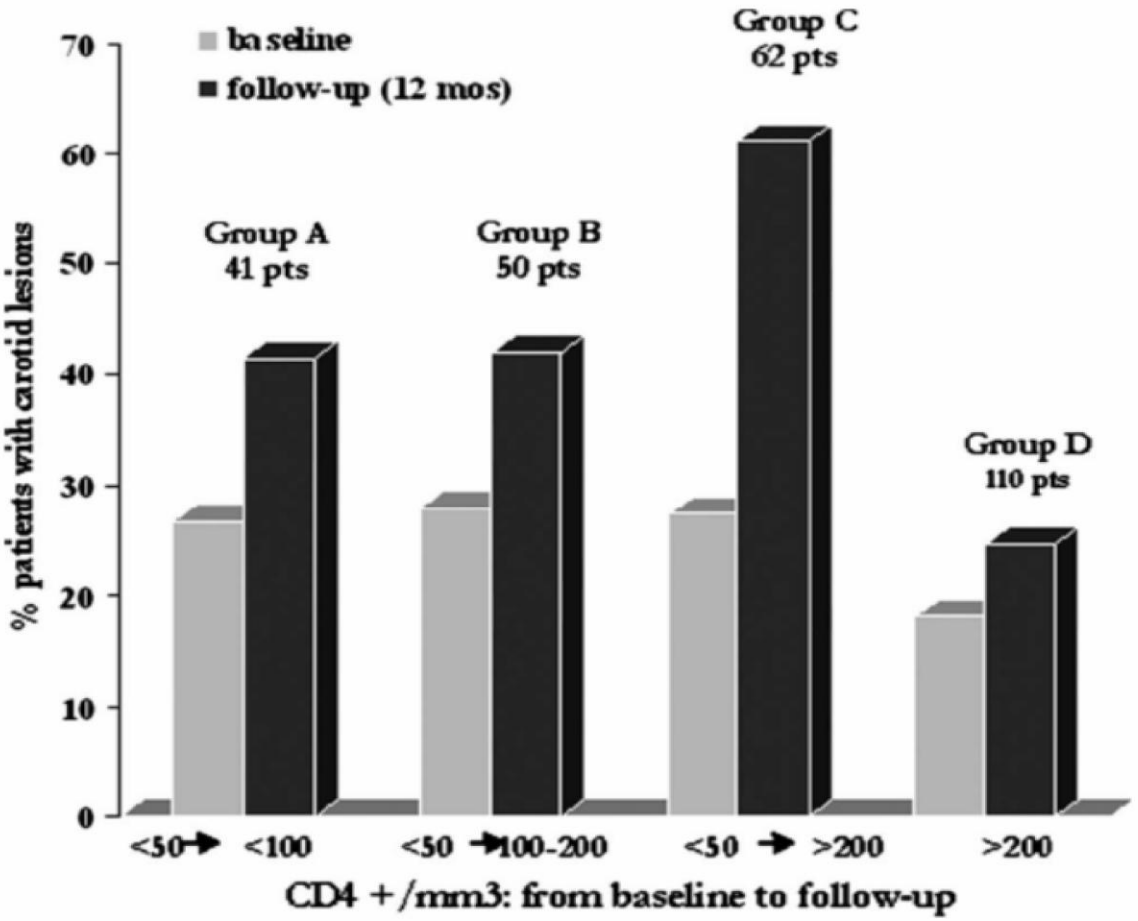
El-Sadr W, *et al. 13th CROI*, Denver 2006, #106LB

J Acquir Immune Defic Syndr • Volume 52, Number 4, December 1, 2009

The Role of Immune Reconstitution in the Onset of Subclinical Atheromasic Lesions

Paolo Maggi, MD*
Anna Volpe, BD*
Chiara Bellacosa, MD*
Giuseppe Pastore, MD*
Francesco Perilli, MD†
Antonio Lillo, MD†
Guido Regina, MD†

*Clinica delle Malattie Infettive, Università degli Studi di Bari, Italy
†Cattedra di Chirurgia Vascolare, Università degli Studi di Bari, Italy



Group	patients with carotid lesions (intima media thickness > 0,9 mm and/or atherosclerotic plaques)				
	baseline		follow up		
	%	#	%	#	
A	26.8	11	41.6	17	p= 0.27
B	28.0	14	42.0	21	p= 0.14
C	27.4	17	61,2	38	**p= 0.0001**
D	18.1	24	24.7	25	p= 0.71

FIGURE 1. Distribution of subclinical carotid lesions at baseline and at follow-up with statistical analysis.

FATTORE DI RISCHIO	ASSOCIAZIONE AL FATTORE
Ospite (fattori genetici e stili di vita)	Il riconoscimento e la correzione dei fattori ambientali che condizionano gli stili di vita (fumo, dieta e attività fisica) rappresentano gli interventi più efficaci per la prevenzione e il trattamento delle patologie non infettive.
Virus (per azione diretta legata alla replicazione virale ovvero azione indiretta legata allo stato di immunodeficit o immunoattivazione)	• La malattia da HIV si caratterizza per uno stato di infiammazione sistemica e tissutale in grado di accelerare i meccanismi di senescenza cellulare e d'organo. • Le coinfezioni associate all'infezione da HIV (virus epatitici, virus herpetici, ecc.) rappresentano un rischio additivo per patologia non infettiva. • Il controllo della replicazione virale di HIV non annulla l'eccesso di rischio associato alla patologia.
Farmaco (associazioni di farmaci antiretrovirali per tossicità legata al regime corrente o all'esposizione cumulativa)	La tossicità farmacologica può incrementare il livello di rischio per danno d'organo [7,8].

Clinical care

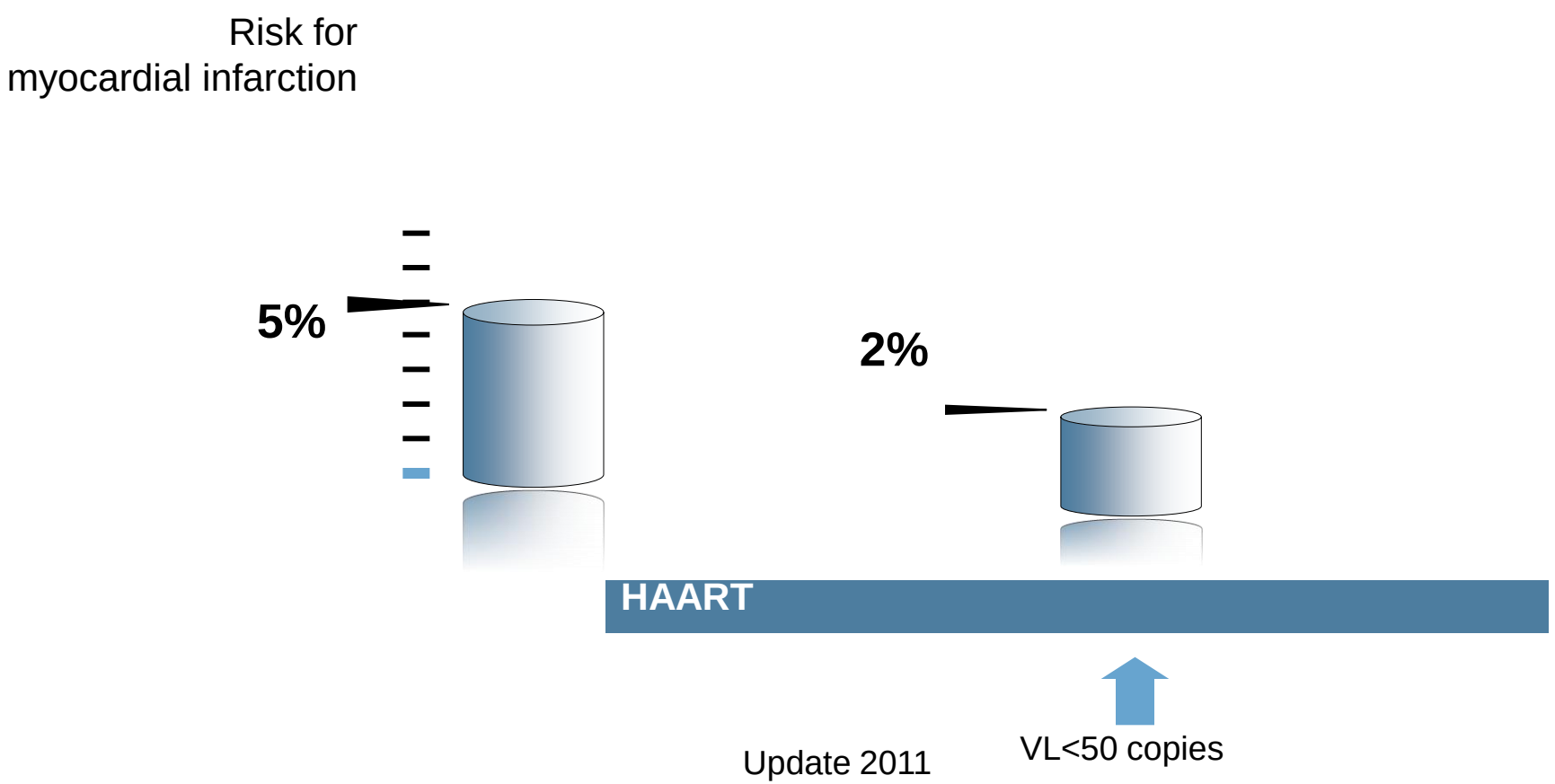
HIV-related Inflammation

Risk for myocardial infarction

Clinical care

HIV-related inflammation

CV-friendly HAART

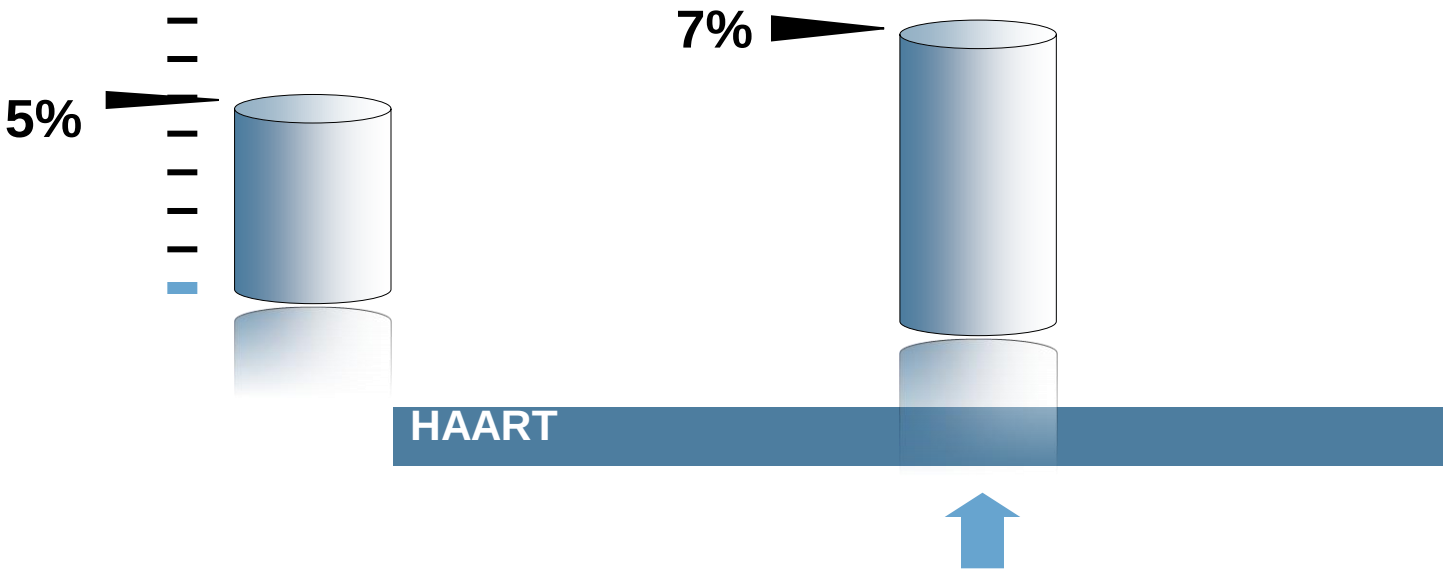


Clinical care

HIV-related inflammation

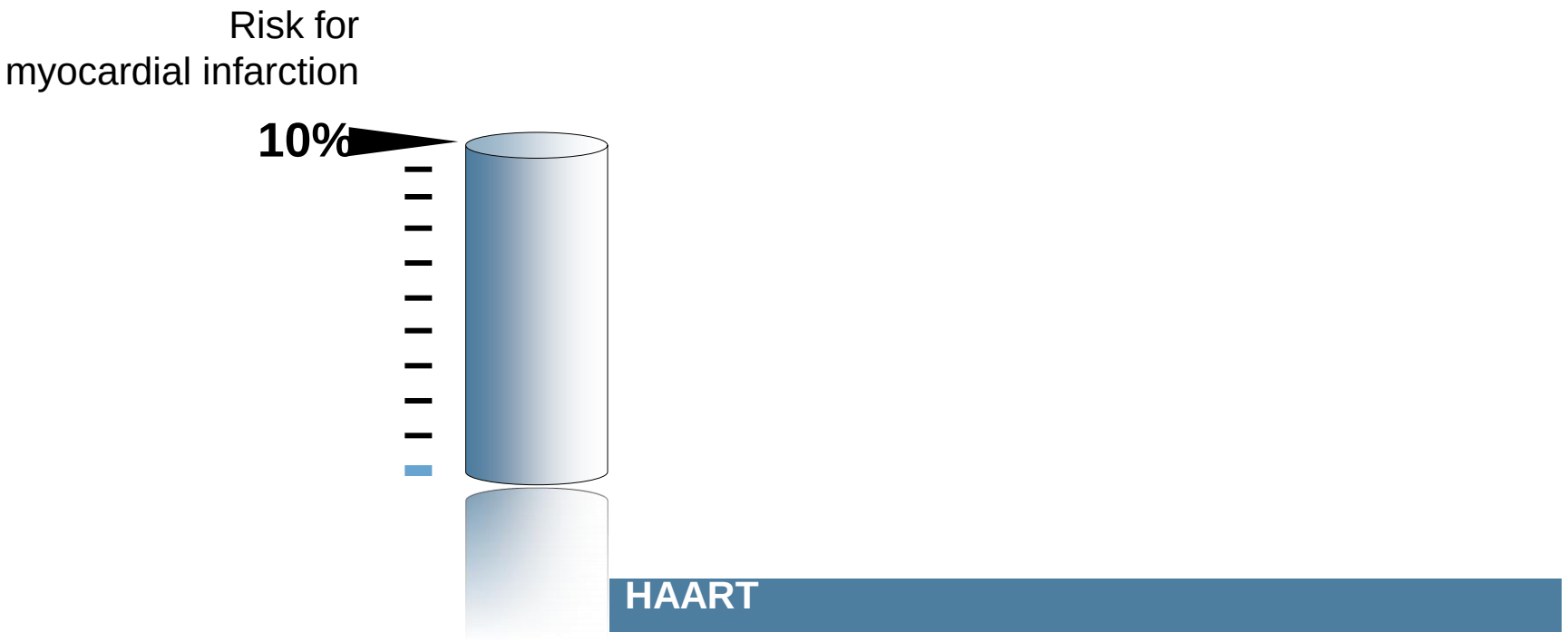
No CV-friendly HAART
(lipodystrophy,
lipids, insulin resistence,
type 2 diabetes…)

Risk for
myocardial infarction



Clinical care

HIV-related Inflammation



Clinical care

HIV-related inflammation

No CV-friendly HAART
(lipodystrophy,
lipids, insulin resistence,
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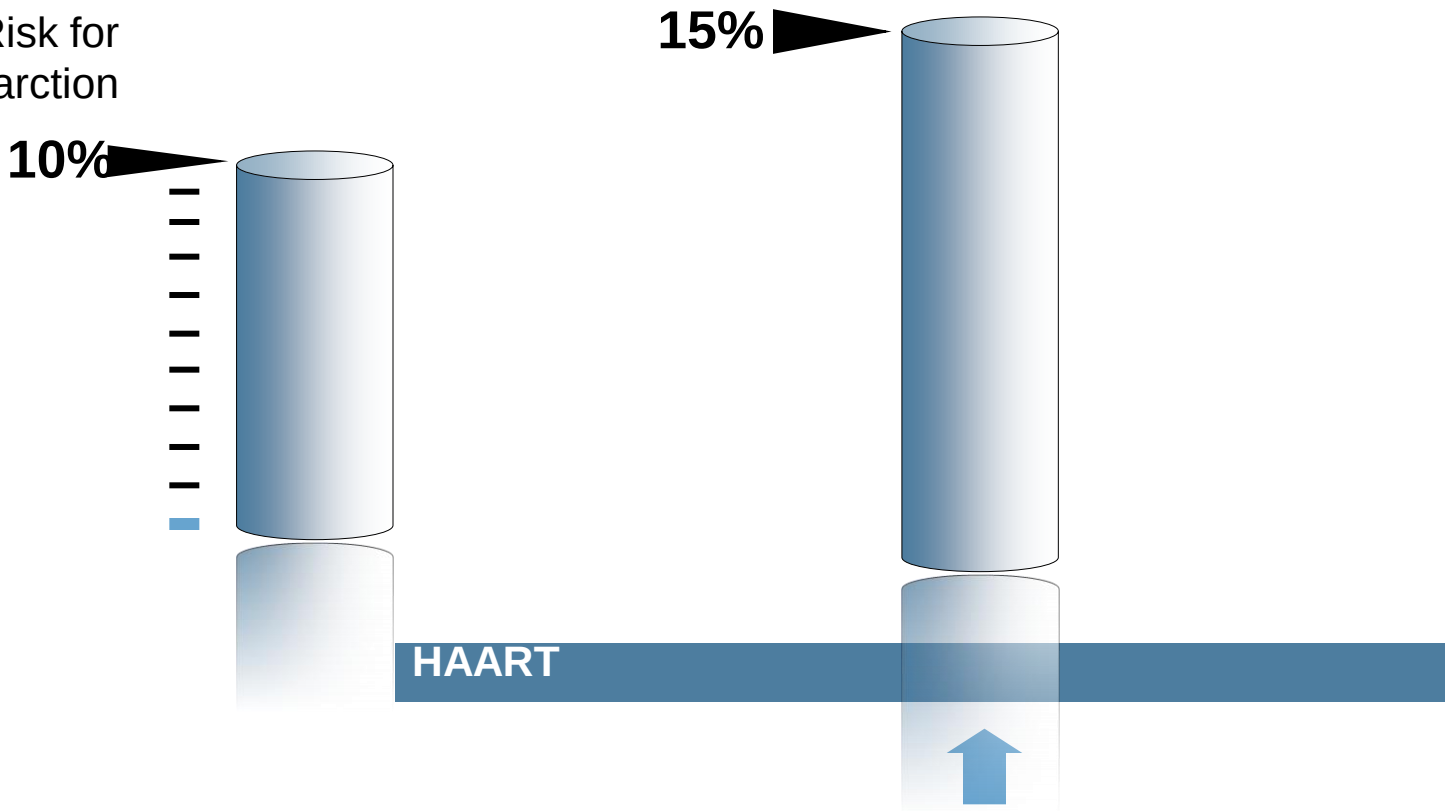
Risk for
myocardial infarction



Decreasing cardiovascular risk in HIV infection between 2005 and 2011

Giuseppe V. De Socio[a], Giustino Parruti[b], Elena Ricci[c], Paolo Maggi[d], Benedetto M. Celesia[e], Giovanni Penco[f], Canio Martinelli[g], Marco Franzetti[h], Antonio Di Biagio[i], Paolo Bonfanti[j], Giacomo Pucci[k] and Giuseppe Schillaci[k] for the CISAI study group

AIDS 2014, **28**:000–000

Objective

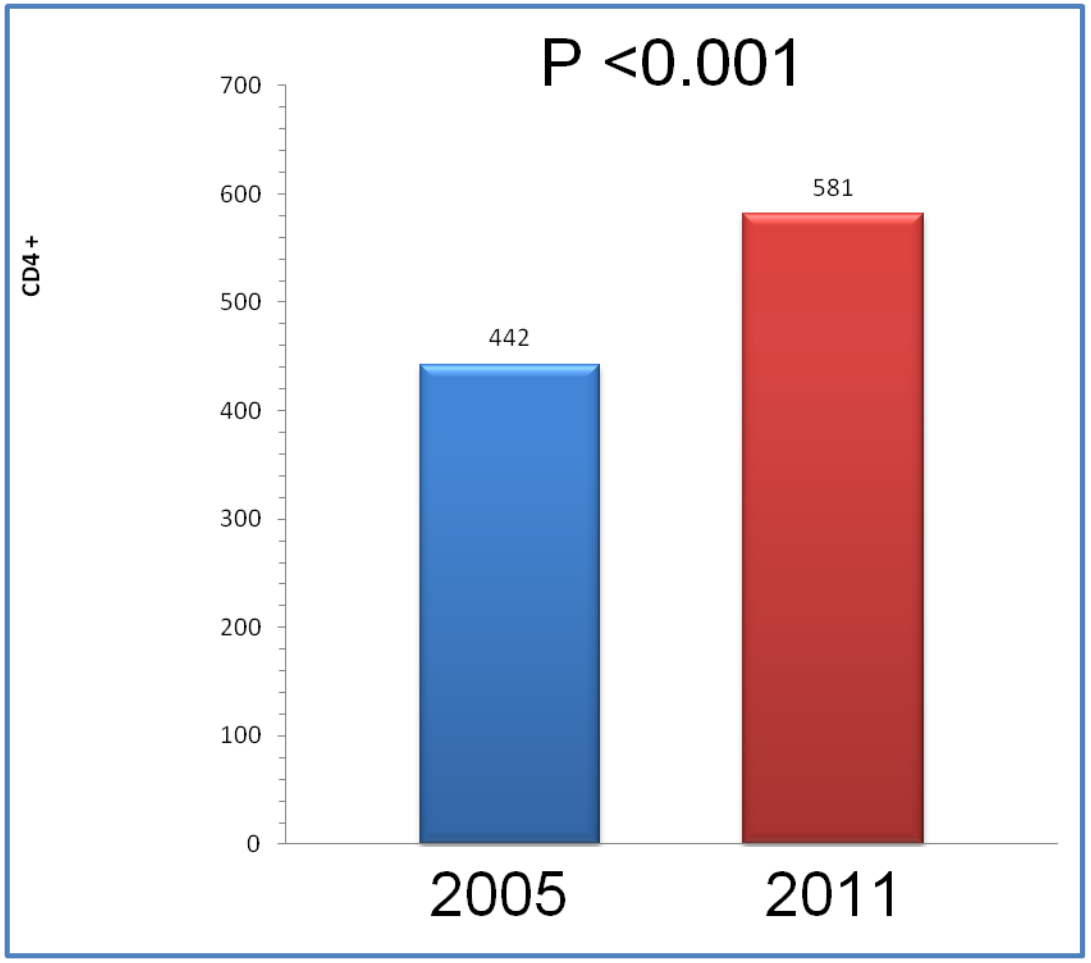
- The aim of the study was to assess whether the cardiovascular (CV) risk profile and prevalence of metabolic syndrome in HIV-infected patients is improved over time in ordinary clinical settings.

Methods

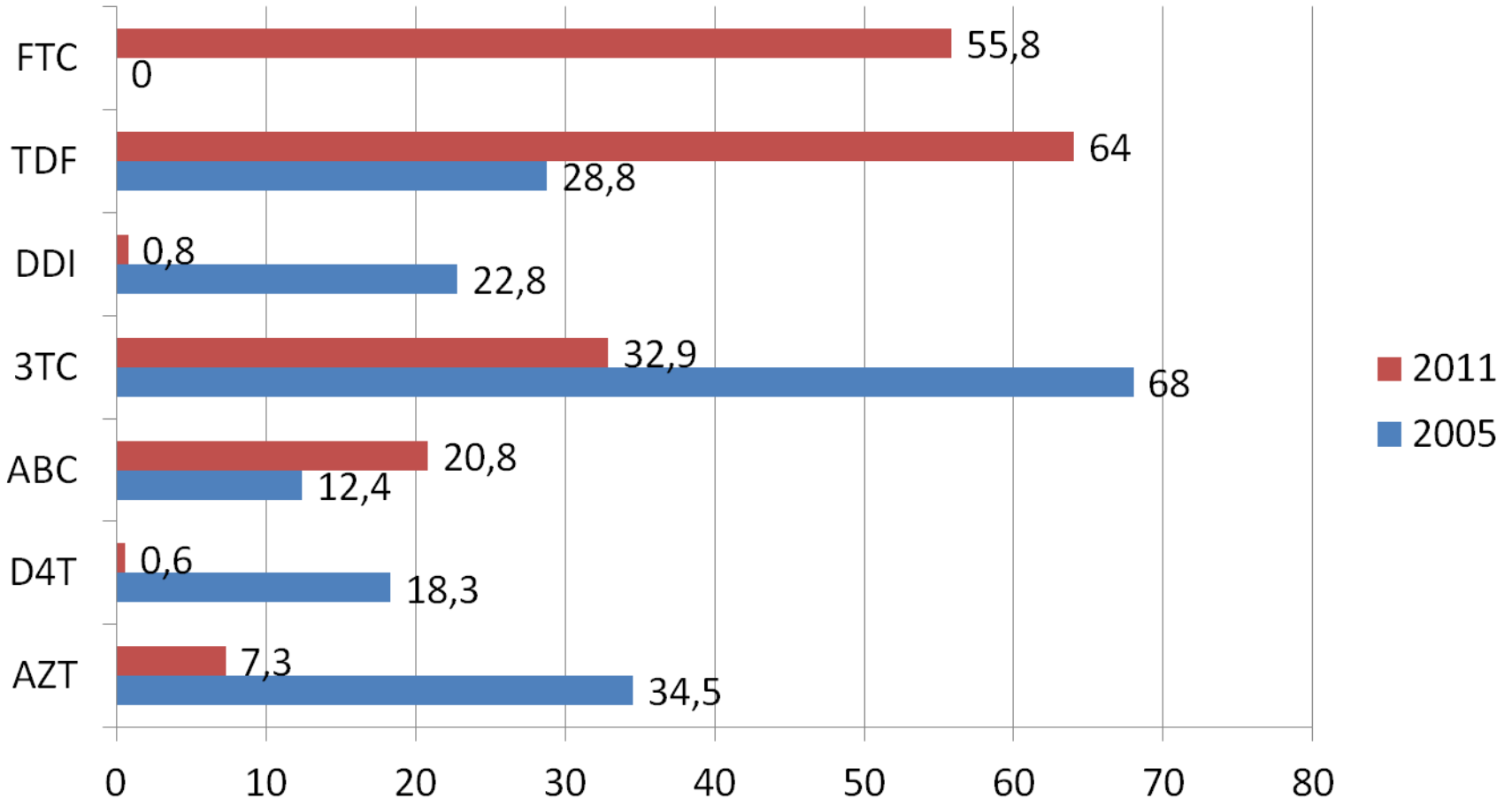
- **Design:** Case control multicenter study assessing CV risk in two periods: 2005 and 2011.
- **Methods:** We analyzed CV risk in 1530 Caucasian HIV infected patients (age 45.6 ± 9.1, men 74.0%) enrolled in two studies performed in 2005 and in 2011 with similar investigation procedures. Patients were individually matched for age and sex. The 10-year probability of major CV events and estimated vascular age was calculated using the Framingham Risk Score (FRS).

Table 1. Clinical and cardiovascular features in HIV-infected patients enrolled in the SiMOne (2005) and HIV-Hy (2011) studies.

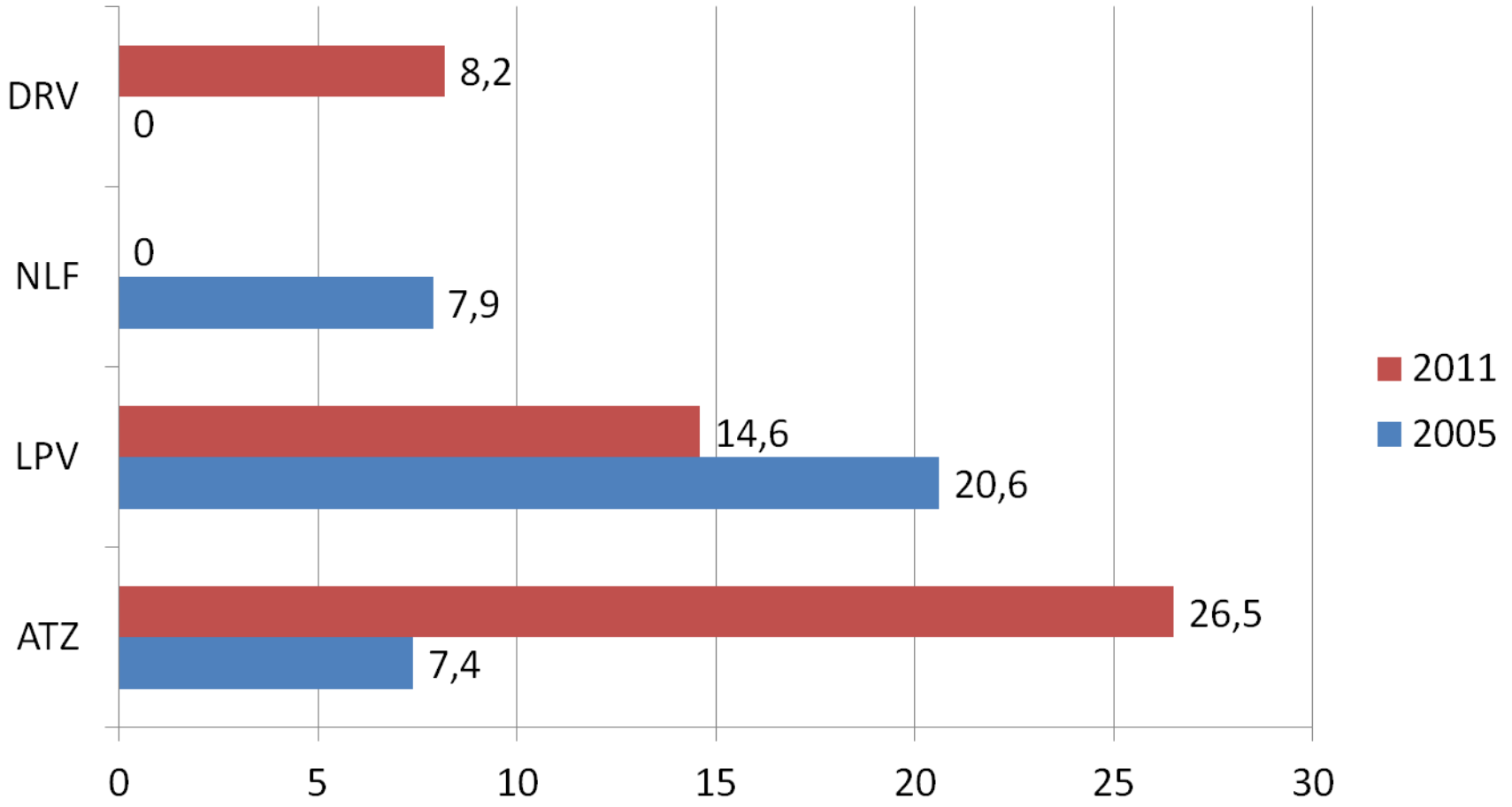
Variable	SiMOne, 2005 ($n=765$)	HIV-Hy, 2011 ($n=765$)	*P*
Men	566 (74.0)	566 (74.0)	n/a
Age, years (mean ± SD)	45.6 ± 9.1	45.6 ± 9.1	n/a
BMI, kg × m^{-2} (mean ± SD)	23.8 ± 3.4	24.2 ± 4.0	0.01
Never smokers	222 (29.6)	286 (37.4)	
Current smokers	453 (60.5)	381 (49.9)	
Former smokers	74 (9.9)	97 (12.7)	0.0002
Diabetes	73 (9.6)	53 (6.9)	0.057
Hypertension	252 (32.9)	228 (29.8)	0.19
SBP, mmHg	124 ± 16	123 ± 15	0.23
DBP, mmHg	79 ± 10	78 ± 10	0.17
Naive to antiretroviral therapy	118 (15.5)	45 (5.9)	<0.0001
ART			
Treatment interruption (all causes)	64 (9.9)	16 (2.2)	
NRTI-based	85 (13.2)	11 (1.5)	<0.0001
PI-based	260 (40.4)	383 (53.4)	
NNRTI-based	213 (33.1)	278 (38.8)	
NNRTI + PI-based	22 (3.4)	8 (1.1)	
Other	0 (0)	21 (2.9)	
10-year global CVD risk – FRS% (median, IQR)	8.6 (4.5–15.6)	7.9 (3.9–15.6)	0.04
Metabolic syndrome	308 (40.3)	236 (33.4)	0.006
Total cholesterol, mmol/l (mean ± SD)	5.02 ± 1.27	5.06 ± 1.11	0.46
HDL cholesterol, mmol/l (mean ± SD)	1.22 ± 0.43	1.19 ± 0.38	0.17
Triglycerides, mmol/l (median, IQR)	1.82 (1.18–2.63)	1.52 (1.05–2.19)	<0.0001
Blood glucose, mmol/l (mean ± SD)	5.36 ± 1.46	5.03 ± 1.00	<0.0001
Lipodystrophy	330 (43.5)	235 (30.8)	<0.0001
$CD4^+$ cell count, cells/μl (median, IQR)	442 (284–642)	581 (429–770)	<0.0001
Vascular age (median, IQR)	51.0 (42.0–64.0)	48.0 (40.0–60.0)	0.01
AIP	0.20 ± 0.35	0.13 ± 0.31	<0.0001


P <0.001
CD4 +
700
600
500
400
300
200
100
0
442
581
2005
2011

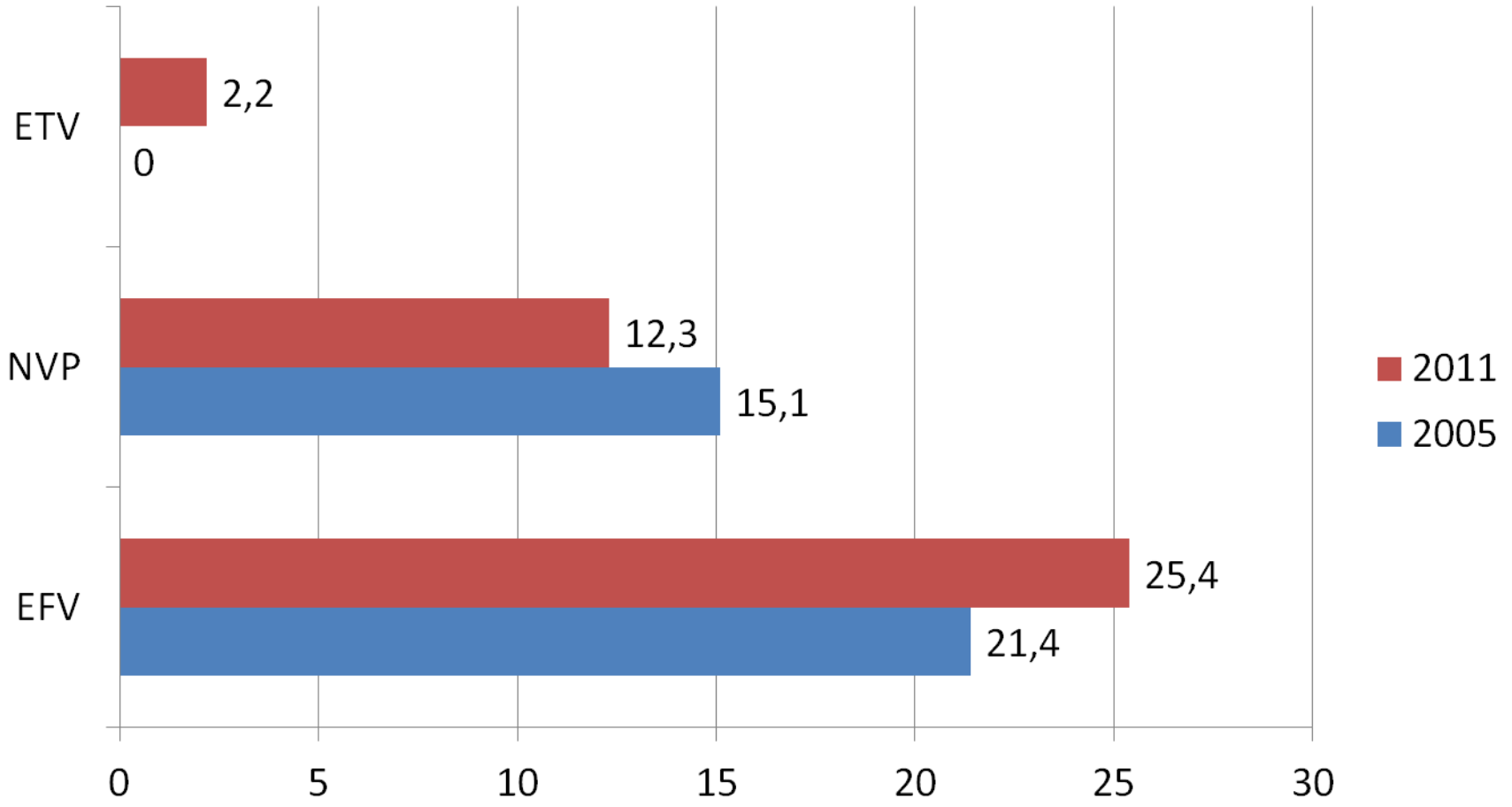
ART: NRTIs 2005 vs 2011

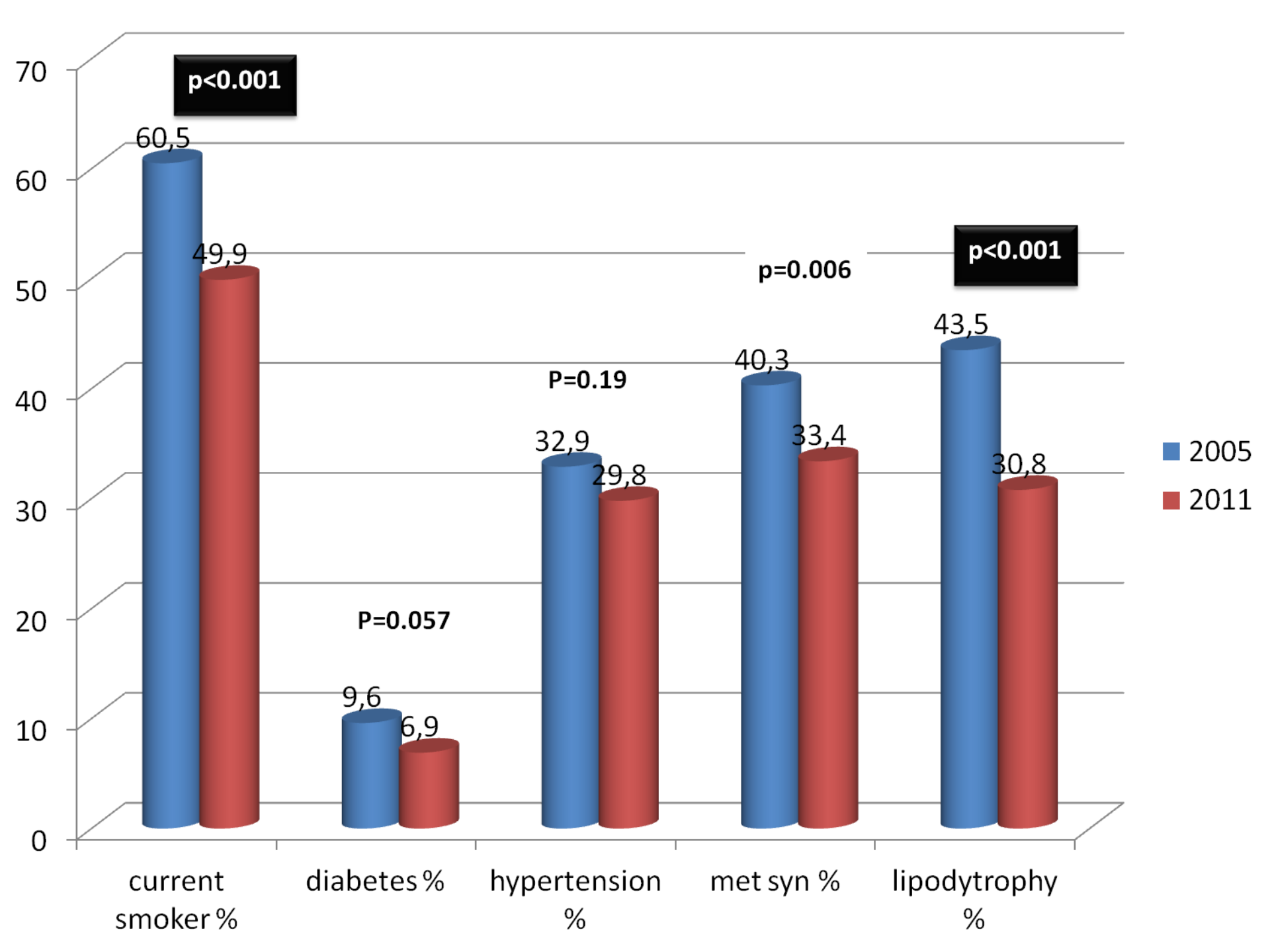


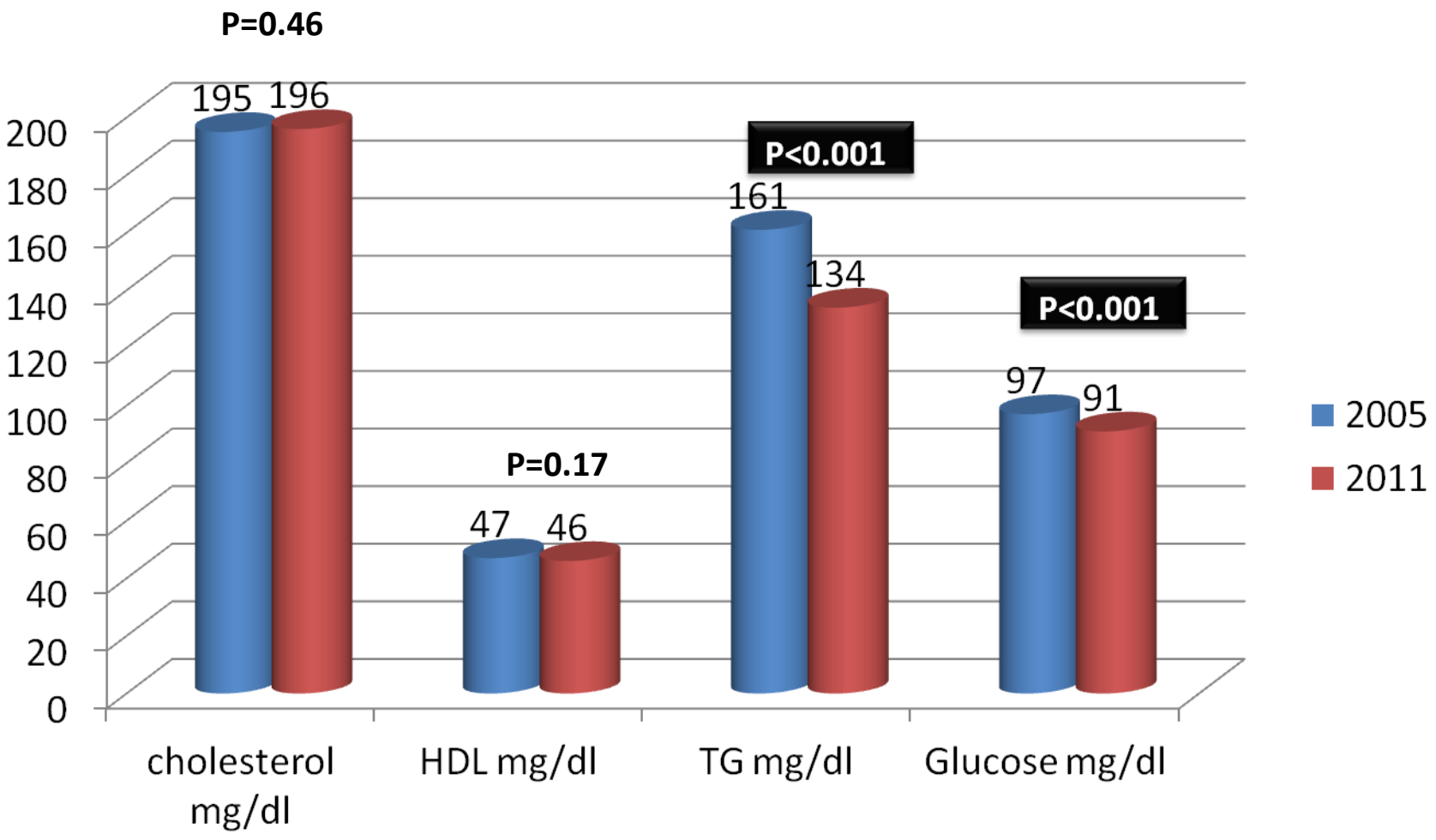
ART: PIs 2005 vs 2011

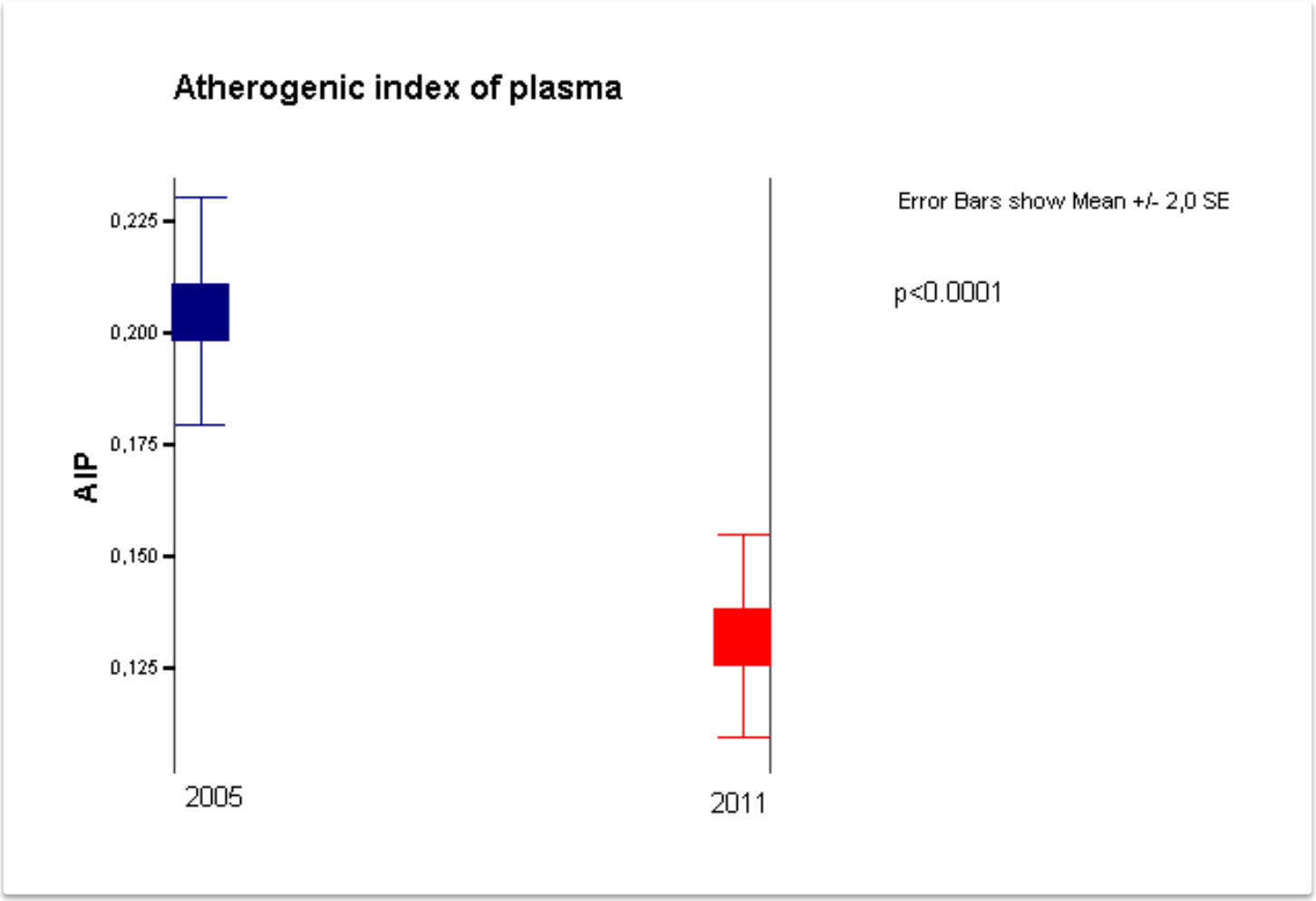


ART: NNRTIs 2005 vs 2011



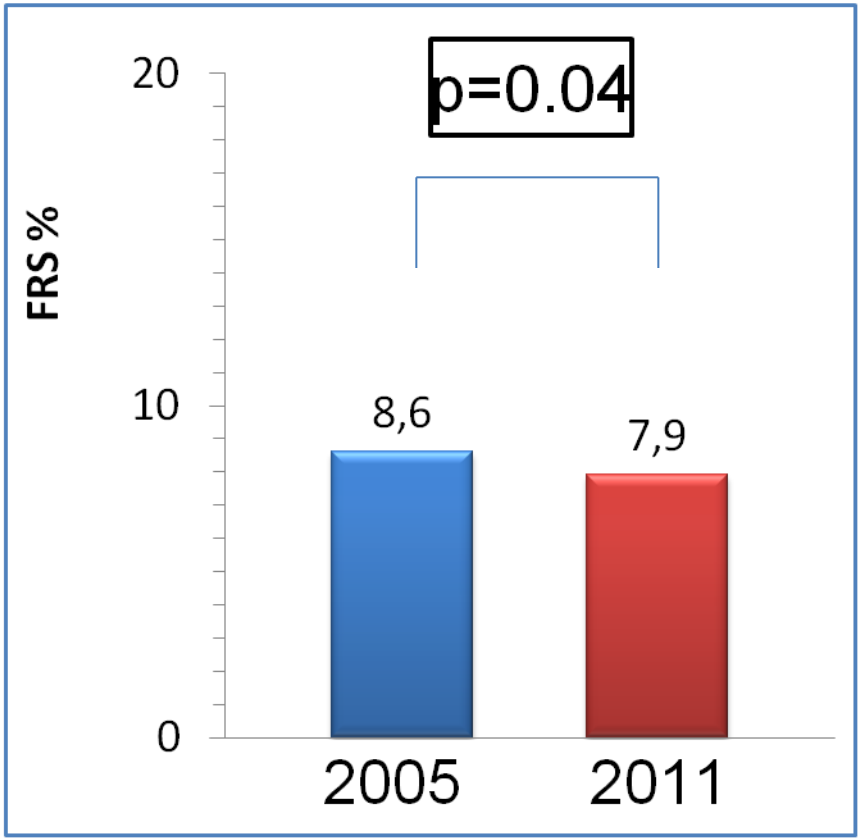

70
60
50
40
30
20
10
0
p<0.001
60,5
49,9
P=0.057
9,6
6,9
P=0.19
32,9
29,8
p=0.006
40,3
33,4
p<0.001
43,5
30,8
2005
2011
current smoker %
diabetes %
hypertension %
met syn %
lipodytrophy %


P=0.46
195
196
200
180
160
140
120
100
80
60
40
20
0
P<0.001
161
134
P<0.001
97
91
P=0.17
47
46
2005
2011
cholesterol mg/dl
HDL mg/dl
TG mg/dl
Glucose mg/dl

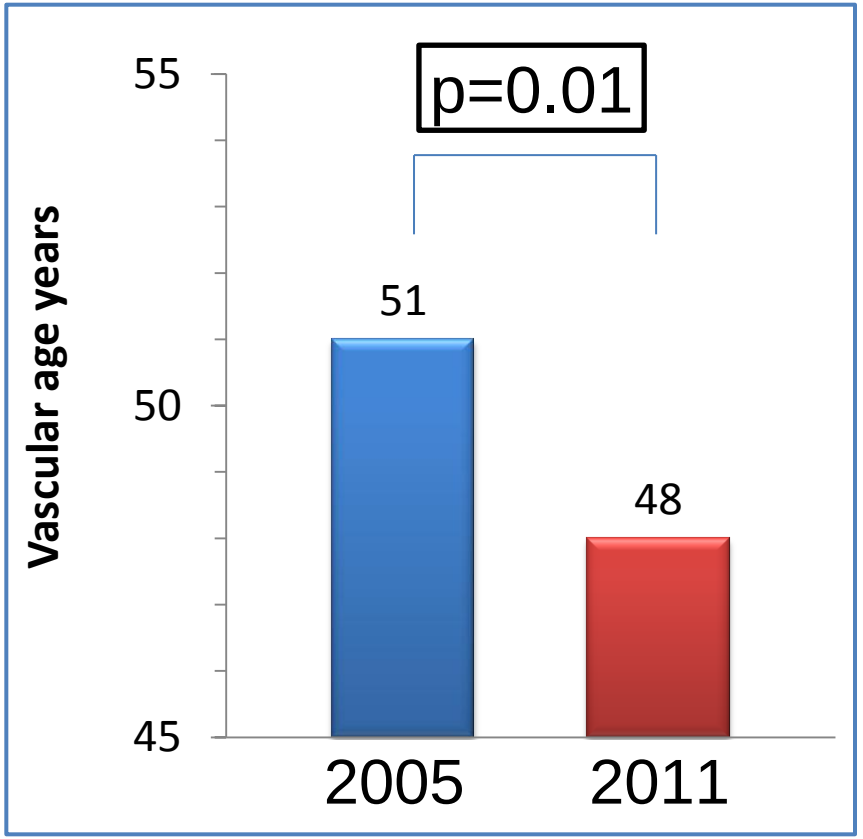


*(AIP)=log(TG/HDL-C) logarithmically transformed ratio of molar concentrations of triglyceride and HDL-cholesterol [Dobiášová M., *Clin. Biochem. 2001. 34: 583–588.]*

10-years global CVD risk (FRS %)



Vascular age



Comparing HIV-infected patients observed in routine clinical care in 2005 and in 2011:

- immunologic improvement
- smoking habit, although it remains highly prevalent, is lower in the last years
- new antiretroviral drugs have a lower impact on glucose and triglycerides metabolism
- the prevalence of lipodystrophy, is substantially reduced
- the global CV risk profile and the vascular age are all more favorable in 2011
- In the last few years, the relevant efforts made in favouring educational and clinical interventions on metabolic aspects in HIV infected patients, as well as the availability of newer drugs likely contributed to improve CV risk profile.

Grazie per l'attenzione