Principales factores implicados en la enfermedad cardiovascular en la actualidad y estrategias para su prevención

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Disclosures

- Research Grant / Principal investigator:

  Gilead Sciences, MSD and ViiV Healthcare

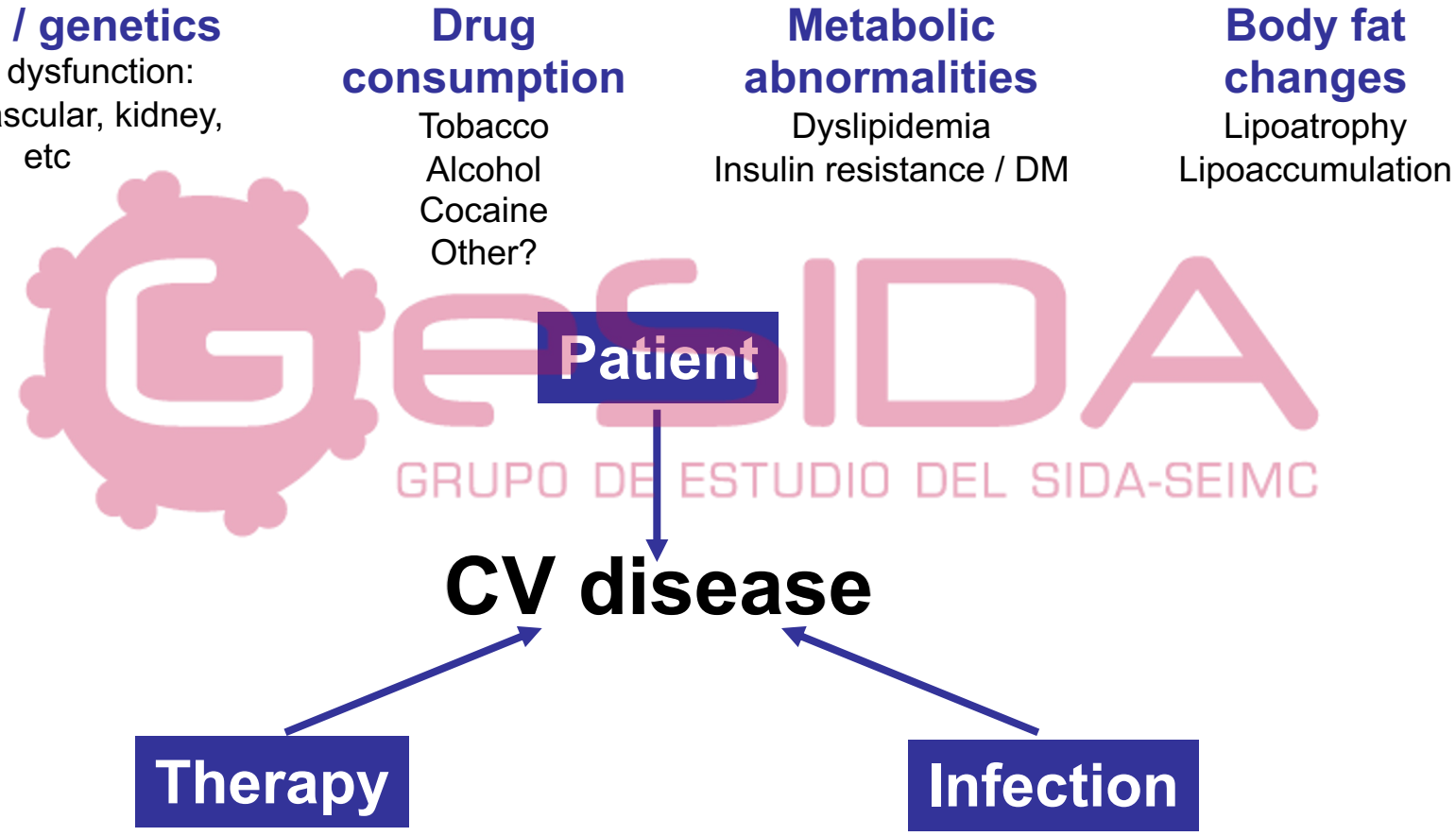
- Consultant:

  Gilead Sciences, Janssen, MSD and ViiV Healthcare

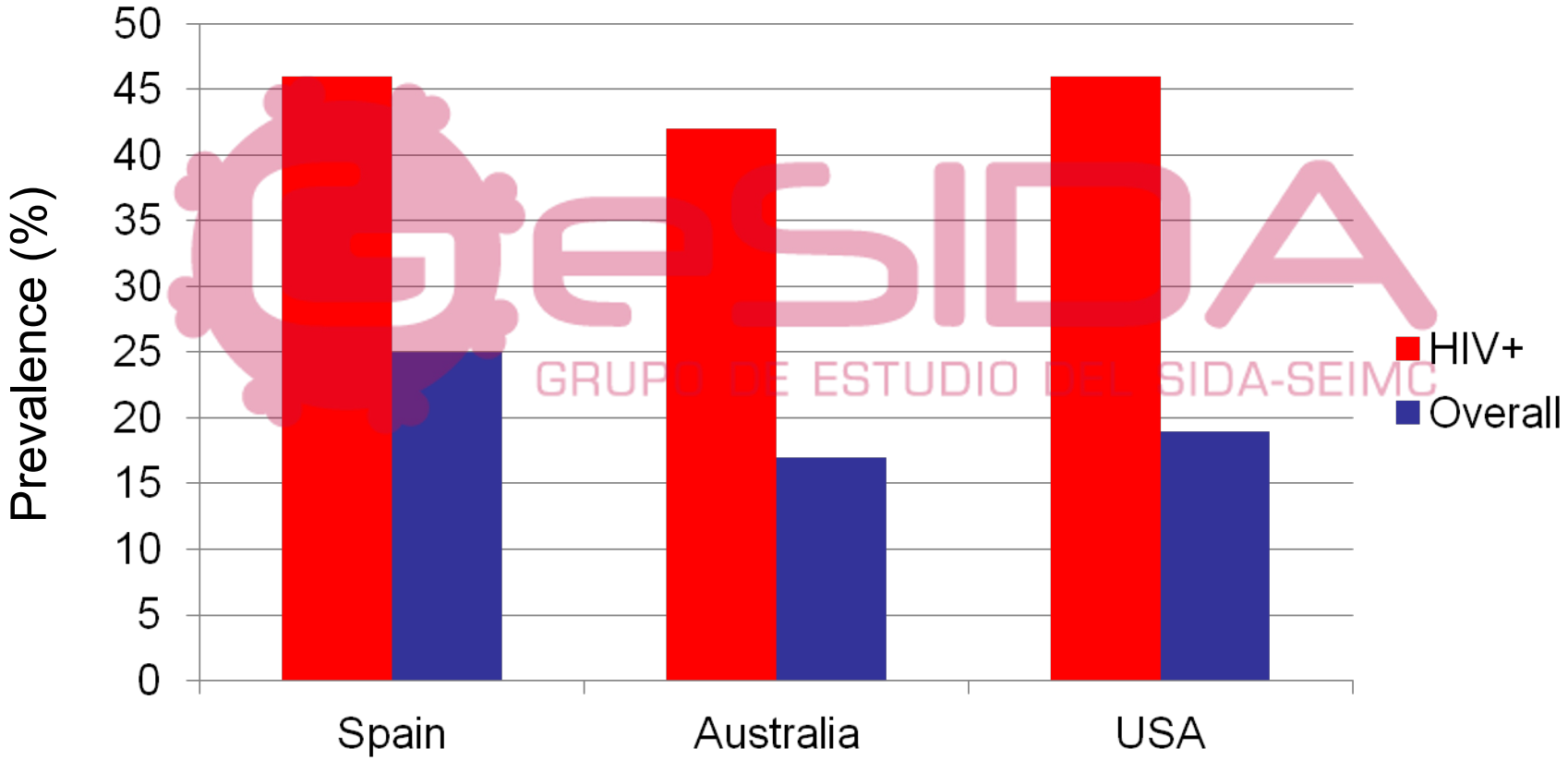
- Lectures:

  Gilead Sciences, Janssen, MSD and ViiV Healthcare

There are many factors contributing to a higher risk of CV disease in HIV-infected patients…

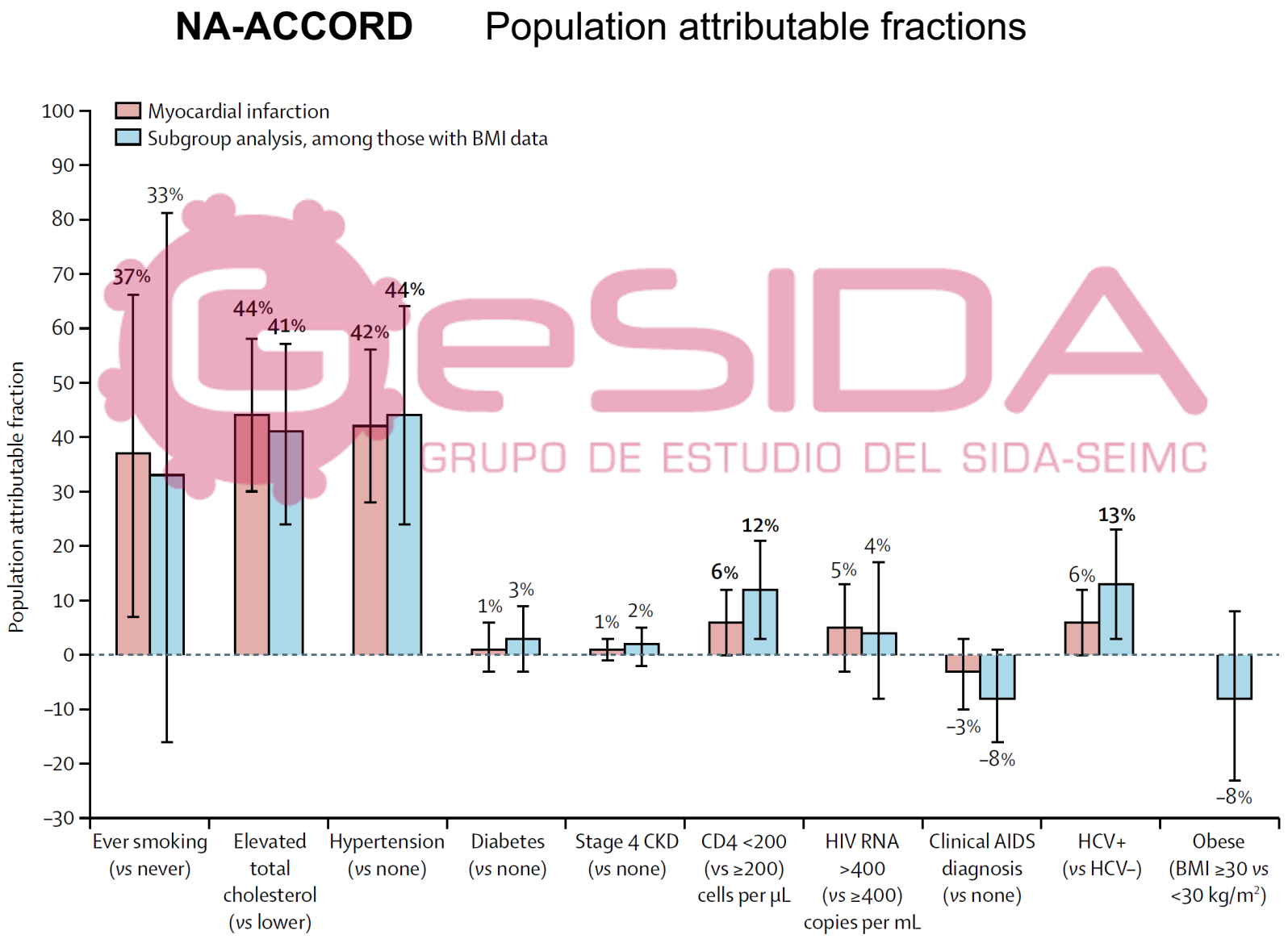


Smoking is two times more common in HIV patients than in the general population



Rodriguez-Martinez M. Rev Esp Com Sal 2010
Masia M et al. Enfer Infecc Microbiol Clin 2012
www.heartfoundation.org.au/hiv
Lifson AR et al. Curr HIV Rep 2012
Oh JY et al. The Open AIDS Journal 2012

Smoking is a major factor for CVD in PWH



Althoff KN et al. Lancet HIV 2019

Smoking contributes to myocardial infarction in HIV patients almost twice as much as in the overall population

Population attributable risk

	Smoking	Diabetes	Hypertension	Combination of all 3 factors
HIV+	54.35%	6.57%	9.07%	60.00%
HIV-	30.58%	17.24%	38.81%	68.75%

Calvo M et al. HIV Med 2013

Negative interaction between alcohol and HIV infection

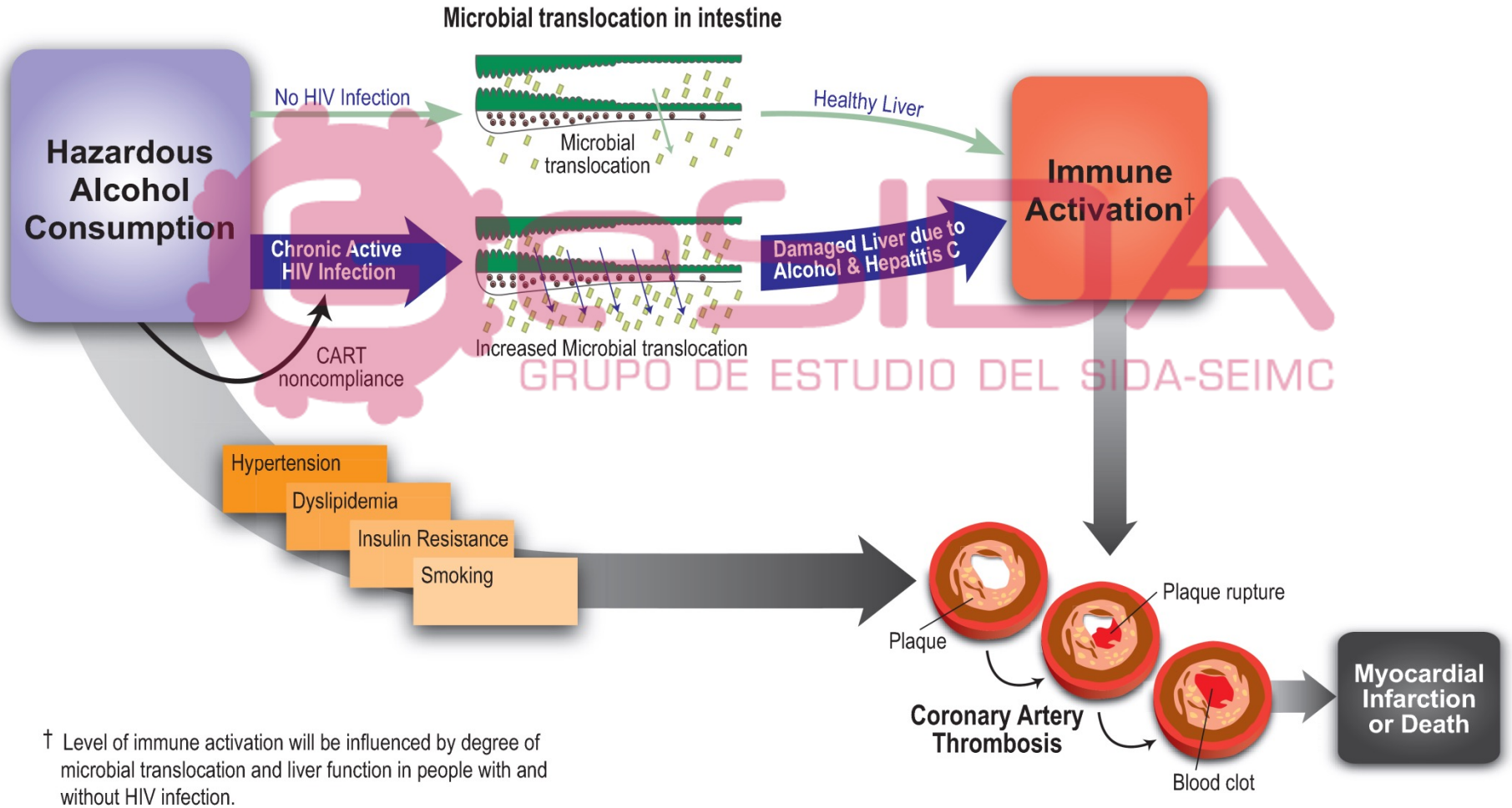
VACS Cohort

	OR (95% CI) [1]	
Alcohol consumption	**HIV+ (n=2143)**	**HIV- (n=2321)**
Infrequent and moderate	1.0 (ref)	1.0 (ref)
Hazardous [2]	1.43 (1.05-1.94)	0.97 (0.75-1.27)
Abuse and dependence [3]	1.55 (1.07-2.33)	0.98 (0.71-1.35)
Past vs. Current [4] drinkers	1.33 (0.99-1.80)	1.30 (1.01-1.67)

1. Adjusted model
2. According to National Institute on Alcoholism and Alcohol Abuse guidelines: >14 drinks per week or ≥6 drinks in 1 occasion less than monthly
3. According to ICD-9
4. Past (>12 months without a drink) vs. Current (≤12 months without a fdrink or currently drinking)

Freiberg MS et al. J Acquir Immune Defic Synd 2010

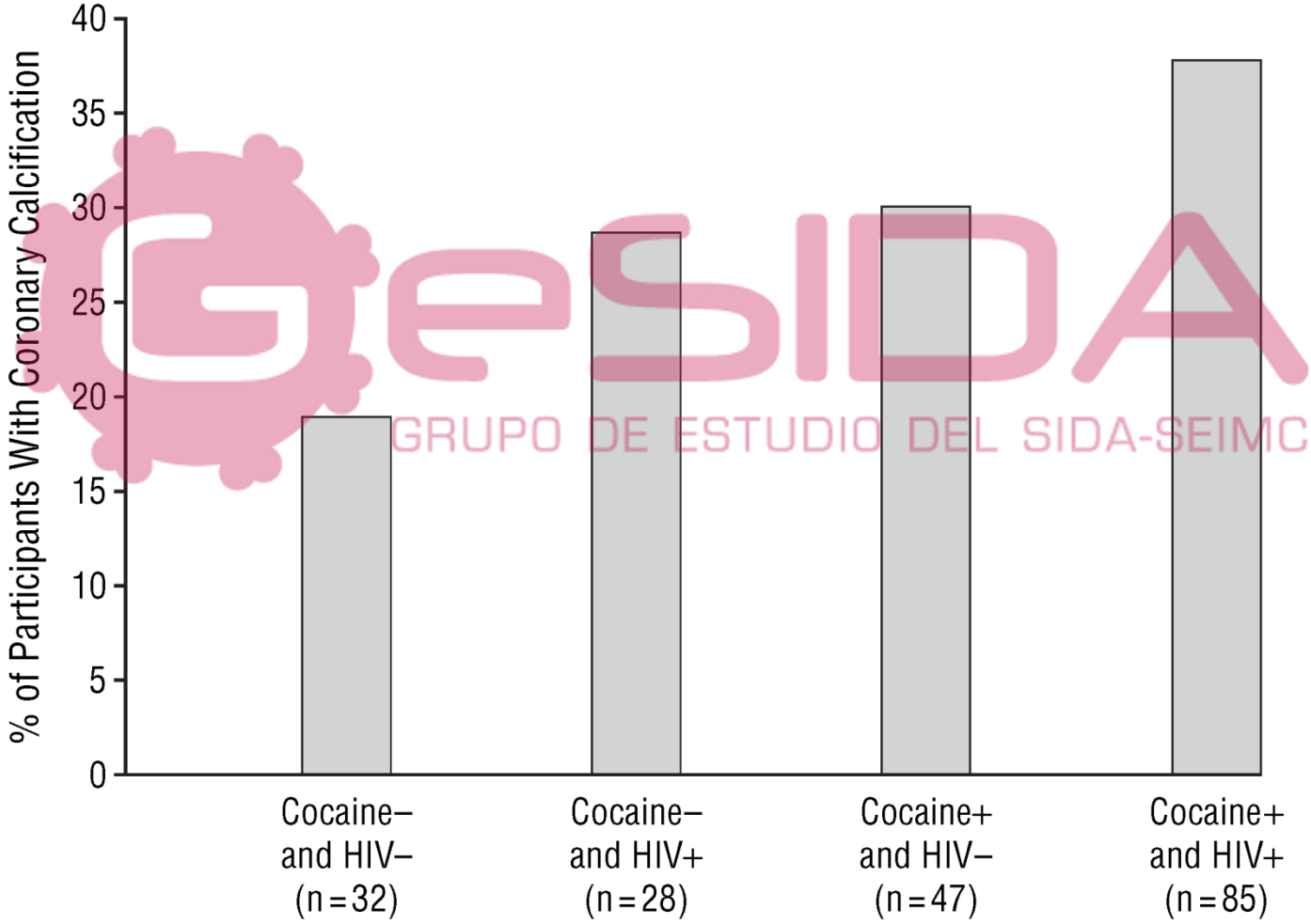
Potential mechanism underlying alcohol and HIV interaction on CV disease



Freiberg MS, Kraemer KL. Alcohol Research & Health 2010

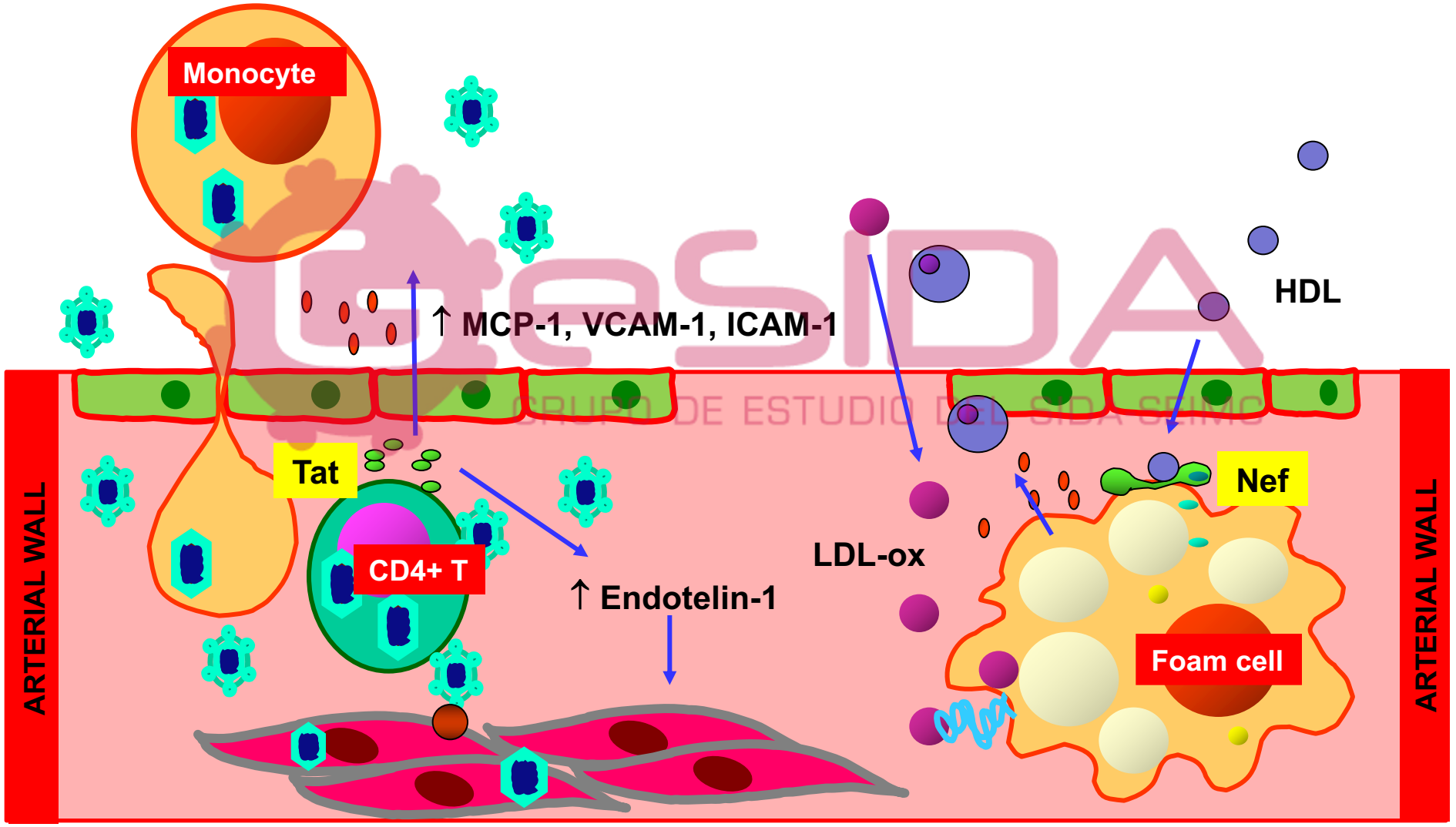
Negative interaction between cocaine use and HIV infection

Baltimore HIV Cohort



Lai S et al. Arch Intern Med 2005

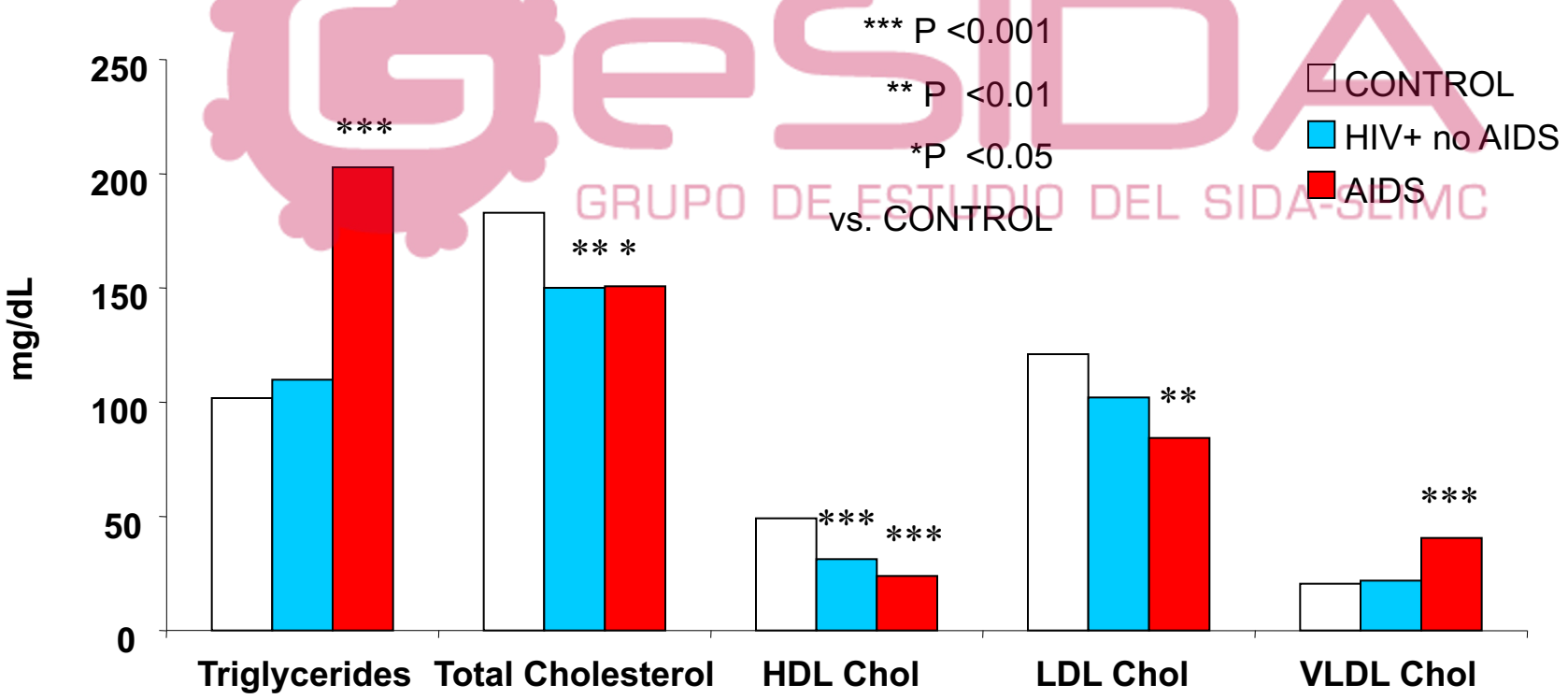
HIV infects arterial wall and promotes atherosclerosis



Eugenin EA et al. Am J Pathol 2008; Liu K et al. Am J Physiol Lung Cell Mol Physiol 2005;
Park IW et al. Blood 2001; Kanmogne GD et al. Biochem Biophys Res Commun 2005
Rasheed S et al. PLoS ONE 2008; Parra S et al. Atherosclerosis 2007

When ART was not available, HIV infection led to ↓ HDL-cholesterol and ↑ triglycerides

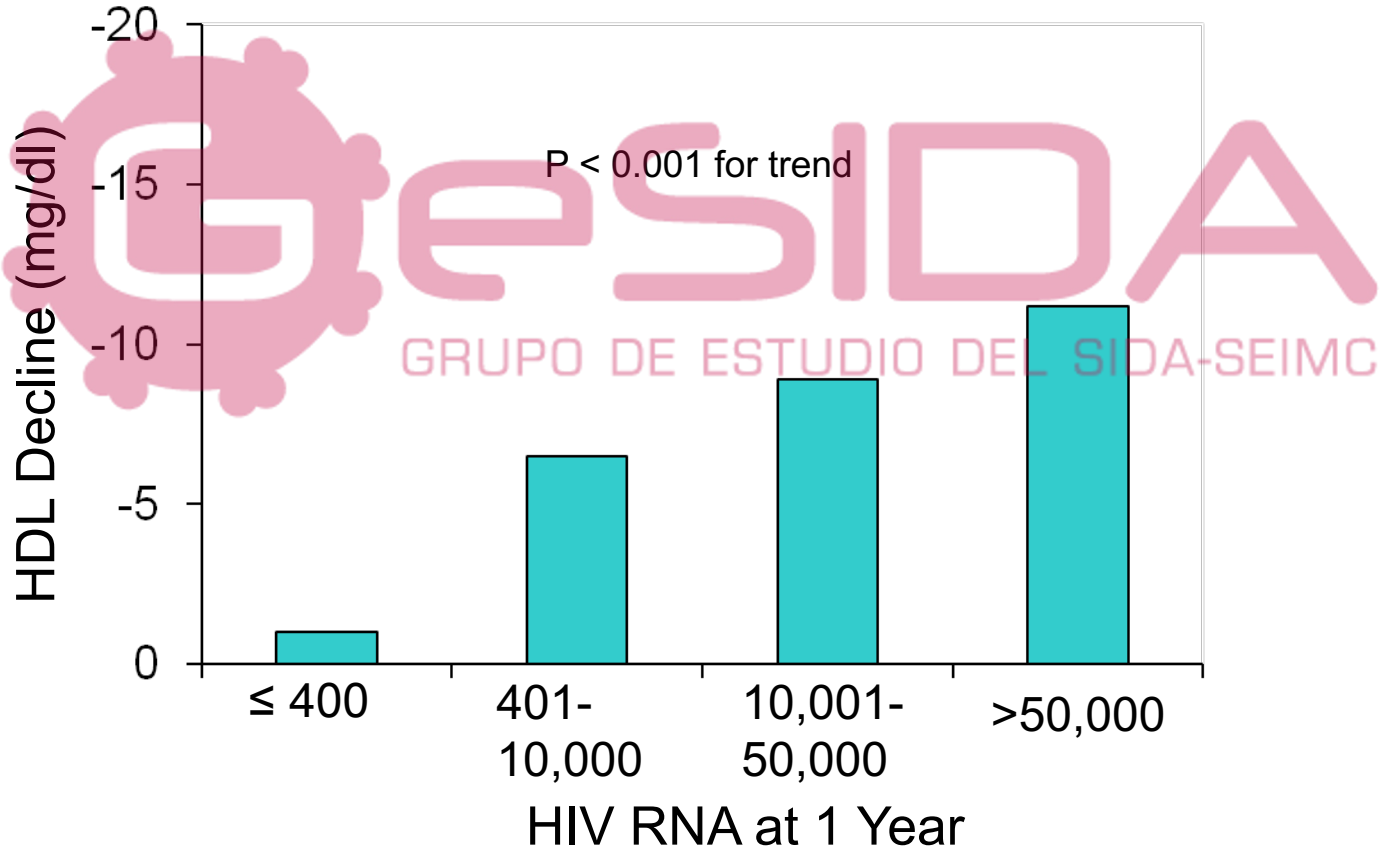
Early ↓ HDL, later ↓ LDL, then ↑TG & VLDL.
↓ HDL may be more pro-atherosclerotic than ↓ TC or LDL are protective



Grunfeld C et al. J Clin Endocrinol Metab 1992

When effective ART is discontinued, uncontrolled HIV leads to further ↓ HDL-cholesterol

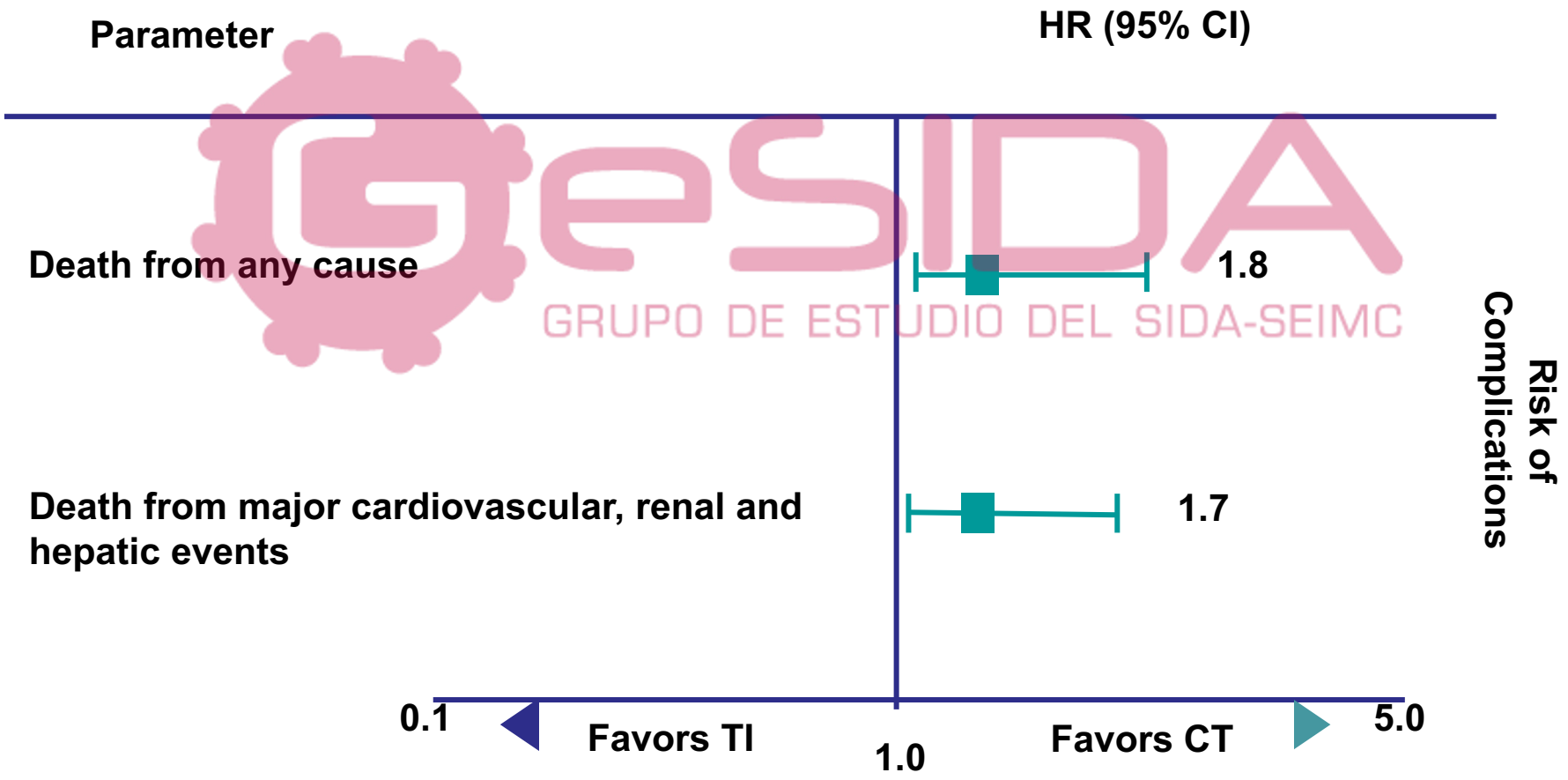
SMART Study



Neaton J. Personal communication

When effective ART is discontinued in PWH with preserved CD4 cells, ↑risk of CV events & death

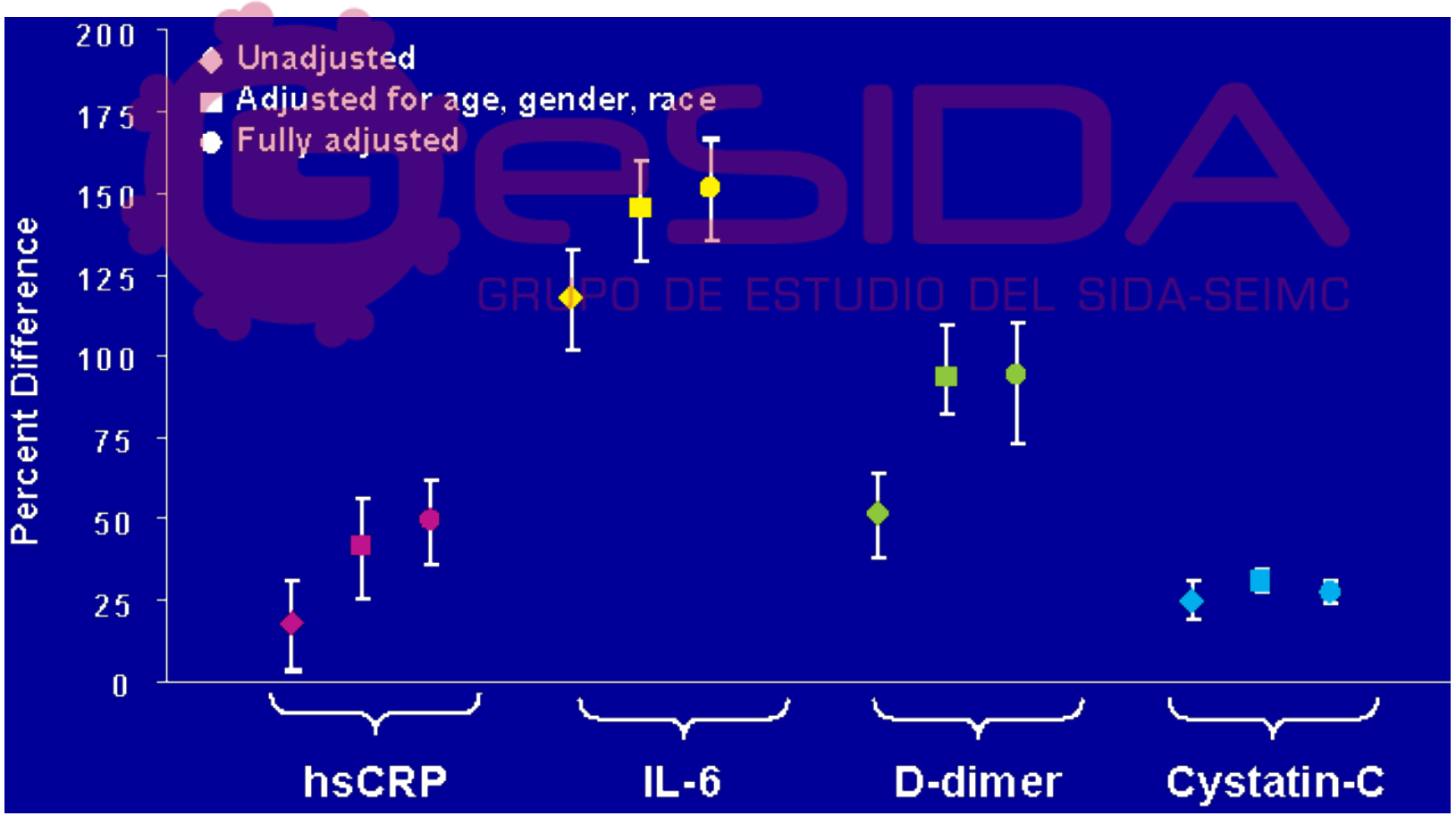
SMART Study



El-Sadr W, et al. N Engl J Med. 2006;355:2283-2296.

Inflammatory markers even in treated HIV+ patients are higher than in HIV- controls

SMART virologic suppression arm (n=494) vs. Multi-Ethnic Study of Atherosclerosis (MESA) (n=5386)



Neuhaus J et al. J Infect Dis 2010; 201:1788-1795

Association between inflammatory and coagulation biomarkers with mortality and CV disease

SMART Study

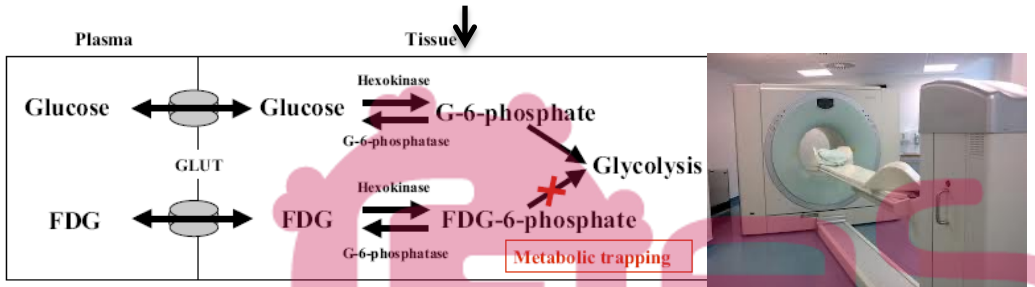
Biomarker	Overall mortality (n=85)		CV disease (n=136)	
	OR	*P*	OR	*P*
Ultrasensitive CRP	3.5	0.004	1.6	0.20
IL-6	12.6	<0.0001	2.8	0.003
Amyloid A	2.3	0.08	1.6	0.12
Amyloid P	1.1	0.90	2.8	0.002
D-dimer	13.3	<0.0001	2.0	0.06

ART Discontinuation → ↑Plasma HIV RNA → ↑Inflammatory & Coagulation markers

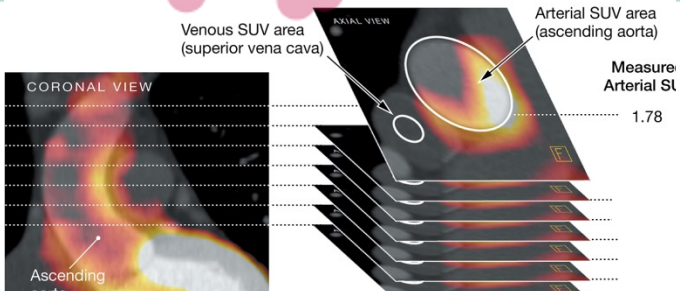
Kuller L et al. PLoS Med 2008; 5: e203

HIV+ patients have higher arterial inflammation than non-HIV controls

Aortic 18FDG-PET TECHNIQUE:

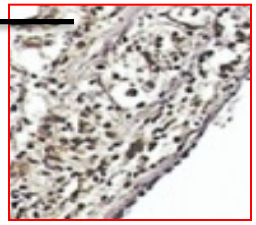


Aortic Target-to-Background Ratio (TBR) = **Mean Arterial Standardized Uptake Value** / **Mean Venous Standardized Uptake Value**

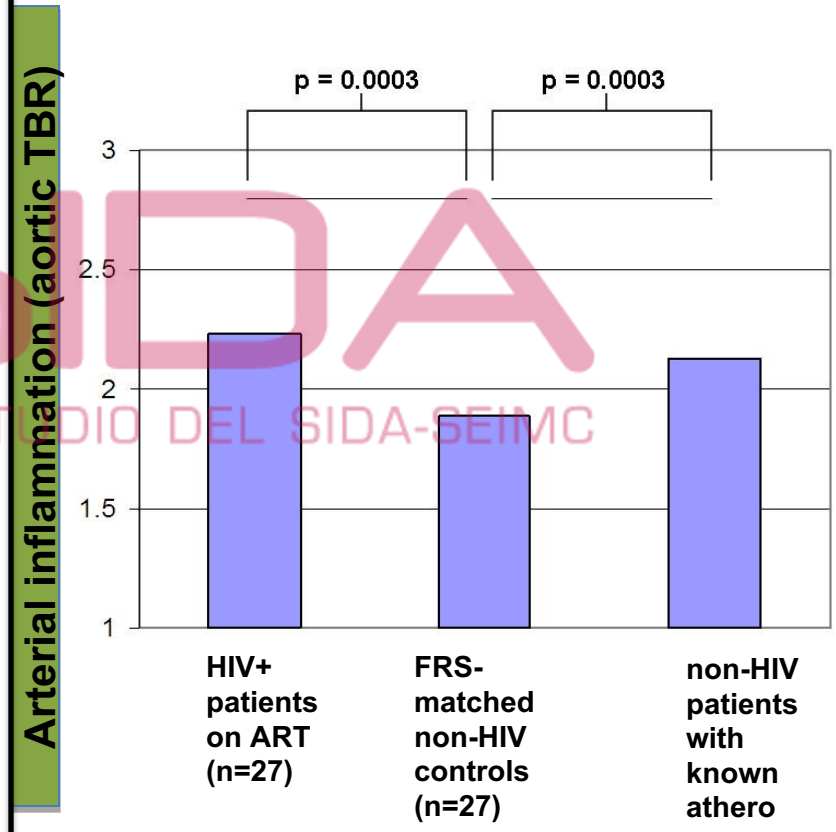


Arterial FDG uptake tracks with CD68+ mØ infiltration

mØ infiltrating artery with high FDG uptake



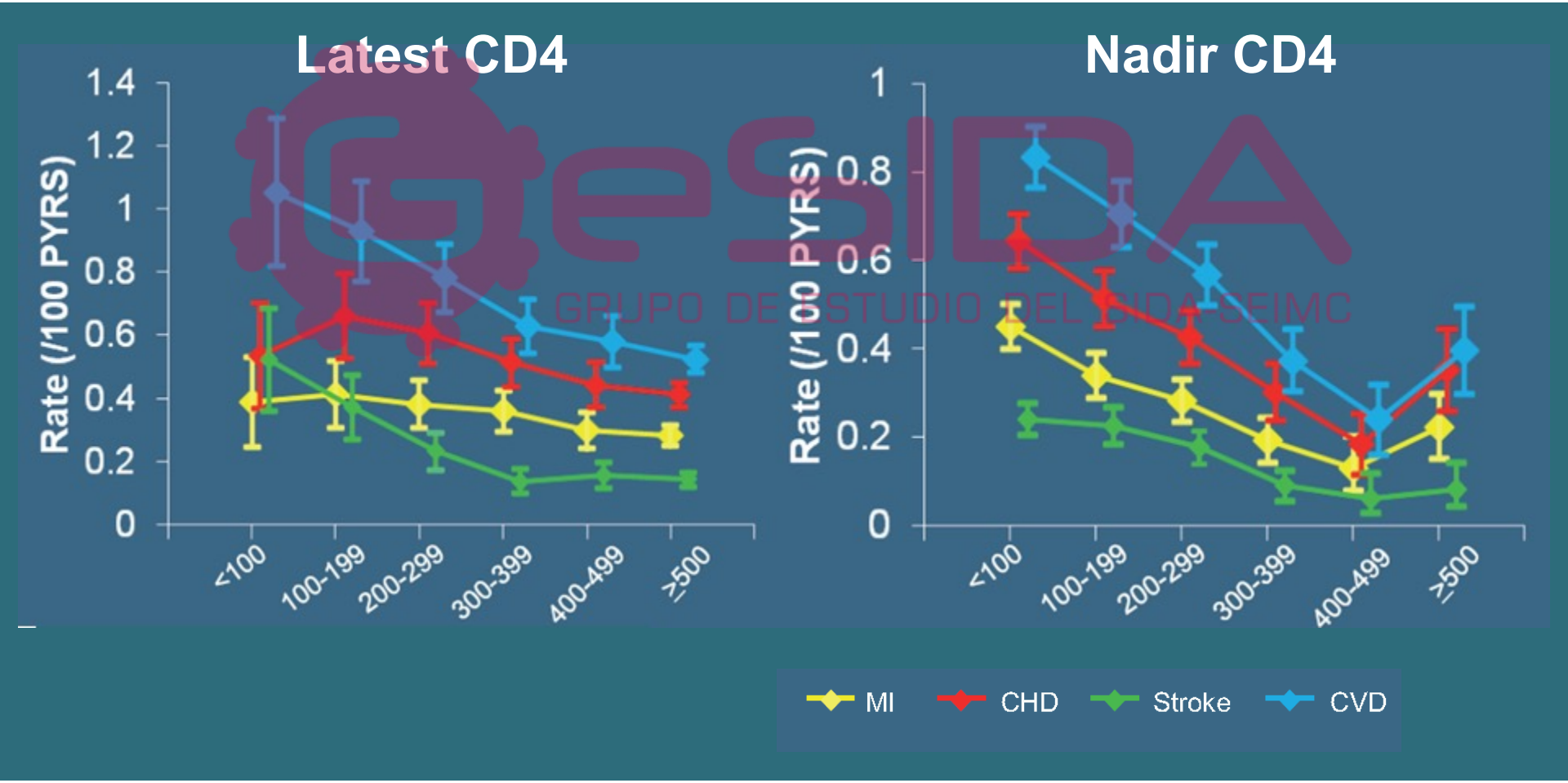
KEY FINDINGS:



Rudd JACC 2010; Rogers JACC CVI 2010; Subramanian JAMA 2012

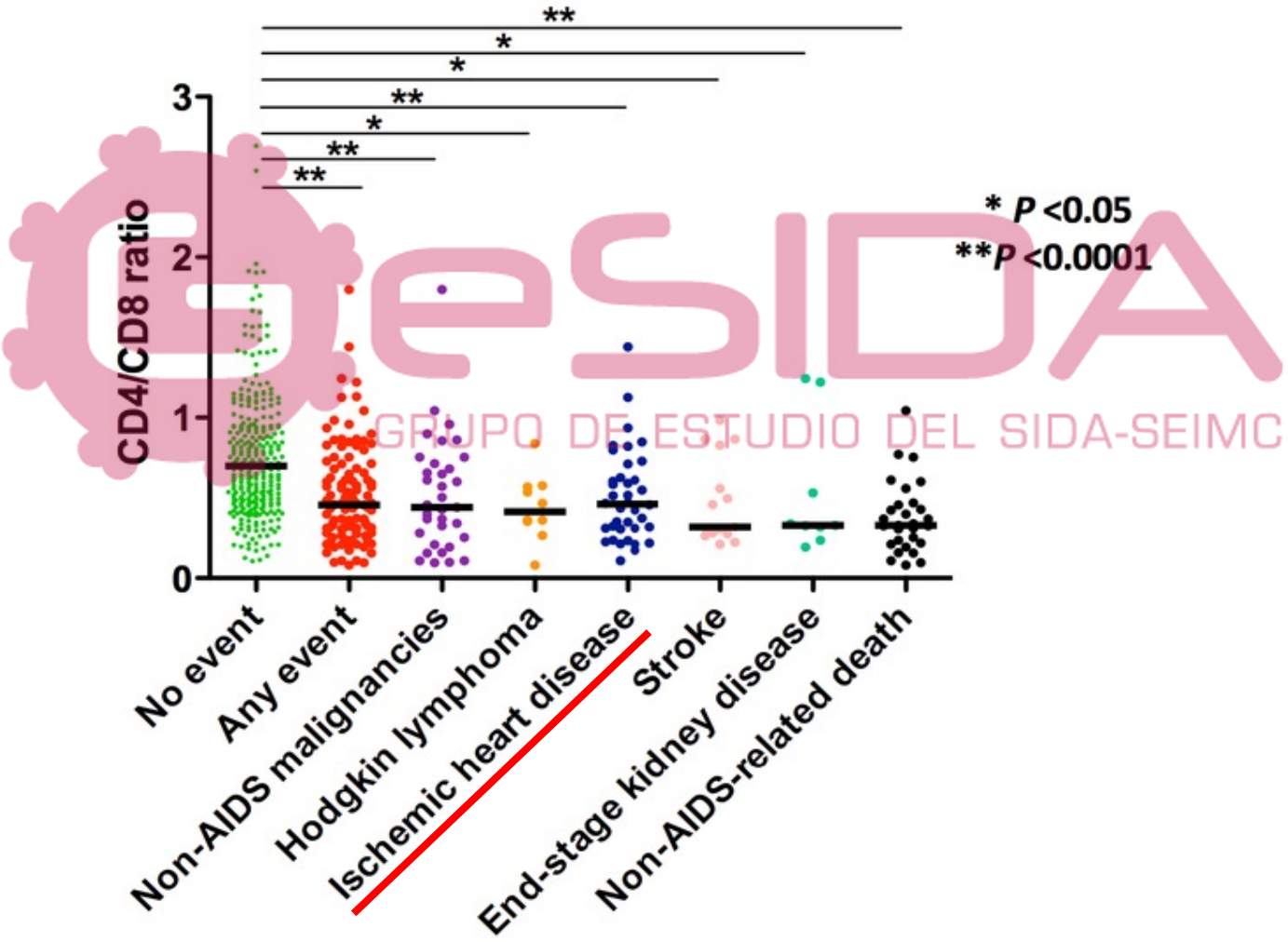
Lower CD4 cell counts associated with higher rates of CV disease

D:A:D Study



Sabin C et al. 19th CROI, Seattle 2012: poster 822

CD4/CD8 ratio is a simple marker of higher risk of non-AIDS events in treated HIV+ patients



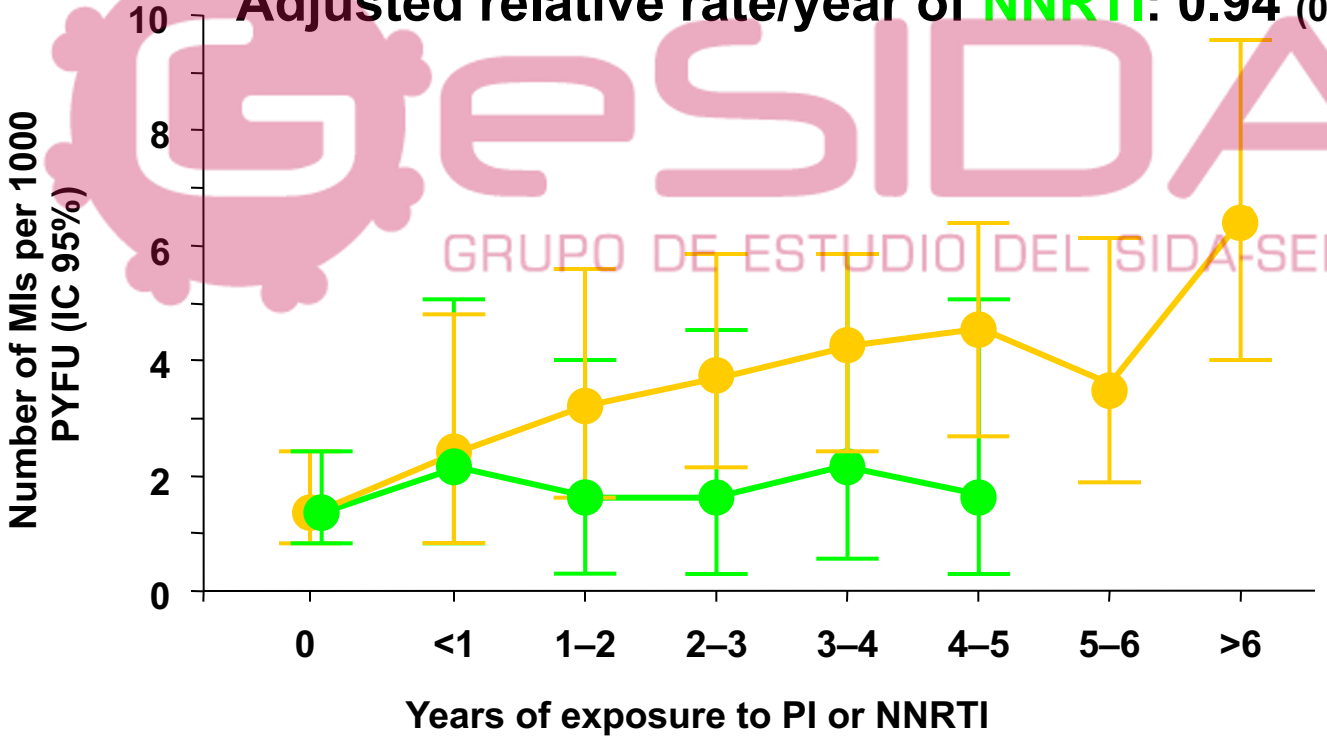
Serrano-Villar S, et al. PLoS ONE 2014

Higher risk of MI with PI exposure (but not with NNRTI exposure)

D:A:D study

Adjusted relative rate/year of PI: 1.15 (1.06, 1.25)

Adjusted relative rate/year of NNRTI: 0.94 (0.74, 1.19)



Friis-Møller, et al. N Engl J Med. 2007;326:1723-1735

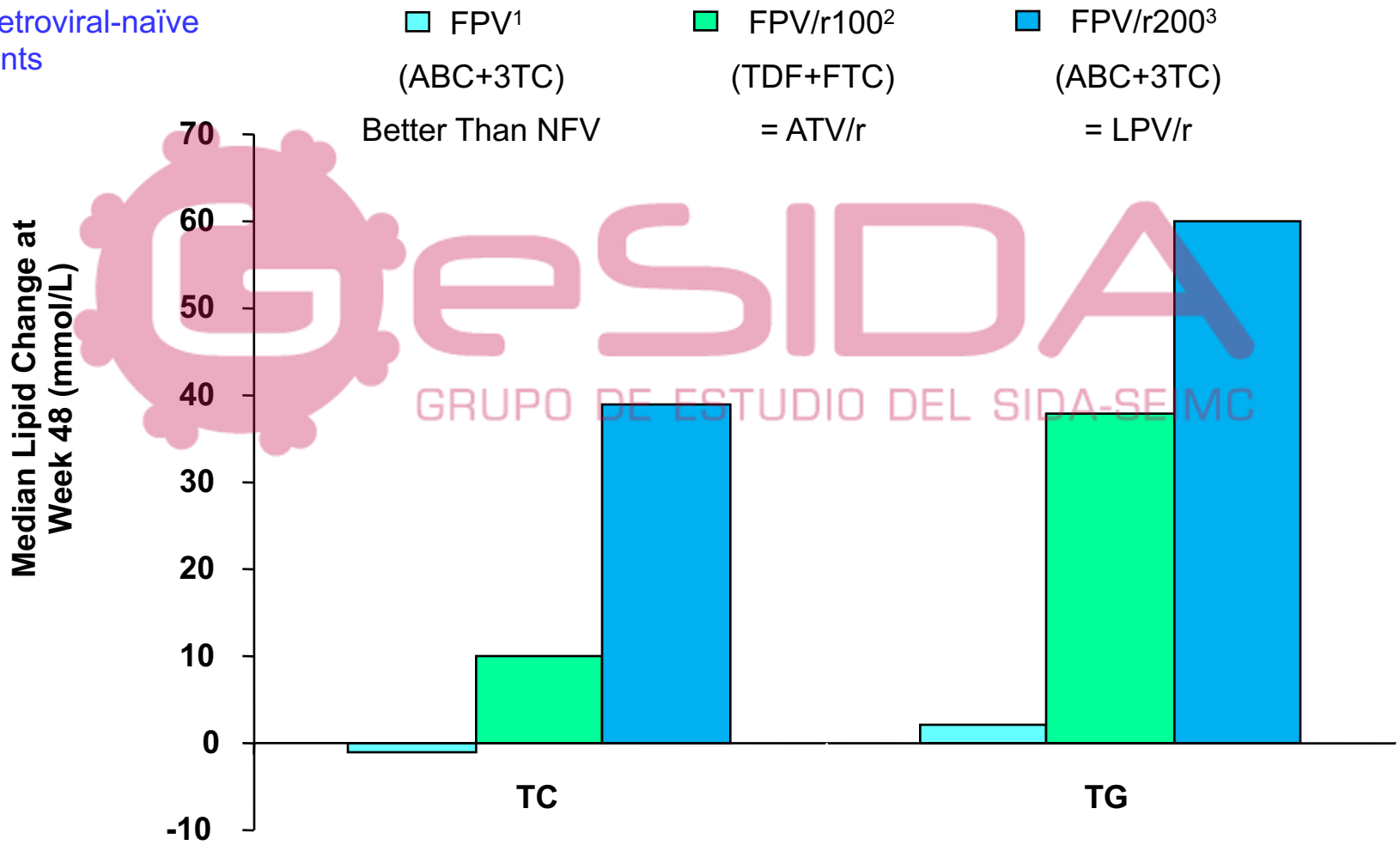
Approximately one third of the PI-related excess risk for MI in D:A:D is due to DM, HT, or lipids

	Adjusted Model 1		Adjusted Model 2	
	Relative Rate (95% CI)	P Value	Relative Rate (95% CI)	P Value
Exposure to PIs (per year)	**1.16 (1.10-1.23)**	**<0.001**	**1.10 (1.04-1.18)**	**0.002**
Age (per 5 yr)	1.39 (1.31-1.46)	<0.001	1.32 (1.23-1.41)	<0.001
Male sex	1.91 (1.28-2.86)	0.002	2.13 (1.29-3.52)	0.003
BMI >30 kg/m^2	1.70 (1.08-2.69)	0.02	1.34 (0.77-2.34)	0.31
Family history of CHD	1.56 (1.10-2.23)	0.01	1.40 (0.96-2.05)	0.08
Smoking status				
Current	2.83 (2.04-3.93)	<0.001	2.92 (2.04-4.18)	<0.001
Former	1.65 (1.12-2.42)	0.01	1.63 (1.07-2.48)	0.02
Previous cardiovascular event	4.30 (3.06-6.03)	<0.001	4.64 (3.22-6.69)	<0.001
Diabetes mellitus	**-**	**-**	**1.86 (1.31-2.65)**	**<0.001**
Hypertension	**-**	**-**	**1.30 (0.99-1.72)**	**0.06**
Total cholesterol (per mmol/L increase)	**-**	**-**	**1.26 (1.19-1.35)**	**<0.001**
HDL cholesterol (per mmol/L increase)	**-**	**-**	**0.72 (0.52-0.99)**	**0.05**

D:A:D Study Group. Clin Infect Dis 2008

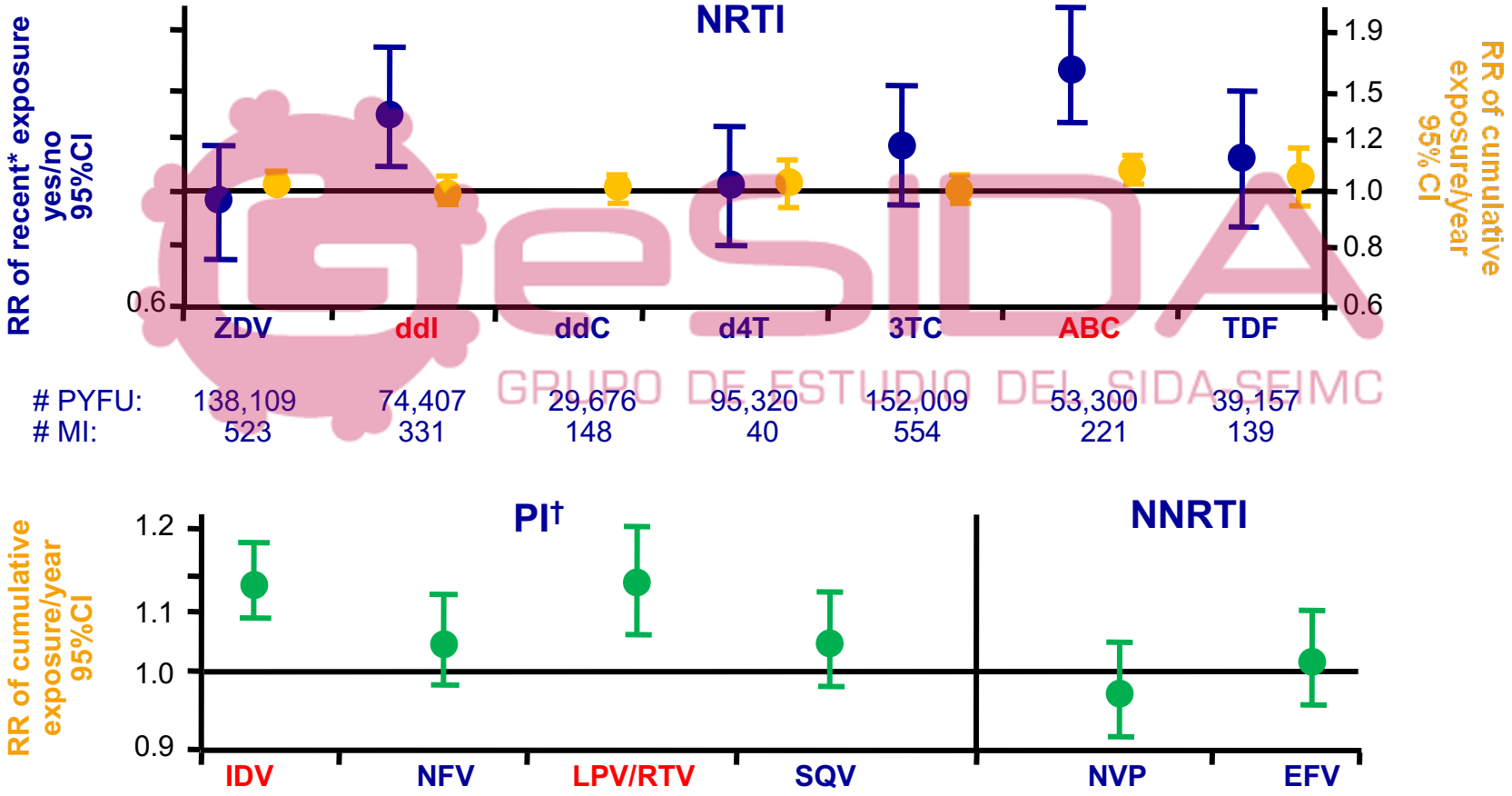
Impact of PIs on lipids depends on RTV-boosting dose

Antiretroviral-naïve patients



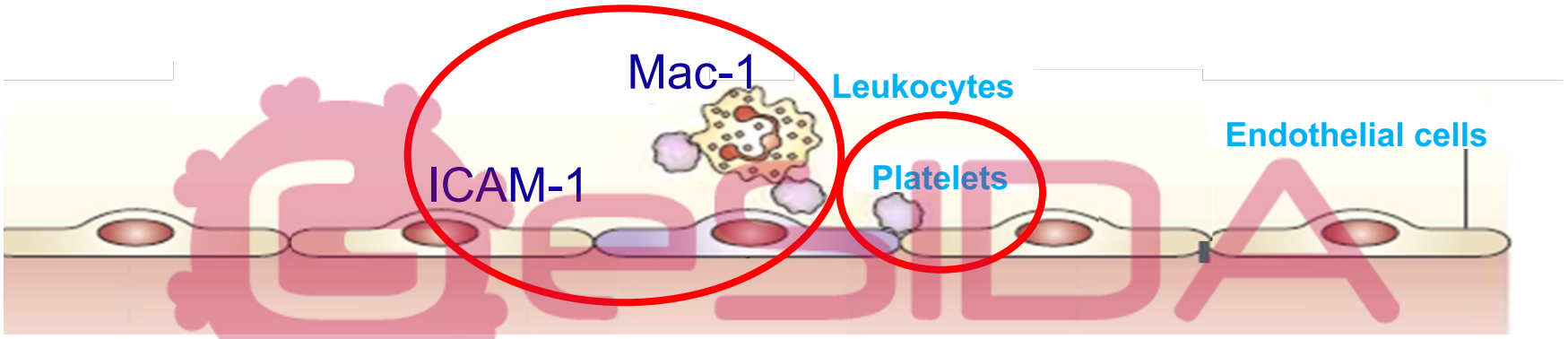
1. Nadler JP et al. 44th ICAAC 2004. Poster H-156 (NEAT Study)
2. Smith K et al. 46th ICAAC 2006; San Francisco. Abstract H-1670a (ALERT Study)
3. Eron J et al. XVI International AIDS Conference 2006; Abstract THLB0205 (KLEAN Study)

D:A:D Study: Recent and/or cumulative antiretroviral exposure and risk of MI



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

Pathogenic link between ABC and MI

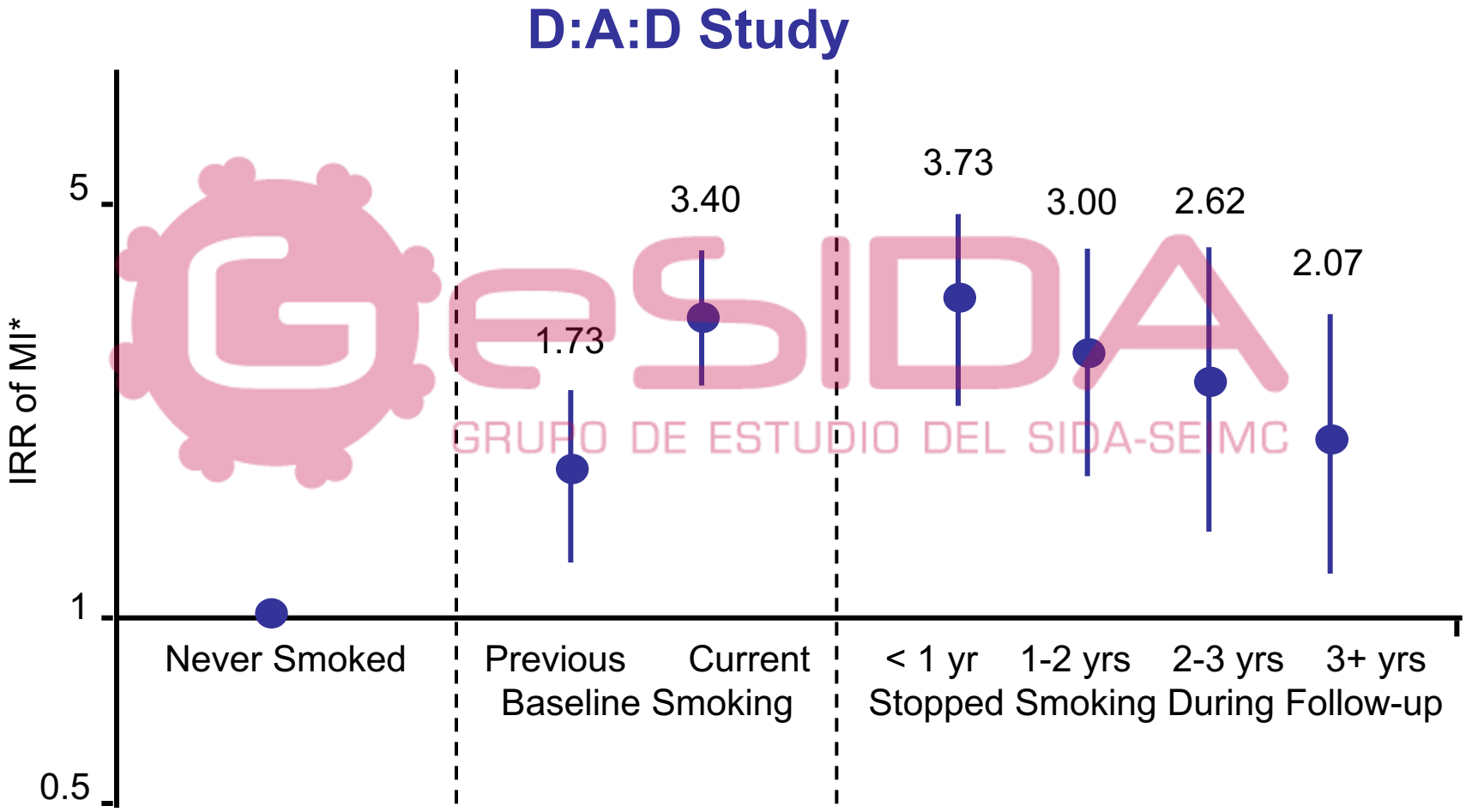


ABC *in vitro*:

- 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]

[1]de Pablo CROI 2010 #716;
[2]Baum CROI 2010 #717;
[3] Satchell CROI 2009 #151LB7;

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 K et al. CROI 2010. Abstract 124

Switching studies showing evidence for improvement in plasma lipids

- **PI switch:**

PI ⇒ABC (CNA30017)

PI ⇒NVP, EFV, o ABC (NEFA)

PI / PIr ⇒ ATV (SWAN)

LPV/r ⇒ ATVr (ATAZIP)

LPV/r or FPV//r ⇒ ATVr or DRV/r (LARD)

ATV/r ⇒ATV (ARIES)

LPV/r ⇒RAL (SWITCHMRK)

PI/r ⇒RAL (SPIRAL)

PI/r-based ⇒RPV/TDF/FTC (SPIRIT)

- **EFV switch:**

EFV ⇒NVP (SIROCCO)

EFV ⇒ETV (SWITCHING, SWITCH-EE)

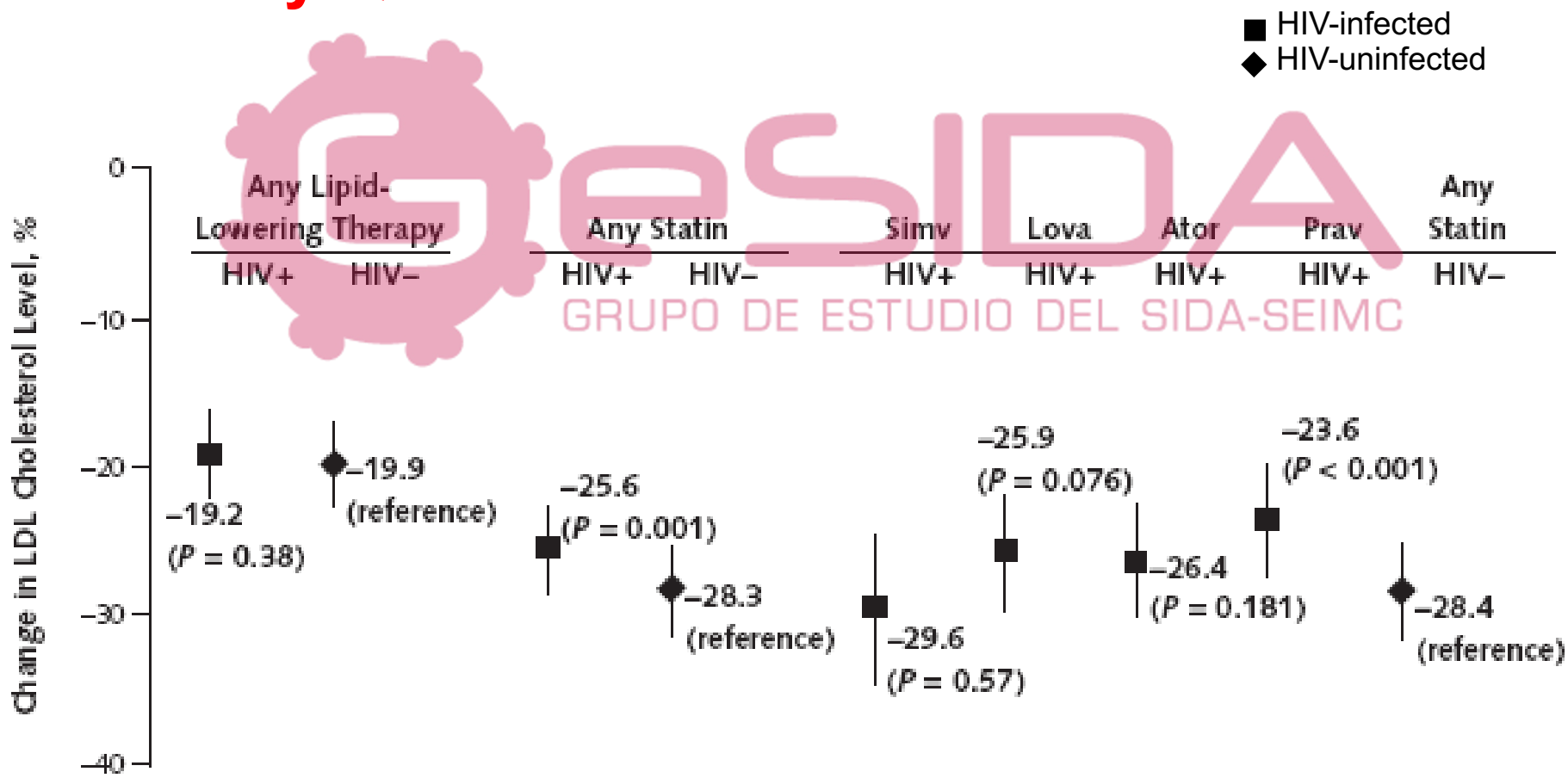
- **AZT or ABC switch:**

AZT/3TC ⇒TDF/FTC (SWEET)

ABC/3TC ⇒TDF/FTC (ROCKET)

How well do statins work to lower LDL-cholesterol in HIV+ patients?

Actually Quite Good!



Silverberg M et al. Ann Int Med 2009

Approximate Dose Equivalency of Statin LDL-C Efficacy

Dose of Agent (mg/day)

Rosuva*	Atorva*	Simva	Pitava	Lova	Prava	Fluva	Approx ↓LDL-C
		10	1	20	40†	40	28-34%
5	10†	20†	2†	40†	80	80†	35-42%
10†	20	40	4	80			39-47%
20	40	(80)					46-52%
40	80						51-55%

*Atorvastatin and rosuvastatin may be *more* effective (½ and 1 doubling, respectively).
†Most commonly used dose in United States.

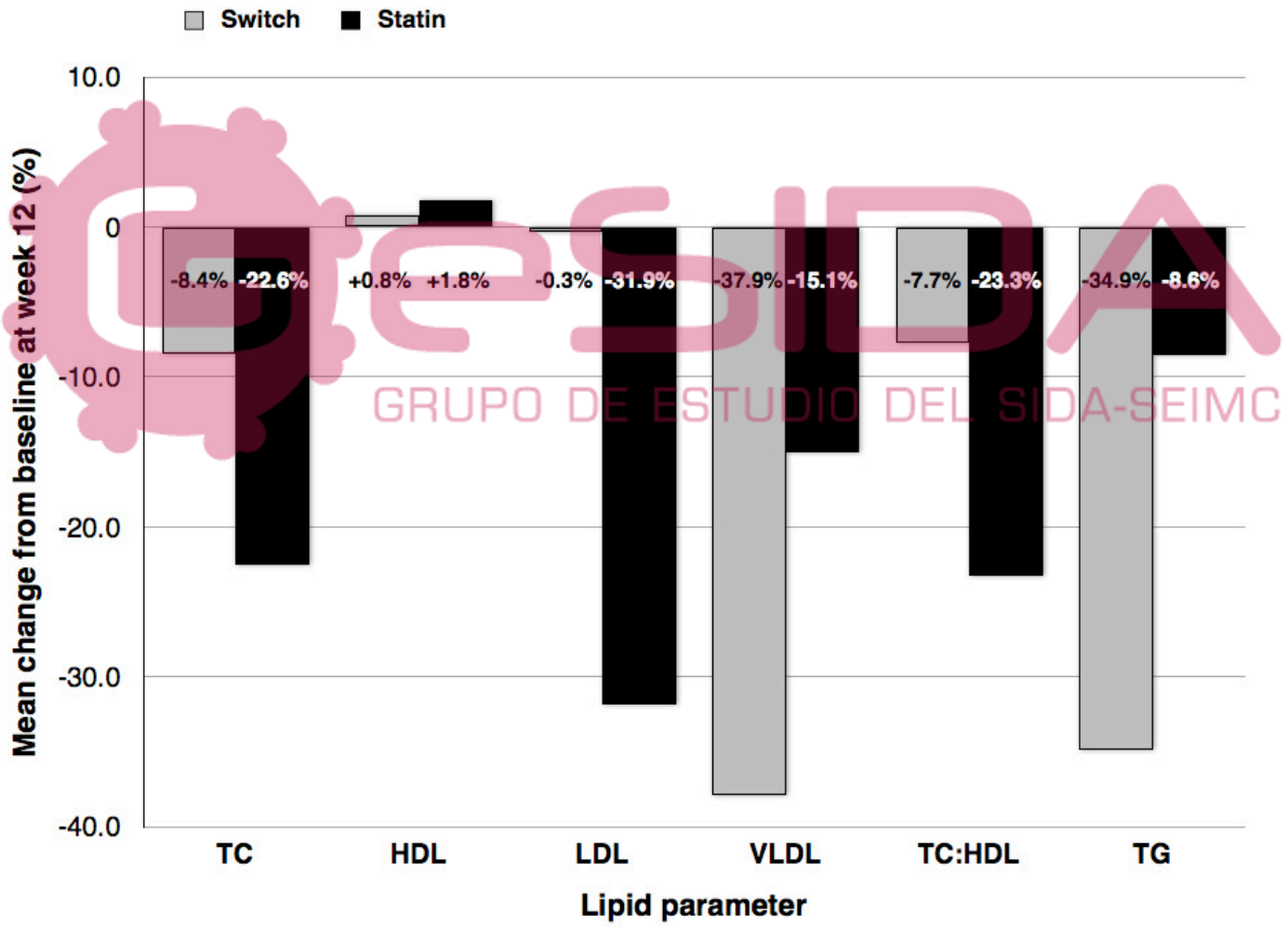
Adapted from: Roberts WC. *Am J Cardiol*. 1997;80:106-107. Stein E, et al. *J Cardiovasc Pharmacol Therapeut*. 1997;2:7-16. Rosuvastatin PI, Pitavastatin PI.

Potential for drug-drug interactions between statins and antiretrovirals

	Non-HIV drugs	ATV	DRV	LPV	RTV [ii]	EFV	ETV	NVP	MVC	RAL
CARDIOVASCULAR DRUGS	atorvastatin	↑	↑	↑	↑	↓	↓	↓*	↔	↔
	fluvastatin	↔*	↔*	↔*	↔*		↑*		↔*	↔*
	pravastatin	↔*	↑	↔	↔	↓	↓*	↔*	↔	↔
	rosuvastatin	↑	↑*	↑	↑	↔	↑*	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓	↓*	↓*	↔	↔
	amlodipine	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔
	diltiazem	↑[iii]	↑*	↑	↑	↓	↓*	↓	E*	↔
	metoprolol	↑*	↑*	↑*	↑*	↔*	↔*	↔*	↔*	↔*
	verapamil	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	E*	↔*
	warfarin	↑ or ↓*	↓	↓	↓	↑ or ↓*	↑*	↑ or ↓*	↔*	↔*

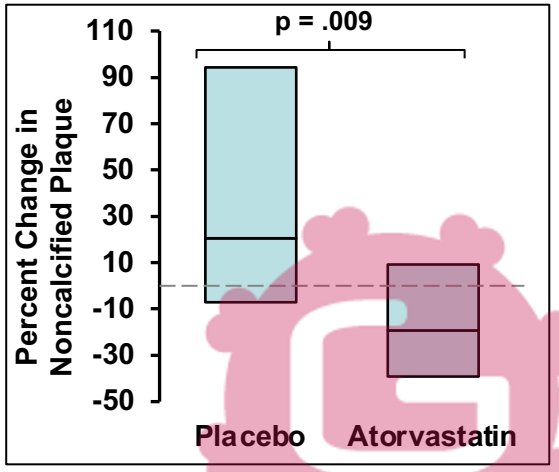
http:// www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EACSGuidelines-v6.1-English-Nov2012.pdf

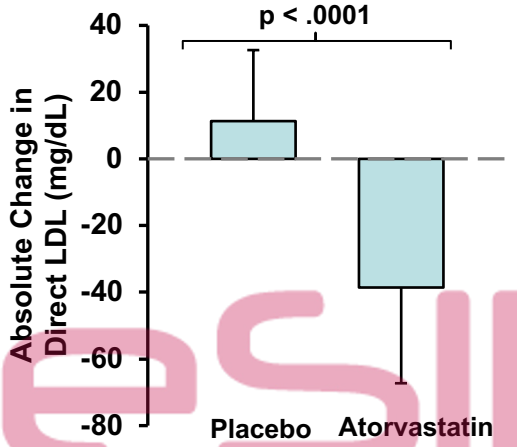
Larger decrease in cholesterol fractions with statin as compared with PI/r switch

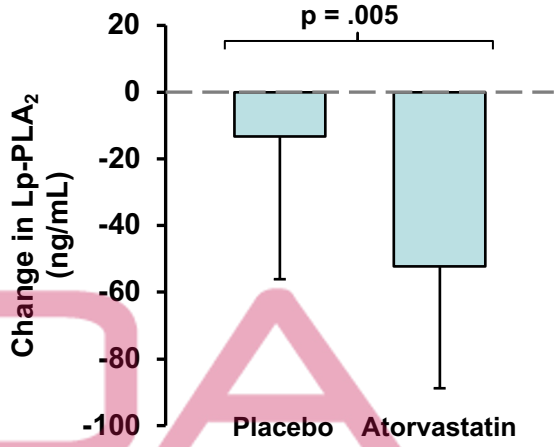


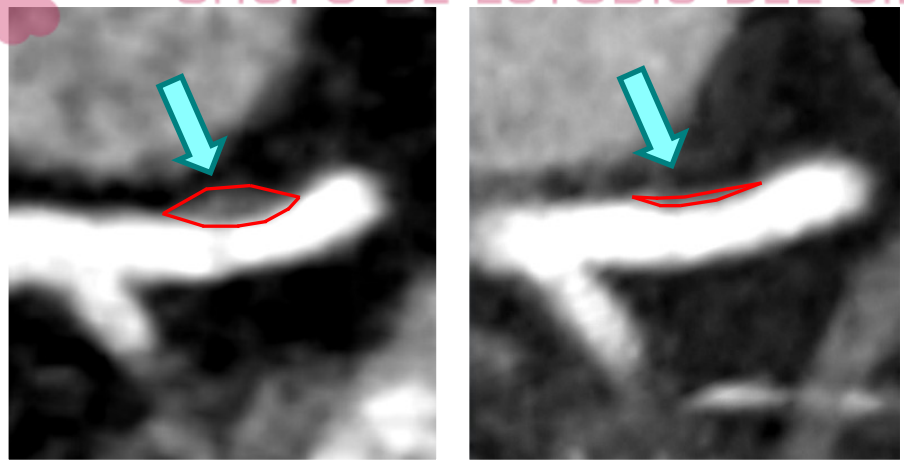
Lee F et al. CROI 2015

Statin effects on coronary artery plaque in PWH





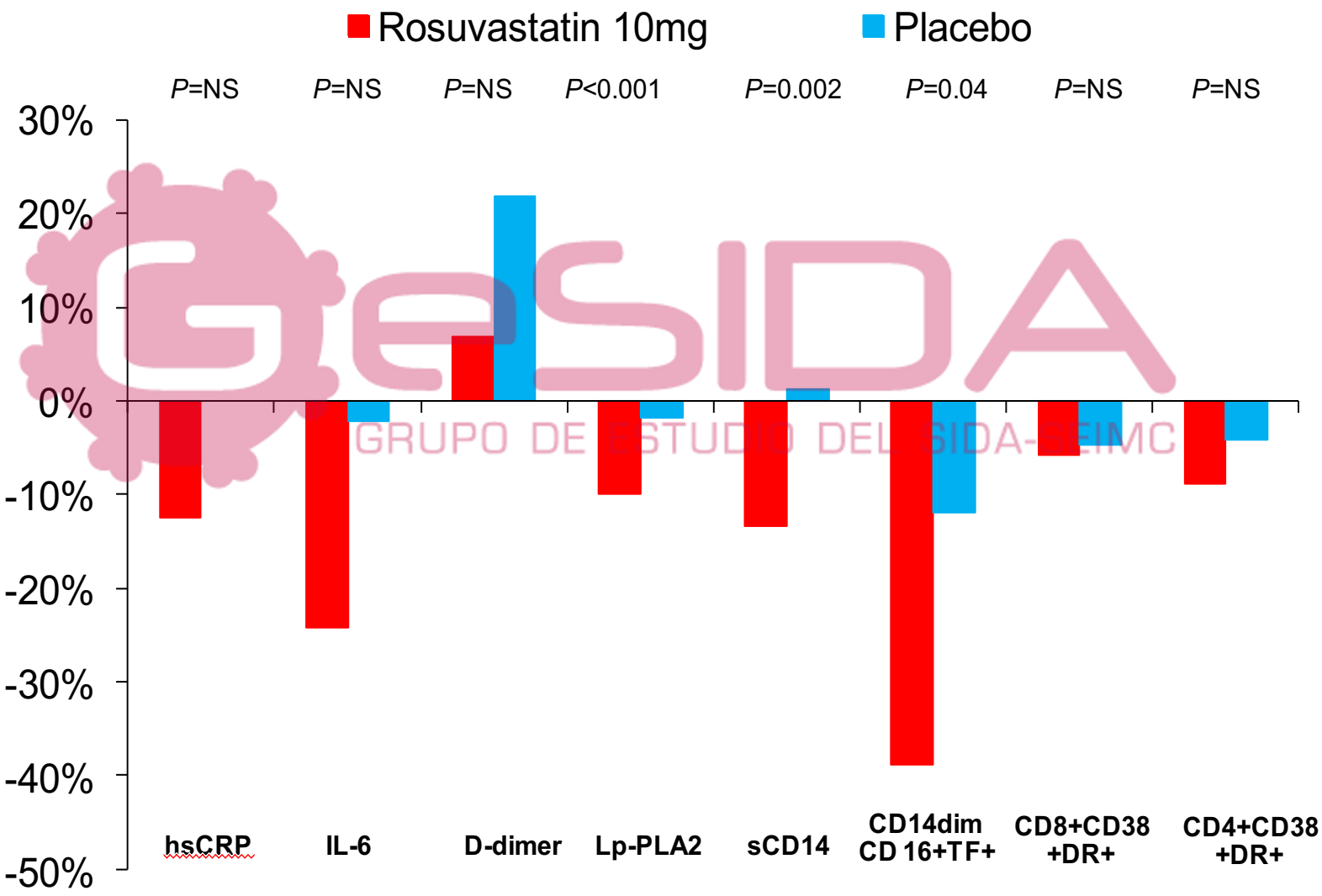




Decreasing non-calcified plaque in proximal left anterior descending (LAD) coronary artery in patient on atorvastatin for 12 months.

Lo J et al. Lancet HIV 2015

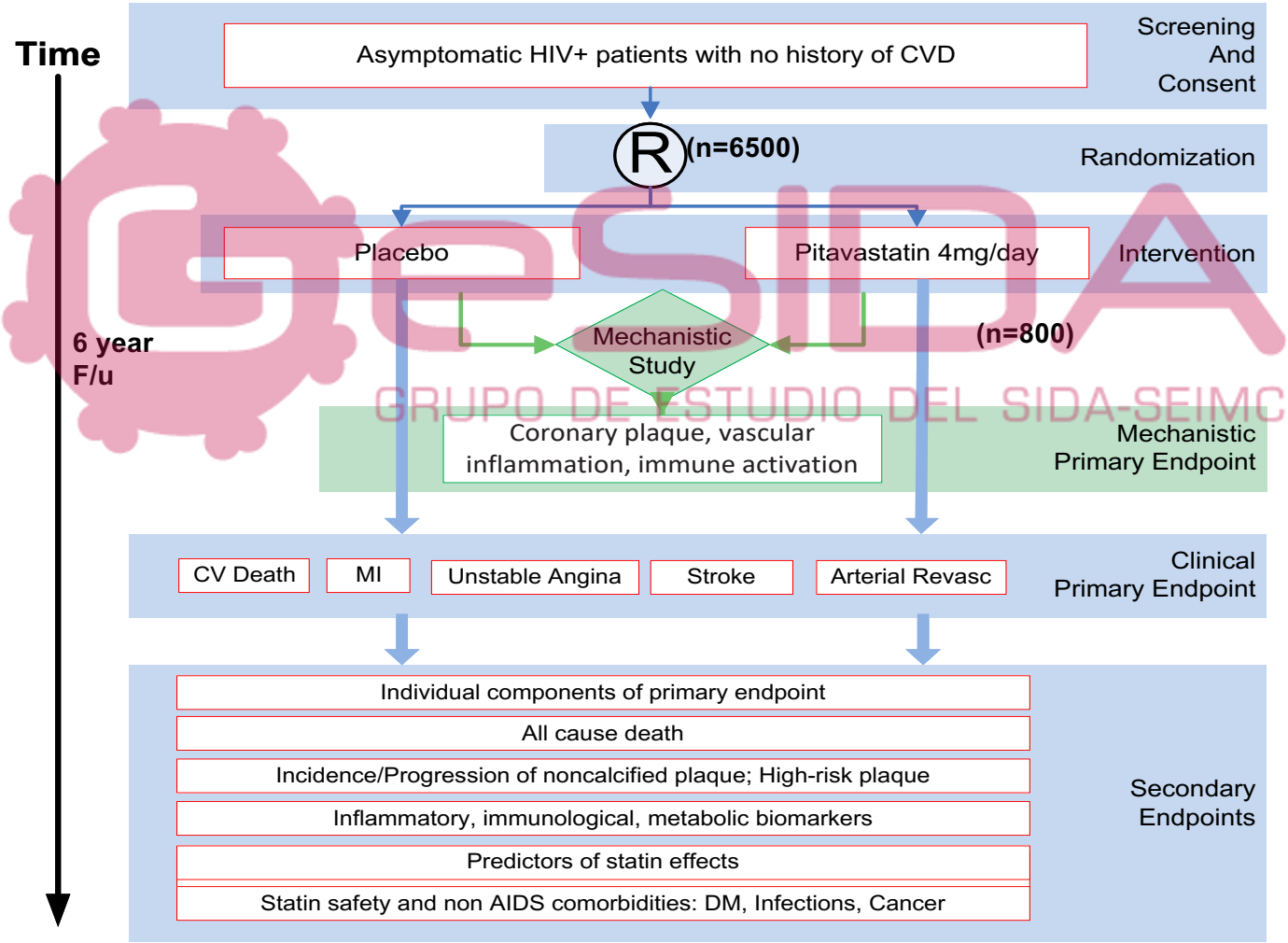
Statins decrease inflammation and immune activation in PWH on ART



Funderburg NT et al. J Acquir Immune Defic 2015

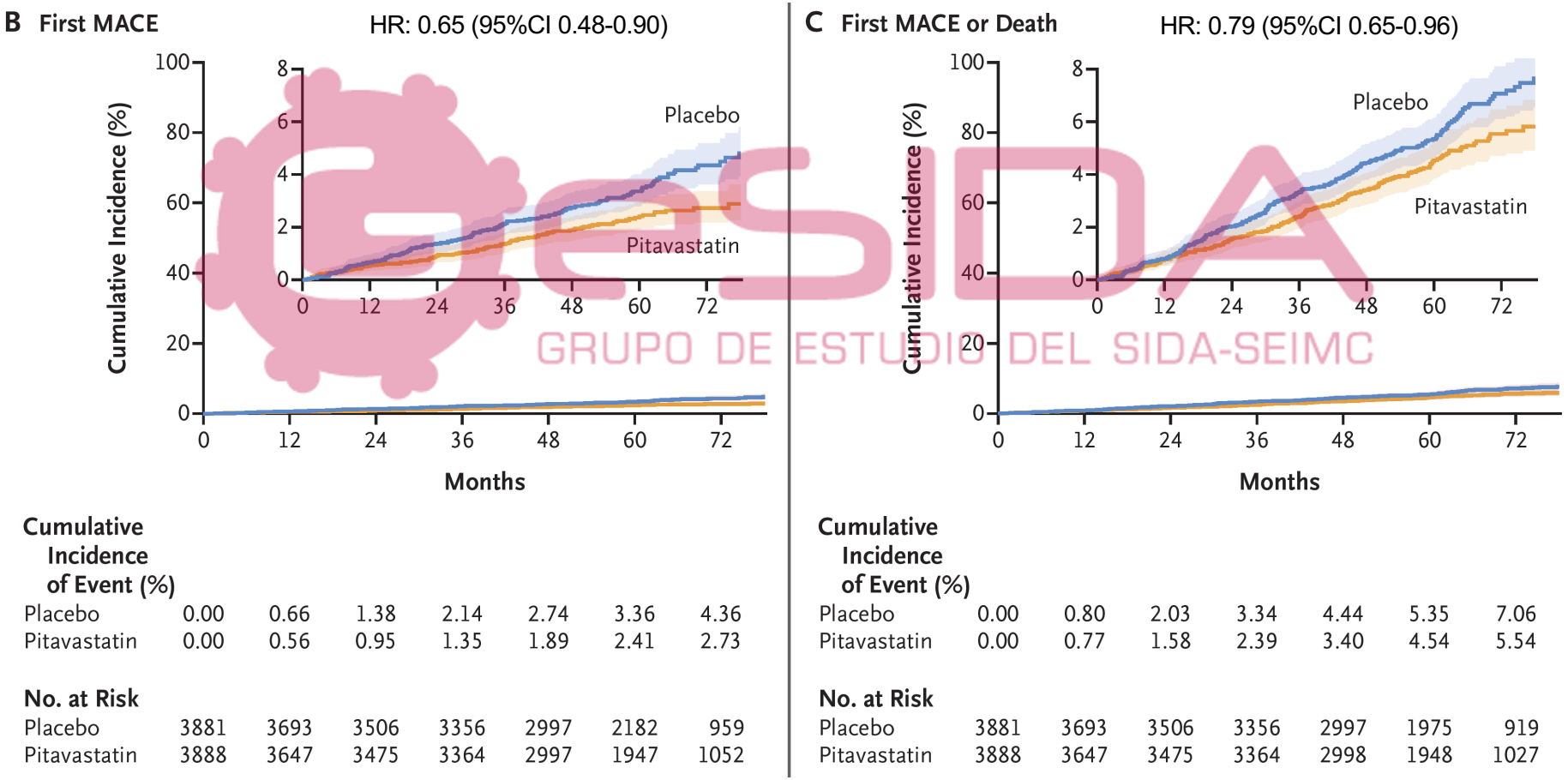
Randomized trial to prevent CV events in PWH on cART with a low estimated CV risk

REPRIEVE (ACTG 5332) study



http://reprievetrial.org

Pitavastatin decreased major adverse CV events in PWH with a low estimated CV risk



Cumulative Incidence of Event (%)							
Placebo	0.00	0.66	1.38	2.14	2.74	3.36	4.36
Pitavastatin	0.00	0.56	0.95	1.35	1.89	2.41	2.73
No. at Risk							
Placebo	3881	3693	3506	3356	2997	2182	959
Pitavastatin	3888	3647	3475	3364	2997	1947	1052

Cumulative Incidence of Event (%)							
Placebo	0.00	0.80	2.03	3.34	4.44	5.35	7.06
Pitavastatin	0.00	0.77	1.58	2.39	3.40	4.54	5.54
No. at Risk							
Placebo	3881	3693	3506	3356	2997	1975	919
Pitavastatin	3888	3647	3475	3364	2998	1948	1027

Grinspoon SK et al N Engl J Med 2023

Summary

- HIV patients have a higher risk of CVD than the general population.

- **Smoking** is a major risk factor for CVD. It is more common and contributes more to CVD and death in HIV patients than in the general population. Alcohol and cocaine are additional important factors. All them are modifiable, but we need to improve.

- **Uncontrolled HIV** is a risk factor for CVD that is exclusive to HIV patients. It contributes to CVD through multiple pathways including direct arterial infection, ↓HDL, inflammation, immune activation, and immunedeficiency. Earlier HIV diagnosis and cART can substantially decrease this additional factor.

- **cART** should be chosen not only for providing long-term efficacy but also for having the lowest impact on ageing co-morbidities such as CVD and the lowest risk for clinically meaningful interactions.

- **Statin** lead to further lipid decreases than switching drugs and is better tolerated. This intervention reduces plaque and probably has other non-CV clinical effects, but induces higher treatment complexity and potential for interactions. REPRIEVE study to change guidelines.