



JORNADAS DOCENTES_03



¿Cómo prevenir la aterosclerosis y el riesgo cardiovascular?

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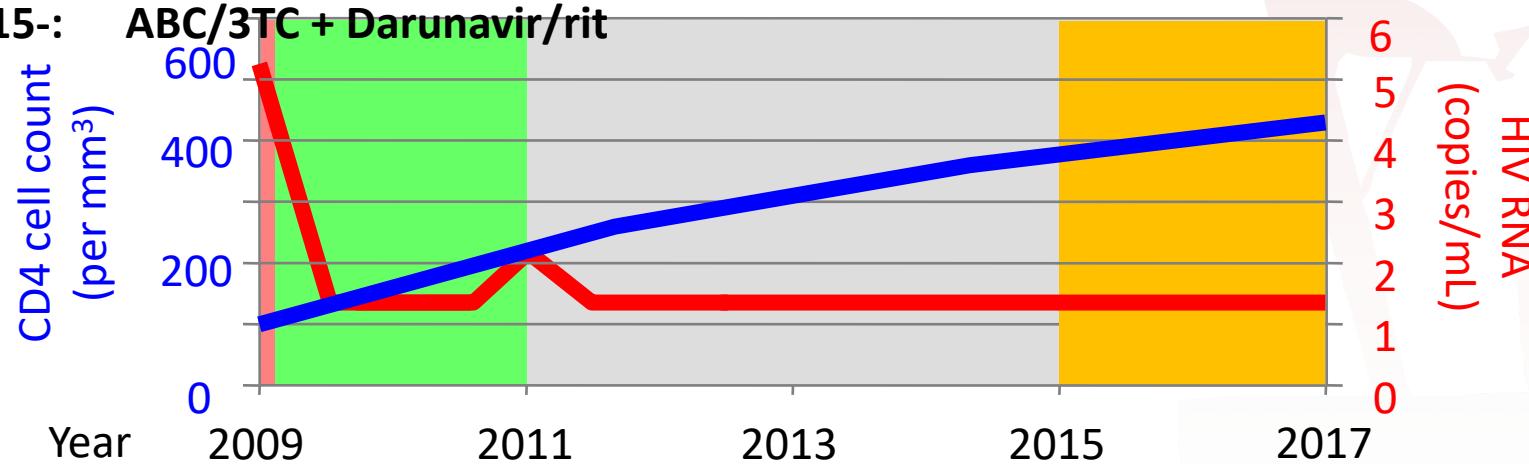
GesIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC



Patient's history

- Male, born 1967
- HIV+ 11/2009, sexual transmission
- Antiretroviral history (from a centre in Argentina):

Period	Regimen	Reason for discontinuation
2009-2009:	ABC/3TC + Efavirenz	sleep disturbances
2009-2011:	ABC/3TC + Nevirapine	low-level viral rebound
2011-2015:	ABC/3TC + Lopinavir/rit	simplification for convenience
2015-:	ABC/3TC + Darunavir/rit	



- Patient transferred to Spain due to laboral reasons in 2017

Patient's characteristics

Smoker 10 cigarettes per day

No illicit drugs

Blood pressure 140/80 mmHg

No hypertension, no diabetes

BMI 25 kg/m²

Total cholesterol 240 mg/dL

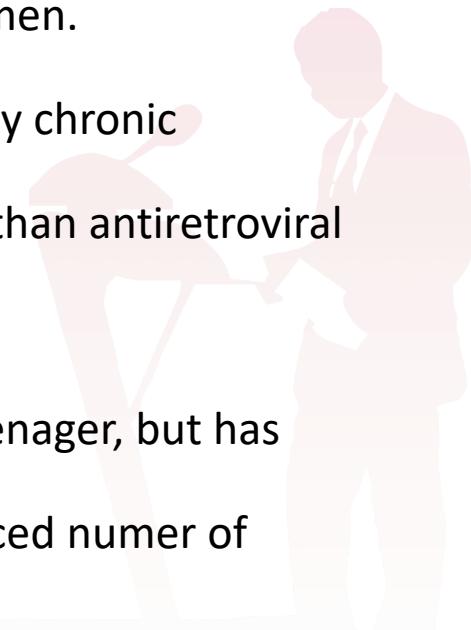
HDL cholesterol 40 mg/dL

LDL cholesterol 180 mg/dL

MDRD GFR 80 mL/min/1.73m²

No proteinuria

- The patient feels great.
- He accepts and tolerates his antiretroviral regimen.
- He is not taking any chronic medication other than antiretroviral therapy.
- Smoker since a teenager, but has substantially reduced number of cigarettes per day.





EACS
European
AIDS
Clinical
Society

GUIDELINES

Version 8.1
October 2016

English



Cardiovascular screening

Smoker 10 cigarettes per day

No illicit drugs

Blood pressure 140/80 mmHg

No hypertension, no diabetes

BMI 25 kg/m²

Total cholesterol 240 mg/dL

HDL cholesterol 40 mg/dL

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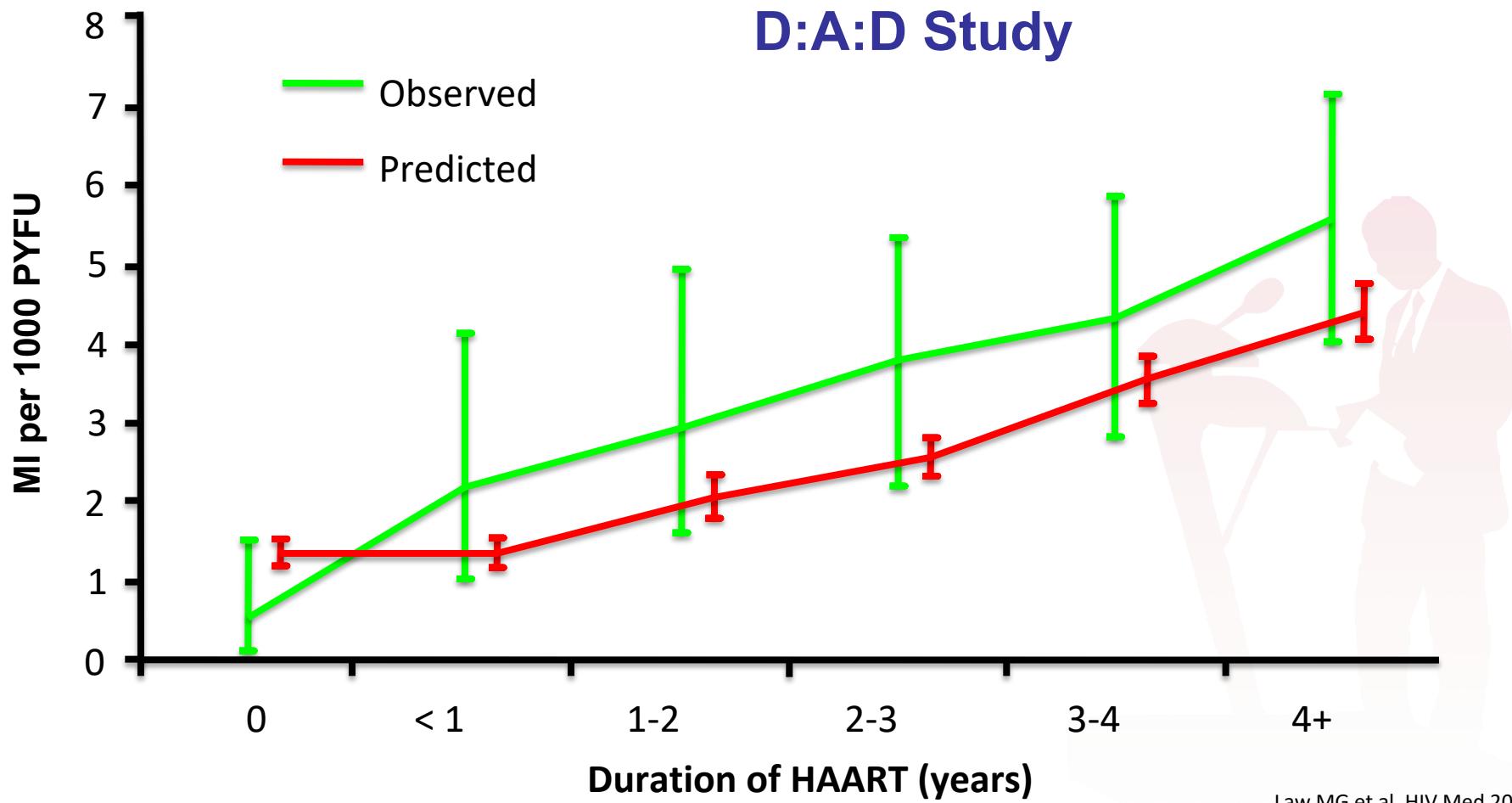
No proteinuria

ECG: Normal

FRAMINGHAM score	Patient case
Age, years	50
Gender, male/female	Male
Smoker, yes/no	Yes
Systolic blood pressure, mmHg	140
Total cholesterol, mg/dL(mmol/L)	240 (6.2)
HDL cholesterol, mg/dL (mmol/L)	40 (1.0)
CHD Risk Score at 10 years (%)	20%

Modifiable risk factors

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

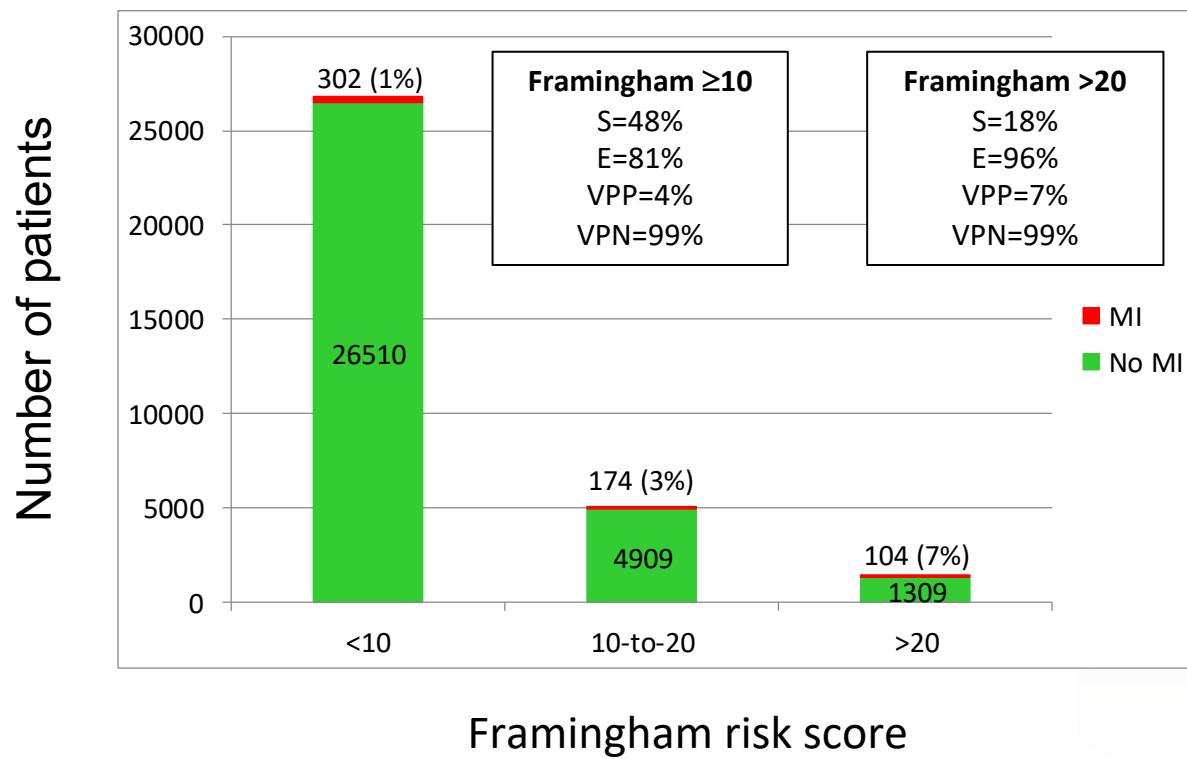


Framingham score: gender, smoking, age, systolic BP, total and HDL cholesterol

Law MG et al. HIV Med 2006

Framingham score has a low sensitivity, but a high negative predictive value

If a patient has a low risk, the likelihood of not having a MI is high





Men have worse CV risk than women

Age:	50	50
Gender:	male	male
Total Cholesterol:	200 mg/dL	240 mg/dL
HDL Cholesterol:	40 mg/dL	40 mg/dL
Smoker:	Yes	Yes
Systolic Blood Pressure:	120 mm/Hg	120 mm/Hg
On medication for HBP:	No	P: No
Risk Score*	12%	17%

Man, ≥50y, smoker = risk >10%

Age:	50	99
Gender:	female	female
Total Cholesterol:	200 mg/dL	200 mg/dL
HDL Cholesterol:	40 mg/dL	40 mg/dL
Smoker:	Yes	Yes
Systolic Blood Pressure:	120 mm/Hg	120 mm/Hg
On medication for HBP:	No	P: No
Risk Score*	3%	8%

Woman, any age, even smoker = risk <10%

Age:	64	64
Gender:	male	male
Total Cholesterol:	200 mg/dL	240 mg/dL
HDL Cholesterol:	40 mg/dL	40 mg/dL
Smoker:	No	No
Systolic Blood Pressure:	120 mm/Hg	120 mm/Hg
On medication for HBP:	No	BP: No
Risk Score*	12%	14%

If non-smoking you need to be almost 15y older to have the same CV risk

However, Framingham does not include HIV-specific factors

- Immune status
- Increased inflammatory markers
- Insulin resistance
- Time on HAART



CV score developed from D:A:D study

DAD 5 Year Estimated Risk calculator

The risk during the next 5 years of CHD is:

Number of years on:

indinavir: 0
lopinavir: 4

Currently on:

indinavir?: No Yes
lopinavir?: No Yes
abacavir?: No Yes

Gender: Female Male

Current age in years: 50

Current cigarette smoker?: No Yes

Previous cigarette smoker?: No Yes

Diabetic?: No Yes

Family CVD history?: No Yes

Systolic blood pressure: 140 unit: mm/Hg cm/Hg kPa

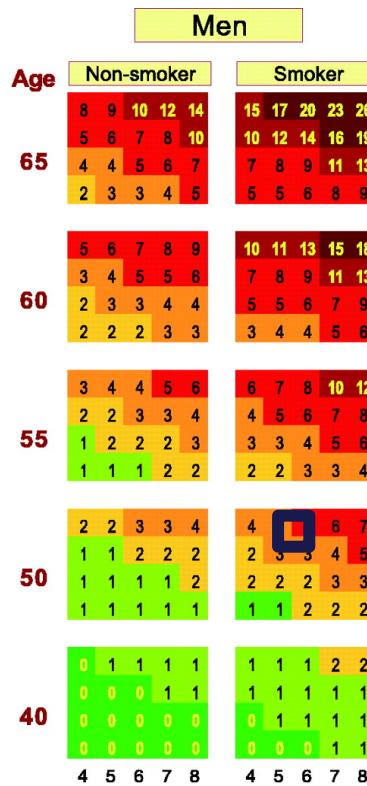
Total cholesterol 240 unit: mmol/L g/L g/dL mg/dL

HDL 40 unit: mmol/L g/L g/dL mg/dL

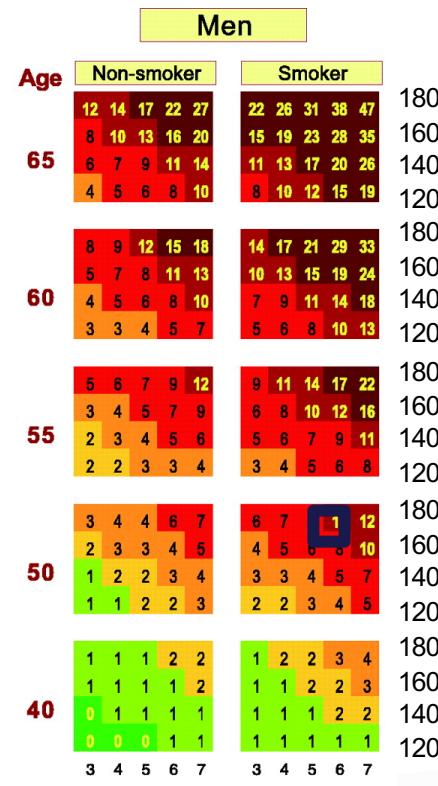
11.8%

Score estimates risk of CV death (used in Europe)

Low-risk countries



High-risk countries



Systolic blood pressure

Total cholesterol (mmol/L)



ASCVD estimator bases on 2013 ACC/AHA guidelines (used un US)

ASCVD Risk Estimator*

10-Year ASCVD Risk



Gender

Male

Female

Age

50

HDL - Cholesterol (mg/dL)

40

Total Cholesterol (mg/dL)

240

Diabetes

Yes

No

Treatment for Hypertension

Yes

No

Race

White

African American

Other

Systolic Blood Pressure

140

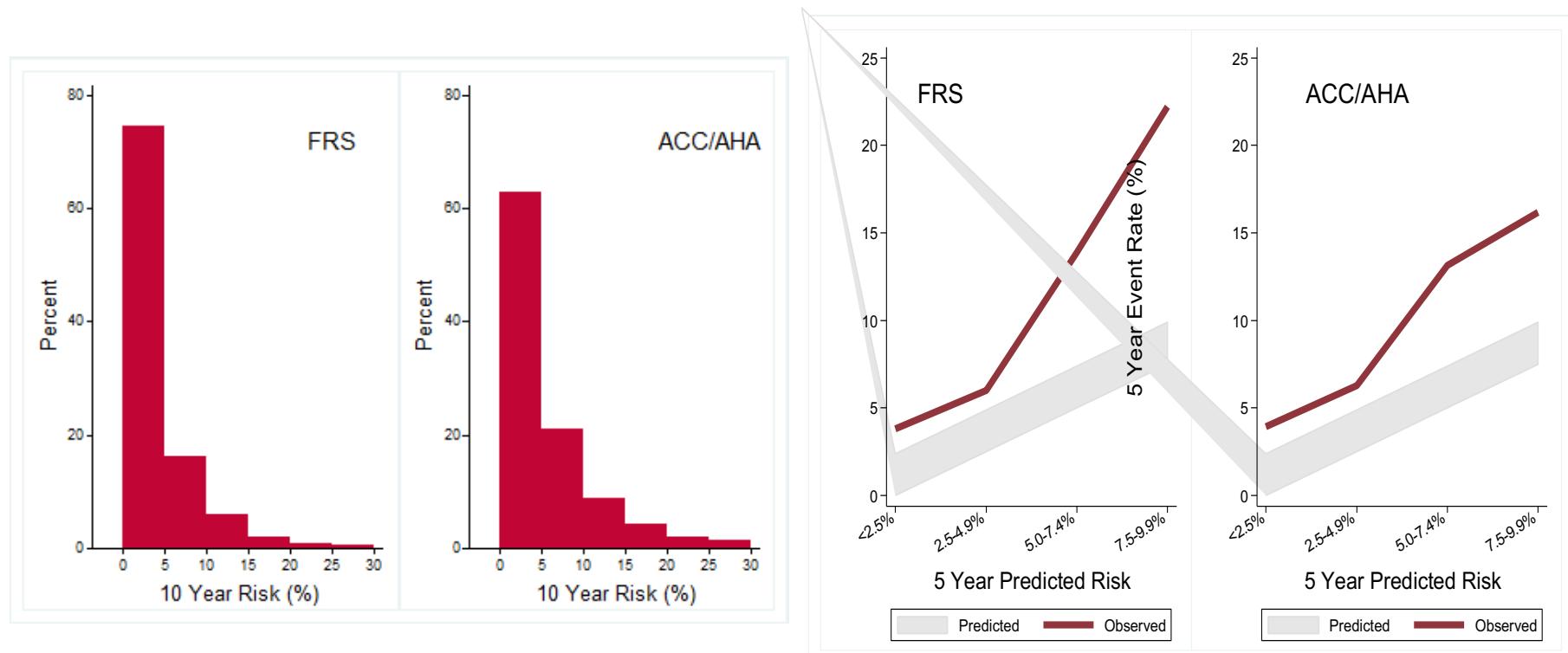
Smoker

Yes

No

2013 ACC/AHA score may estimate CV events better than Framingham score

Partners HealthCare System HIV longitudinal cohort (n=2270), comprised of patients seen at Brigham & Women's Hospital or Massachusetts General Hospital in Boston, MA

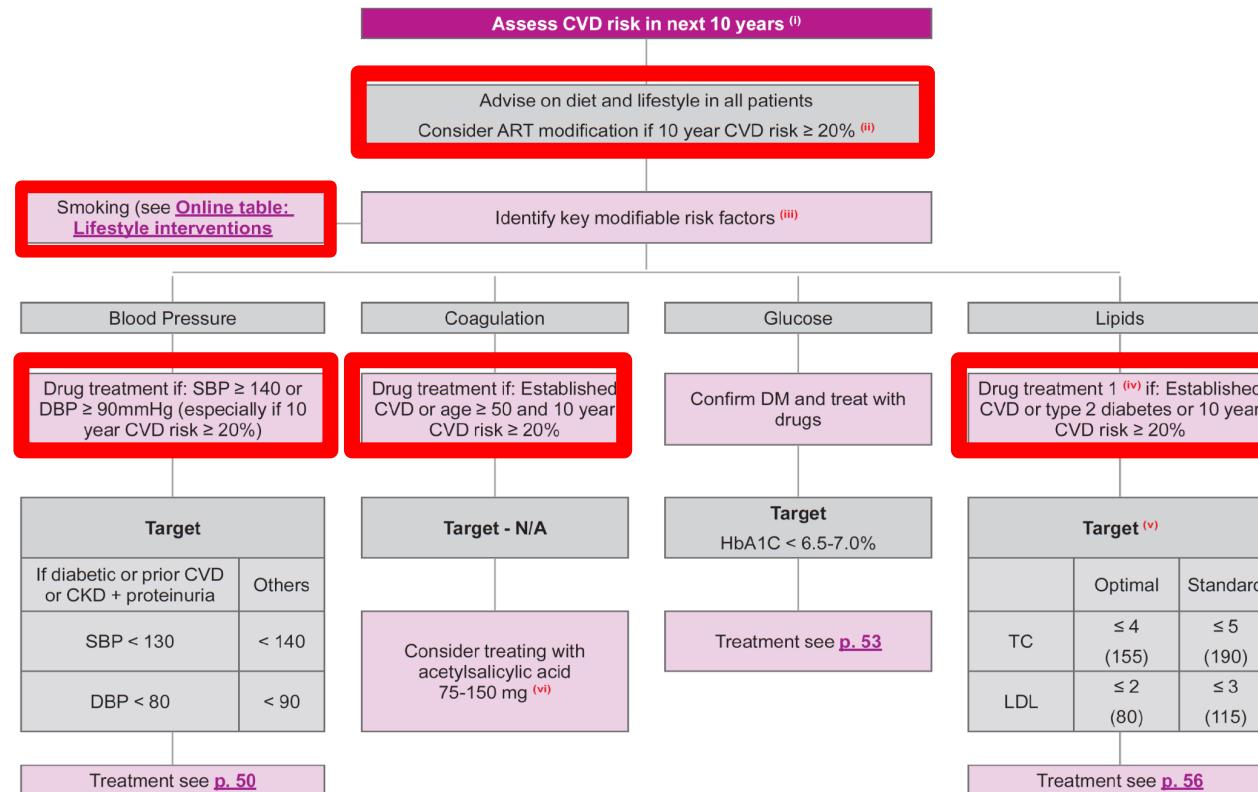




EACS prior to 2015

Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated ⁽ⁱ⁾. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in patients with a history of CVD.





Risk of subclinical CV disease is higher than predicted

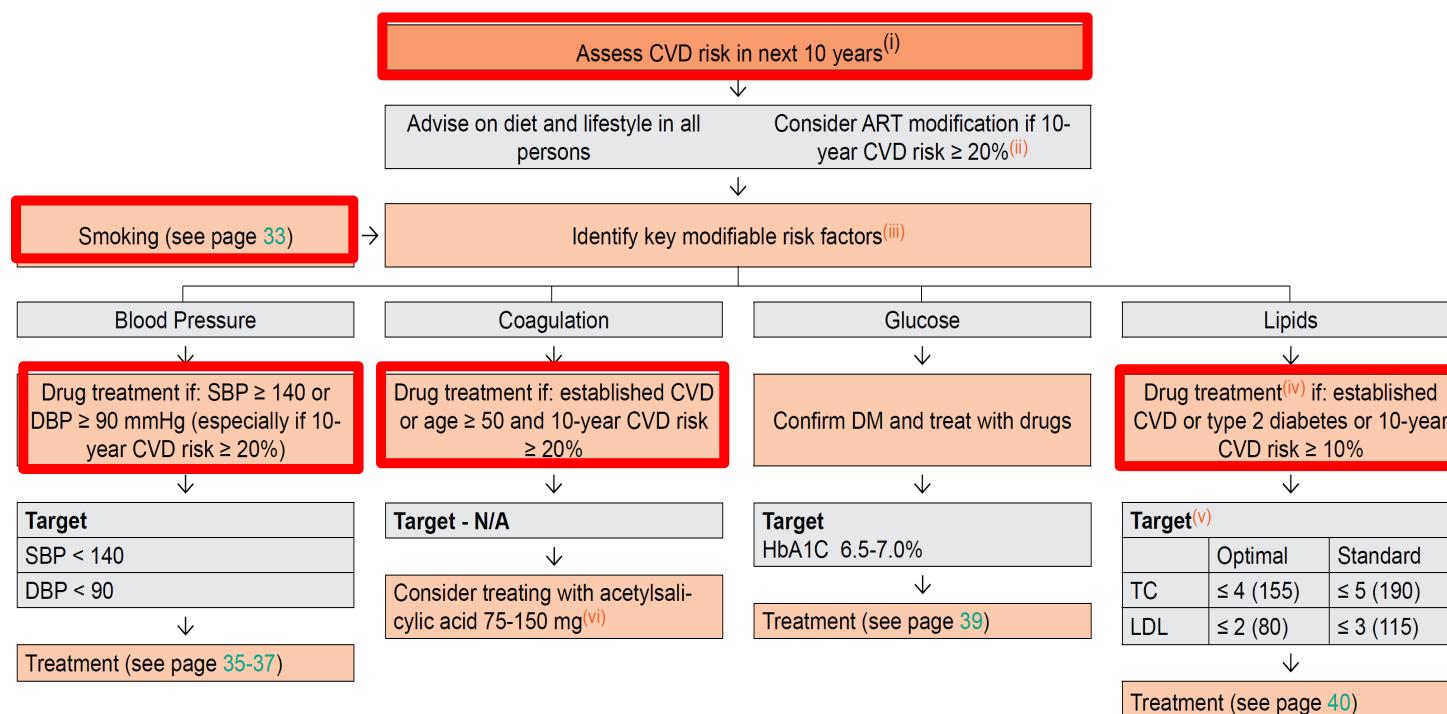
Nr of patients	108
Age, years (IQR)	46 (40-52)
Current smoking (%)	50
Total cholesterol (mg/dL)	175
LDL cholesterol (mg/dL)	98
HDL cholesterol (mg/dL)	49
10-year Framingham score, % (IQR)	3 (1-5)
10-year ASCVD score, % (IQR)	3.3 (1.6-6.6)
CD4 cells/mm ³	528
Viral load (copies/mL)	<50
Patients with any coronary plaque (%)	45
Patients with high-risk plaques (%)	36
Statins recommended 2004 ATP III (%)	8
Statins recommended 2013 ACC/AHA (%)	21



EACS from 2015 on

Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated⁽ⁱ⁾. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in persons with a history of CVD.





Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	< 70 mg/dL < 1.8 mmol/L	70 to < 100 mg/dL 1.8 to < 2.5 mmol/L	100 to < 155 mg/dL 2.5 to < 4.0 mmol/L	155 to < 190 mg/dL 4.0 to < 4.9 mmol/L	> 190 mg/dL > 4.9 mmol/L
< 1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	I/C	I/C	IIa/A
≥ 1 to < 5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	IIa/A	IIa/A	I/A
> 5 to < 10, or high risk	Lifestyle intervention consider drug*	Lifestyle intervention consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class/Level	IIa/A	IIa/A	IIa/A	I/A	I/A
≥ 10 or very high risk	Lifestyle intervention consider drug*	Lifestyle intervention and immediate drug intervention			
Class/Level	IIa/A	IIa/A	I/A	I/A	I/A

European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

www.escardio.org/guidelines





ASCVD estimator (based on 2013 ACC/AHA guidelines)

ASCVD Risk Estimator*

10-Year ASCVD Risk



Gender

 Male Female

Age

50

HDL - Cholesterol (mg/dL)

40

Total Cholesterol (mg/dL)

240

Diabetes

 Yes No

Treatment for Hypertension

 Yes No

Race

 White African American Other

Systolic Blood Pressure

140

Smoker

 Yes No



Consider potential for drug-drug interactions between ARVs and other drugs

<u>High</u>	<u>Moderate</u>	<u>Low/No</u>
ATV/rit	NVP	NRTIs (all)
DRV/rit	EFV	RPV
ATV/cobi	ETV	MVC
DRV/cobi		RAL
EVG/cobi		DTG



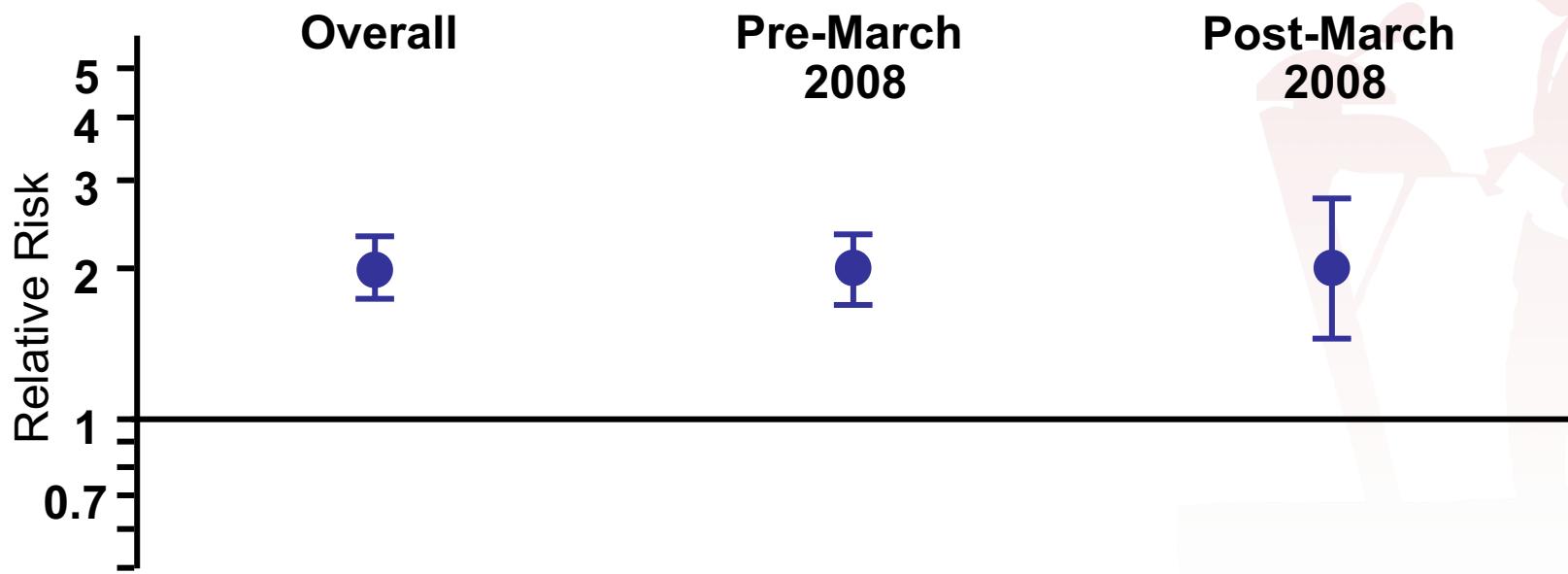
Risk of interactions between statins and PI/r or NNRTI

Drugs used to lower LDL-c

DRUG CLASS	DRUG	DOSE	SIDE EFFECTS	ADVISE ON USE OF STATIN TOGETHER WITH ART	
				use with PI/r	use with NNRTI
Statin (i)	Atorvastatin (ii)	10-80 mg qd	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose (v) (max: 40 mg)	Consider higher dose (vi)
	Fluvastatin (iii)	20-80 mg qd		Consider higher dose (vi)	Consider higher dose (vi)
	Pravastatin (iii)	20-80 mg qd		Consider higher dose (vi,vii)	Consider higher dose (vi)
	Rosuvastatin (ii)	5-40 mg qd		Start with low dose (v) (max: 20 mg)	Start with low dose (v)
	Simvastatin (ii)	10-40 mg qd		Contraindicated	Consider higher dose (vi)
Cholesterol uptake↓ (i)	Ezetimibe (iv)	10 mg qd	Gastrointestinal symptoms	No known drug-drug interactions with ART	

ABC and MI risk persists in D:A:D despite change in ABC use

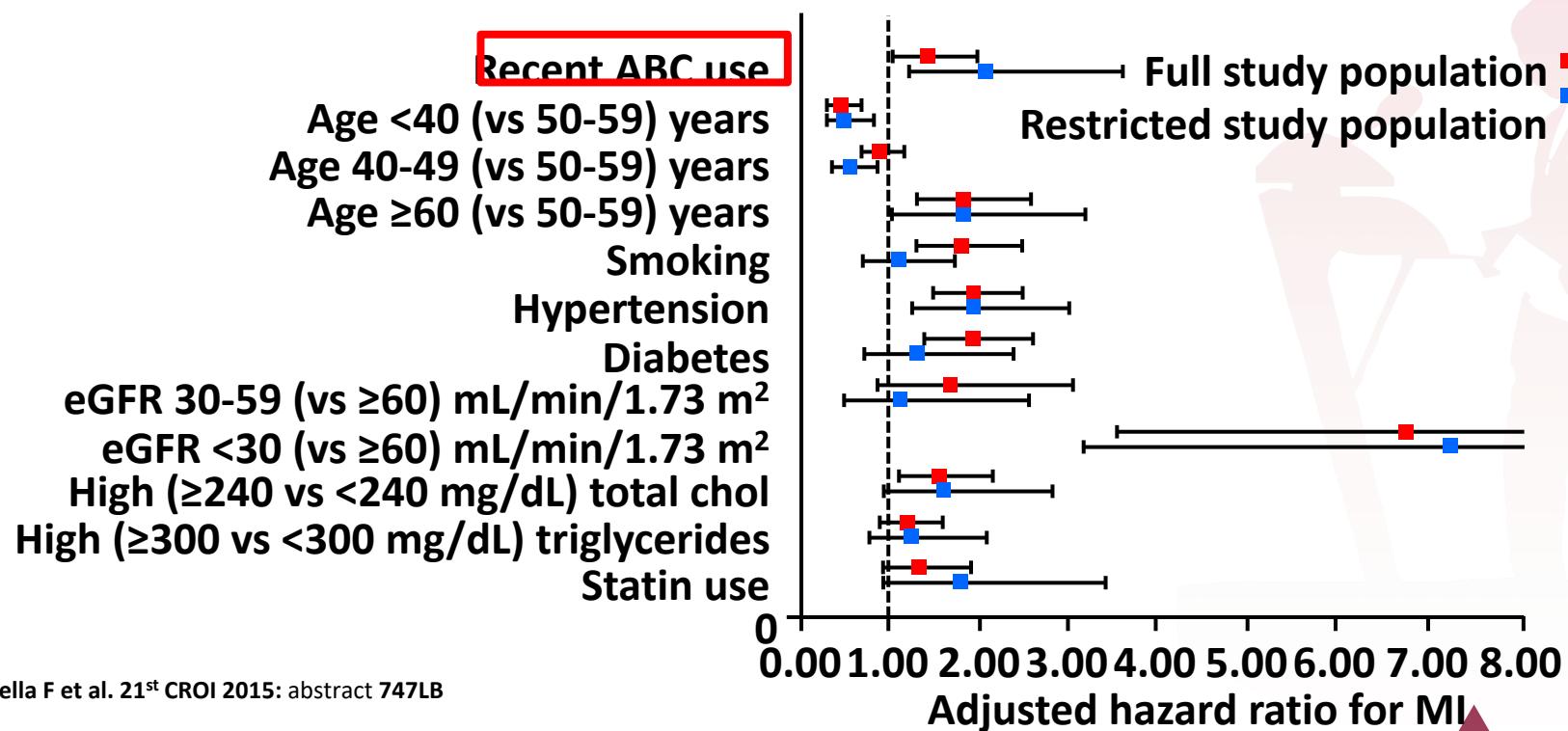
- Analysis of MI risk with ABC pre and post 3/08 in D:A:D cohort
- There were trends to less ABC use in high risk individuals post 3/08
- RR with ABC 1.98 (1.72-2.29), Pre 3/08 1.97, Post 3/08 1.97



Recent ABC and MI risk: Controversy in NA-ACCORD

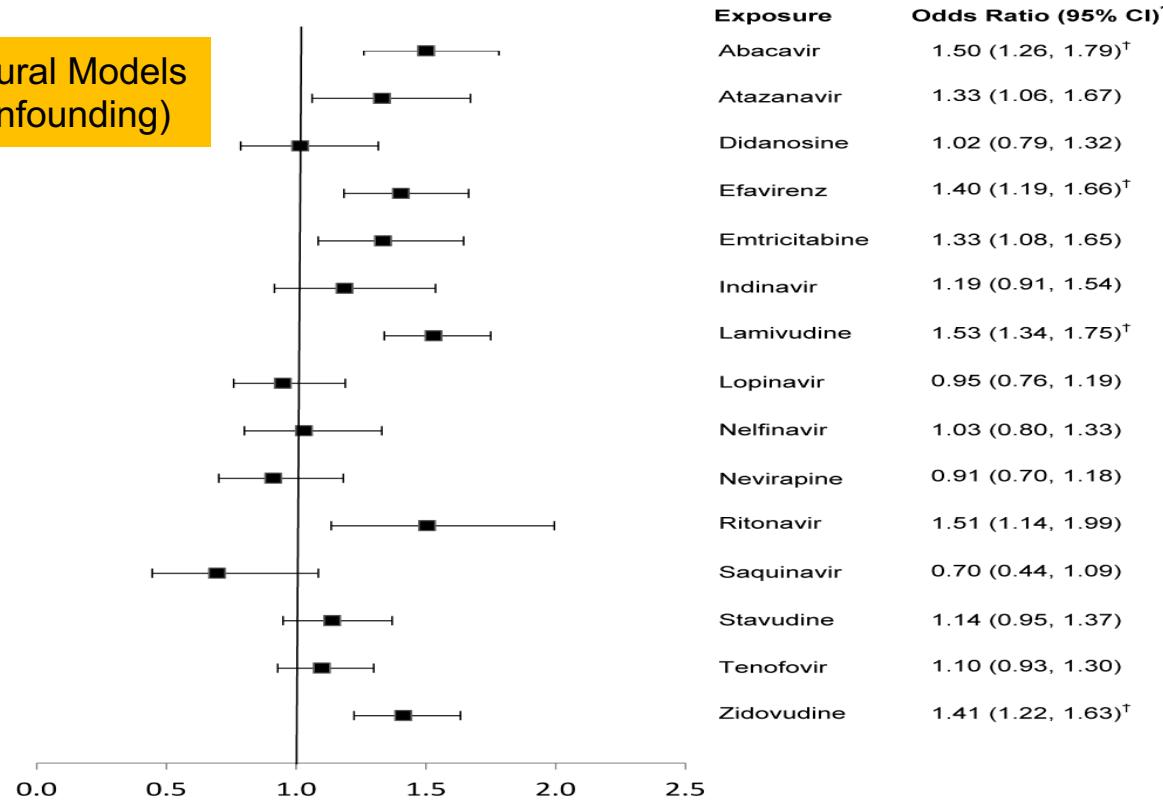
Many significant differences in clinically relevant characteristics between ABC and non-ABC users

- Adjusted Hazard Ratios of CVD Risk Factors Significantly Associated With MI



Current ARV drugs and MI risk: New data from US Veterans

Marginal Structural Models
(to minimise confounding)



* Point estimates are interpreted as increase/decrease in odds of cardiovascular events given current exposure to therapy relative to not currently exposed to therapy.

† Statistically significant according to the Bonferroni adjusted p-value.

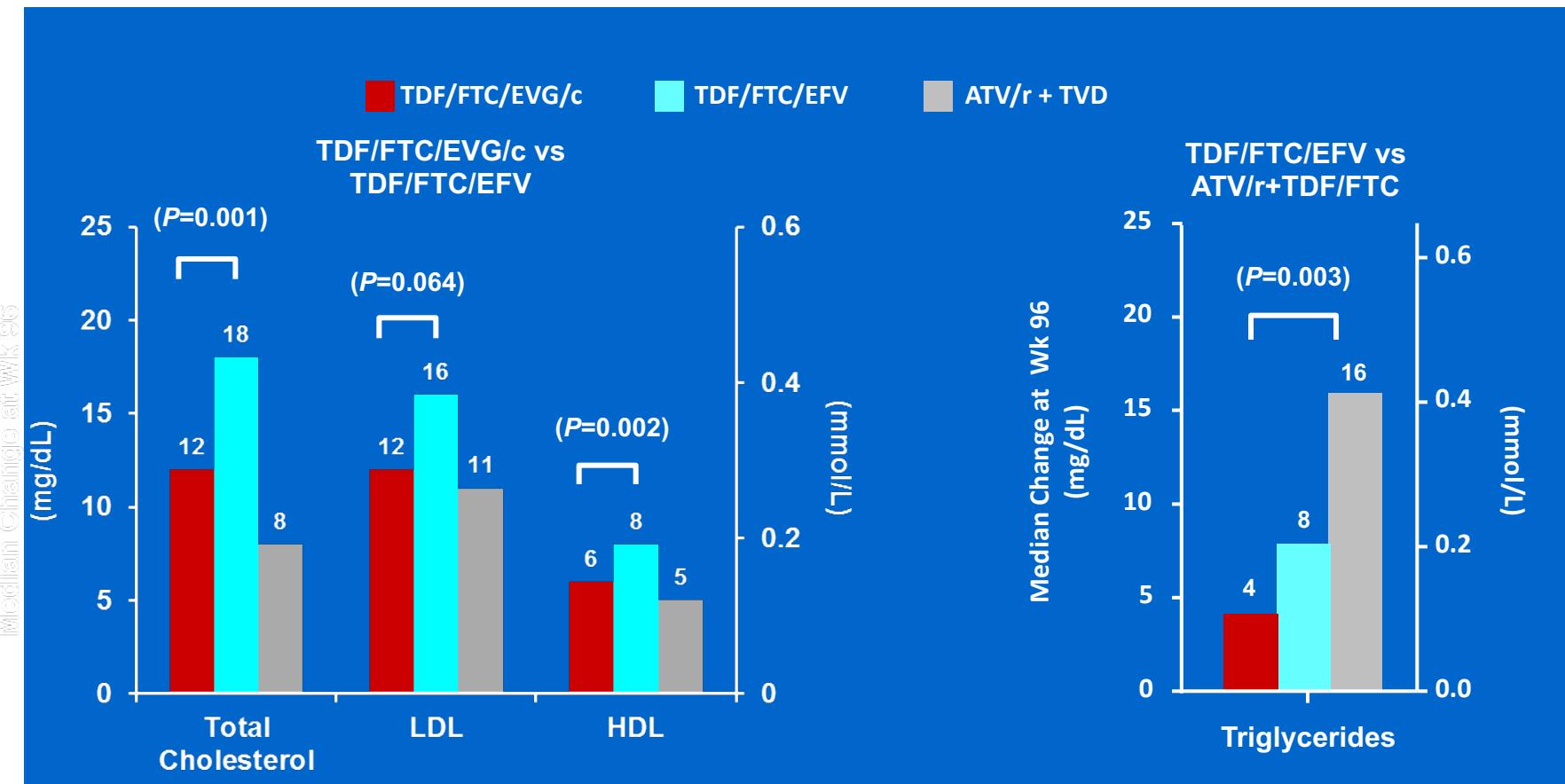


Approximately one third of the PI-related excess risk for MI in D:A:D is due to DM, HT, or lipids

	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

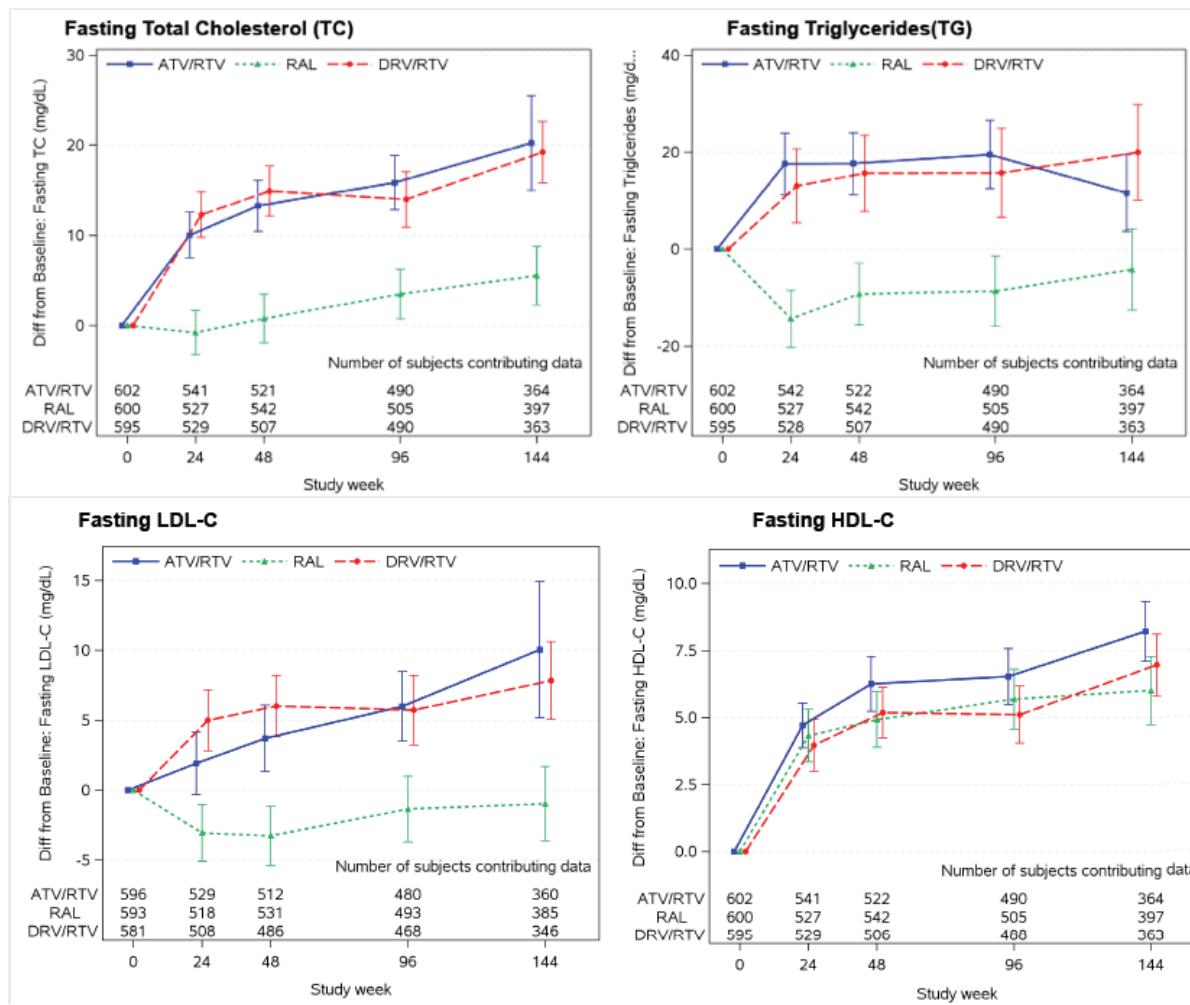
The distinctive lipid effect of PI/r is an increase in triglycerides, but not cholesterol

Studies 102 and 103



Lipid changes in ACTG 5257

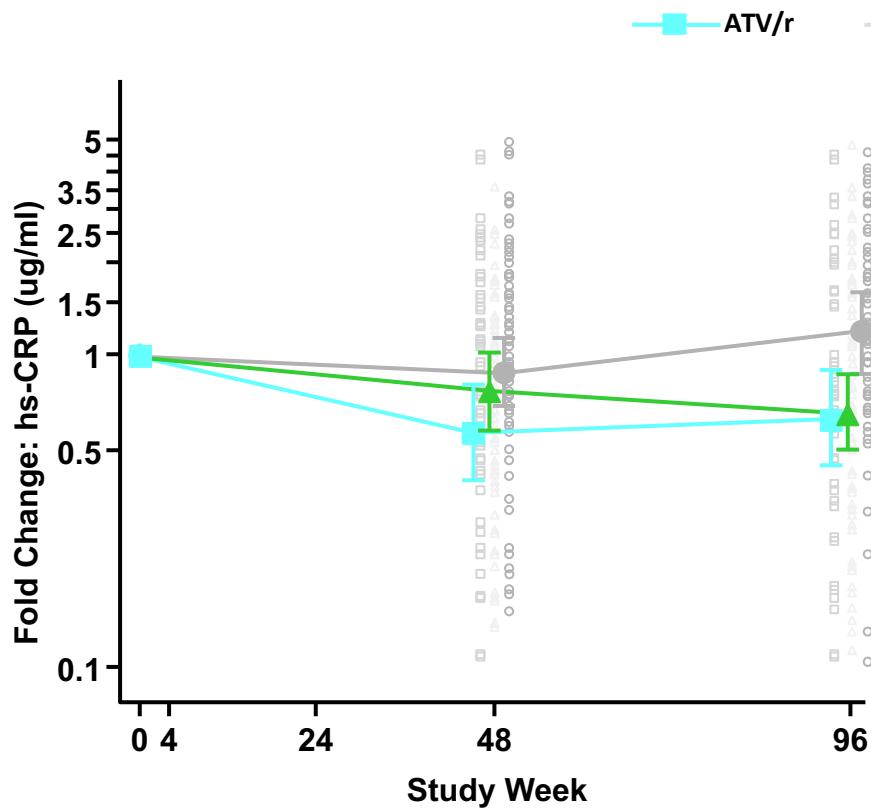
ACTG 5257



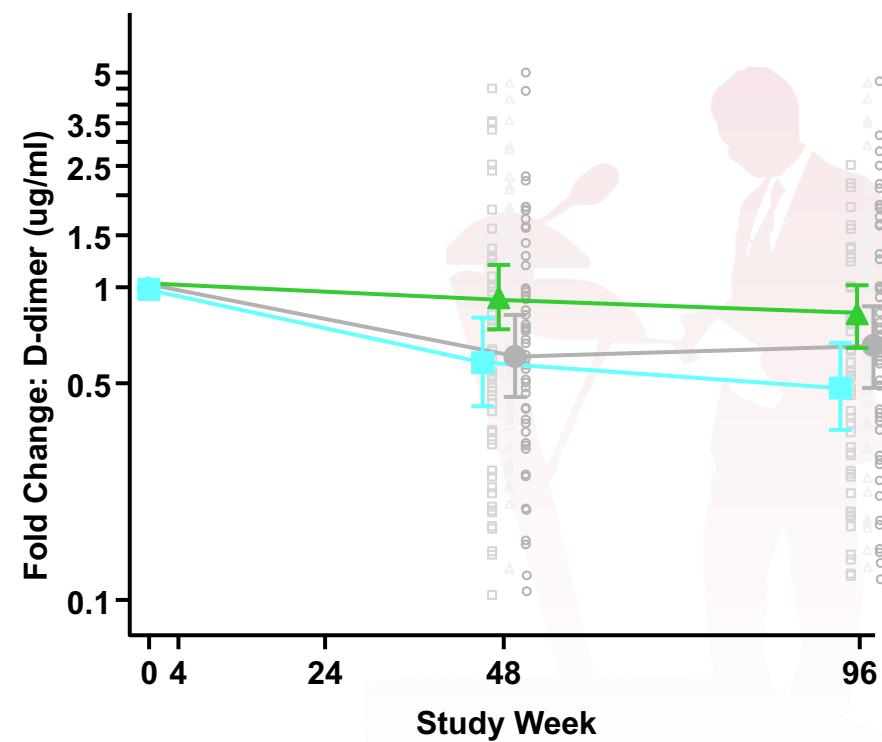
Less inflammation and hypercoagulability with ATV/r

ACTG 5257

Hs-CRP Declined with ATV/r and RAL

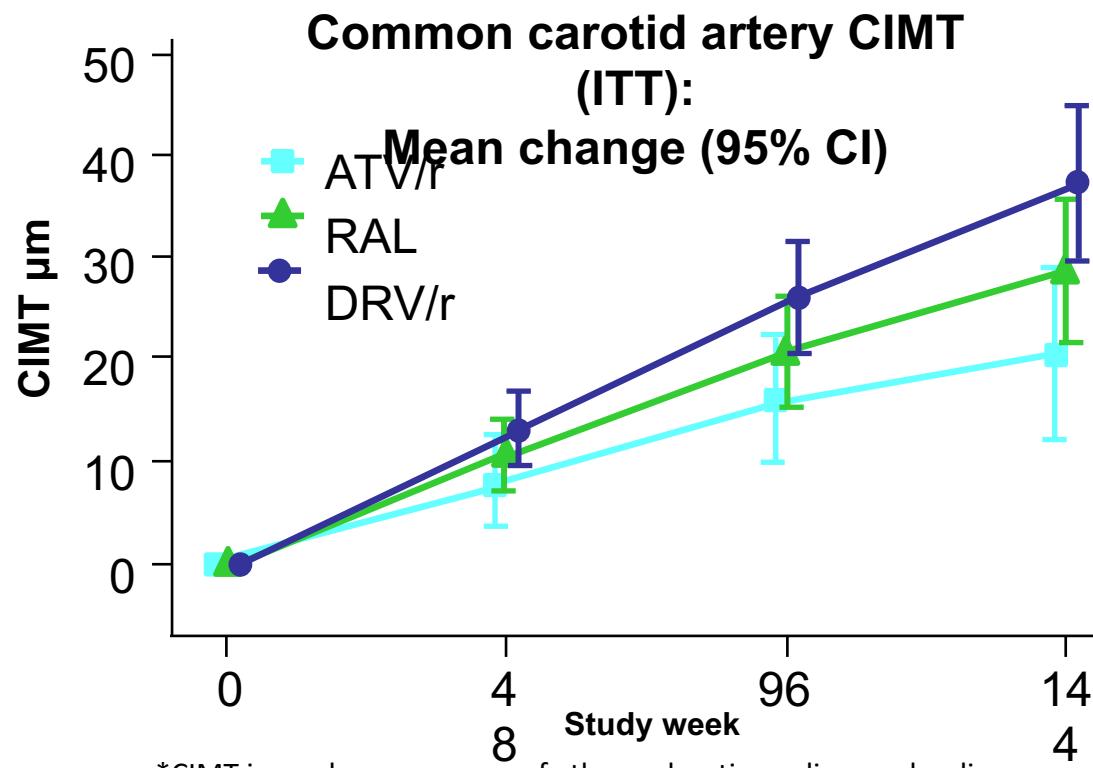


D-dimer Declined with ATV/r and DRV/r



Slower progression of clIMT with ATV/r vs. DRV/r

ACTG 5260s



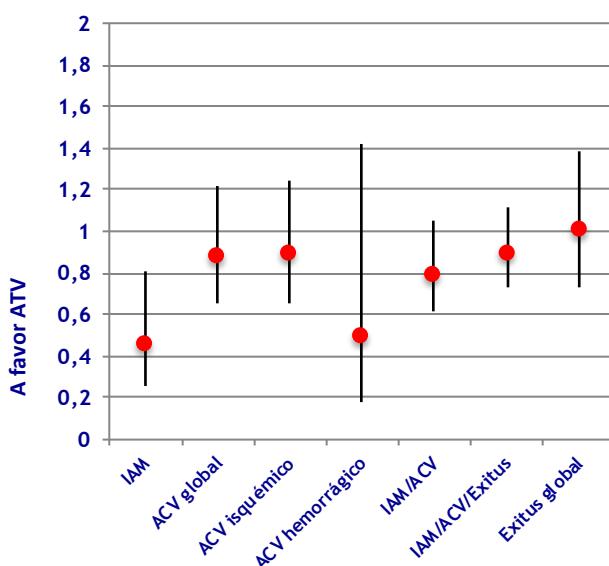
- ATV/r progressed more slowly than DRV/r (ATV/r (8.2 $\mu\text{m}/\text{year}$ 95% CI [5.6–10.8]) vs DRV/r (12.9 $\mu\text{m}/\text{year}$ [10.3–15.5]); $p=0.013$)
- Intermediate progression for RAL (10.7 $\mu\text{m}/\text{year}$ [9.2–12.2] ($p=0.15$ vs ATV/r; $p=0.31$ vs DRV/r))

- *CIMT is used as a measure of atherosclerotic cardiovascular disease
- CIMT: Carotid intima-media thickness

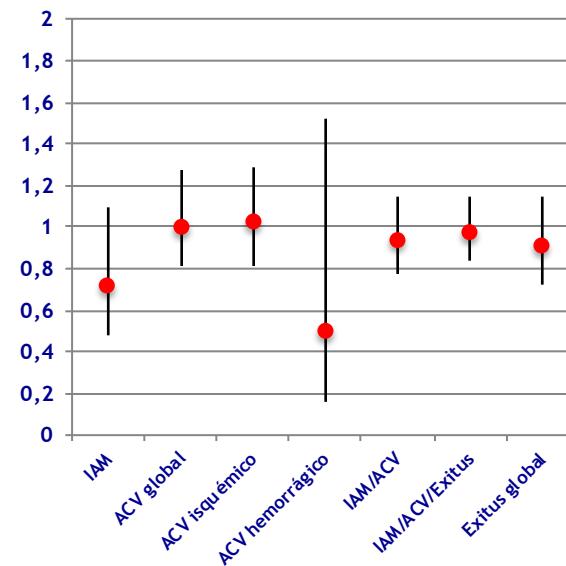
Eventos cardiovasculares con ATV en pacientes VIH

- Inicio de TAR en la cohorte de Veteranos (2003-2015) ($n = 10.385$).
- Edad media 50 años; 93% hombres; 56% raza negra y 30% caucásicos.

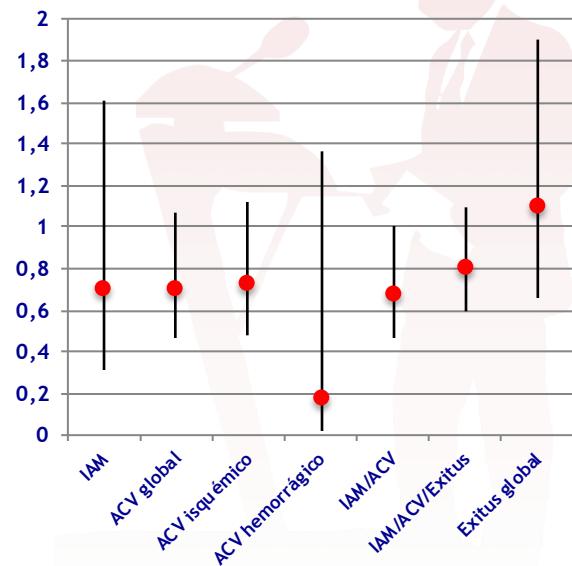
ATV vs Otros IP \pm r
(HR, IC 95%)



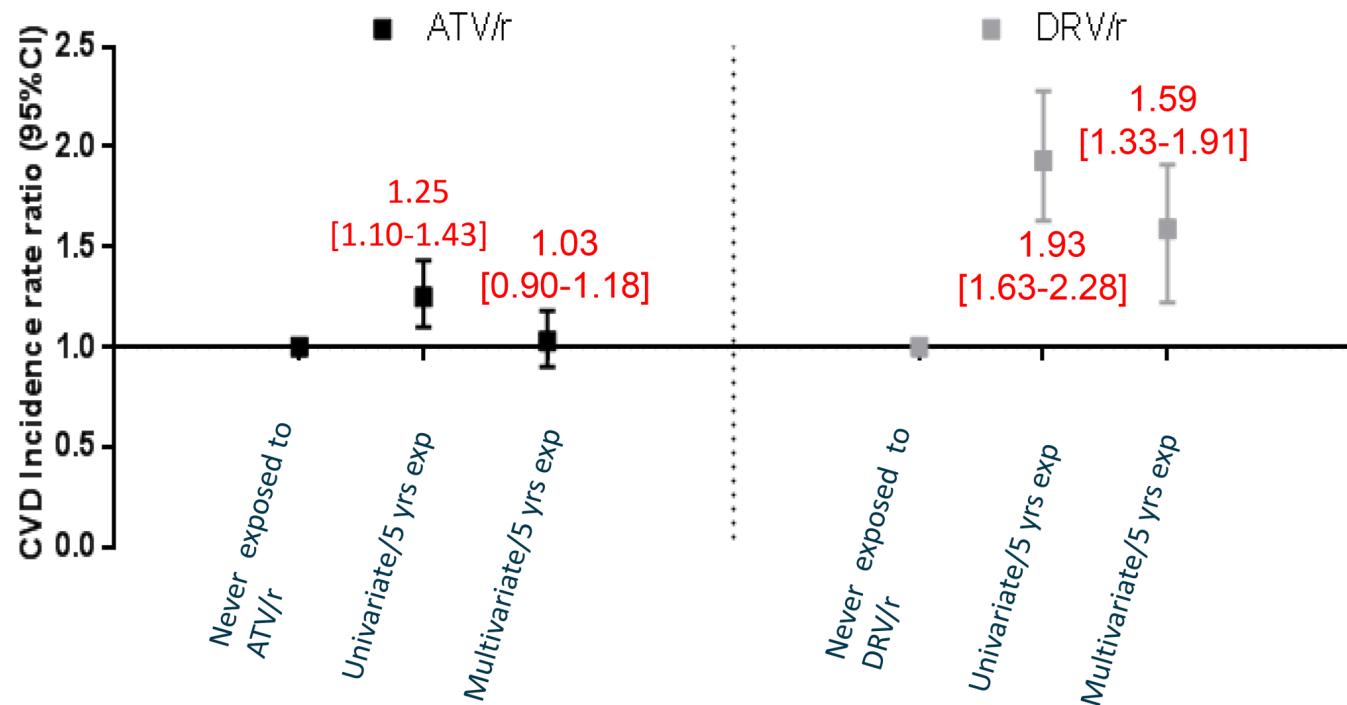
ATV vs NNRTIs
(HR, IC 95%)



ATV vs INSTIs
(HR, IC 95%)

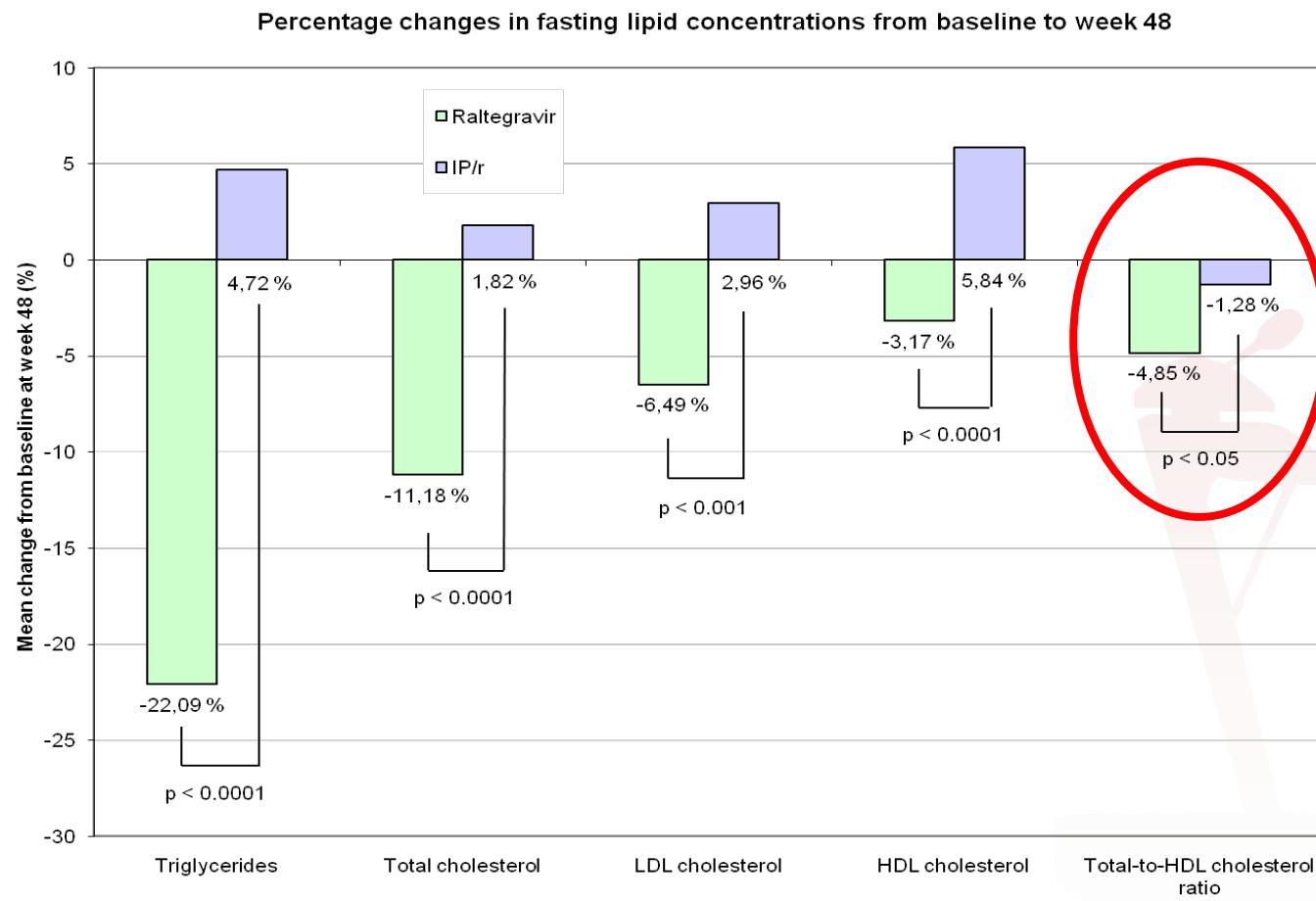


Association between CVD and cumulative ATV/r or DRV/r use



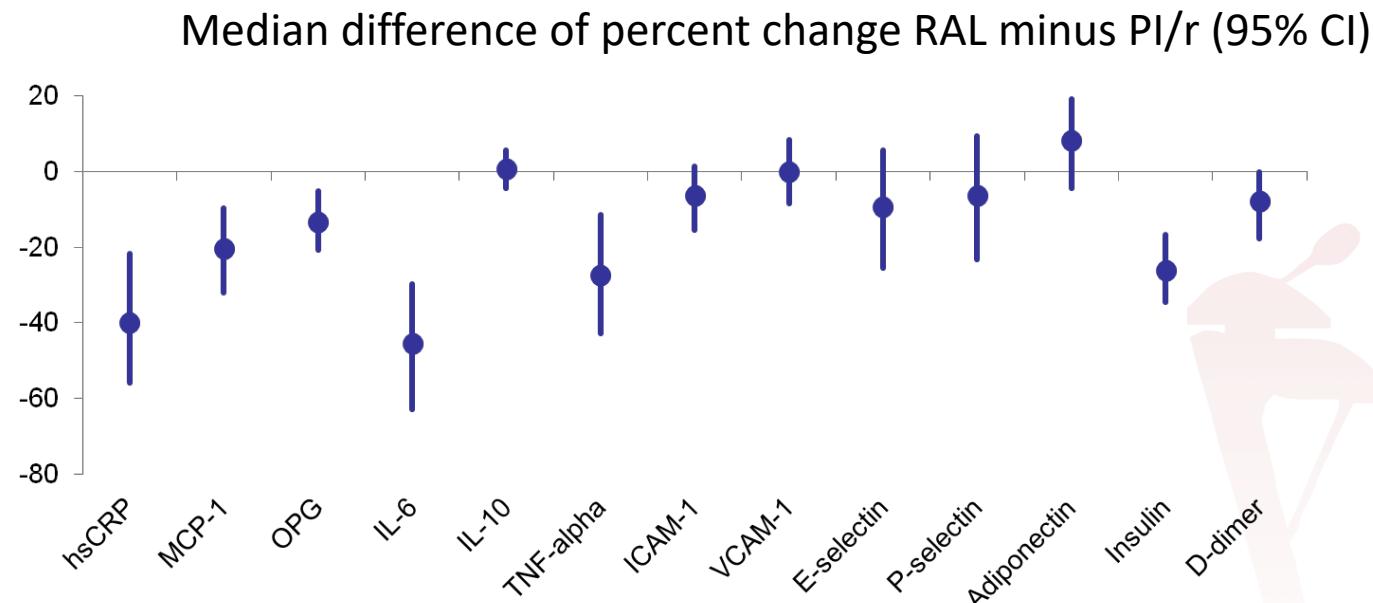
Multivariate models were adjusted for gender, age, race, HIV risk of acquisition, enrollement cohort, baseline date, prior CVD, CD4 nadir, CD4, BMI, diabetes, dyslipidamia, eGFR (all fixed at baseline), cumulative exposure to DRV/r, ATV/r, LPV/r and IDV, recent exposure ABC, prior AIDS, viral load, hepatitis B & C, family history of CVD, hypertension, smoking (all time updated)

Switch to RAL in SPIRAL led to ↓total-to-HDL cholesterol ratio



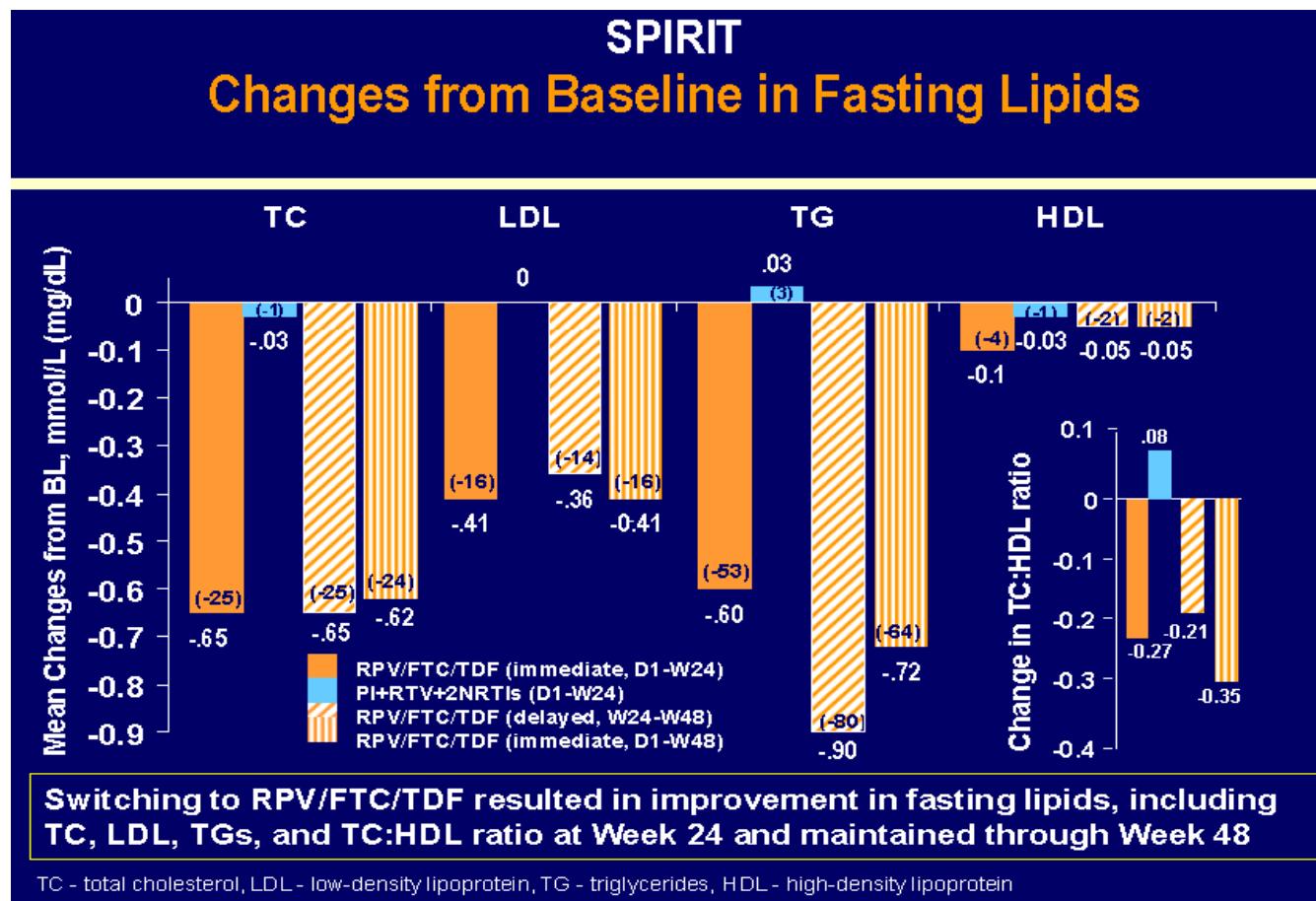
Switching from PI/r to RAL decreased CV biomarkers

SPIRAL Biomarkers Sub-study



- Generally modest or no significant correlation between changes in biomarkers and changes in lipids

Switch to RPV/TDF/FTC in SPIRIT led to ↓total-to-HDL cholesterol ratio





Switch to EVG/cobi/TDF/FTC in STRATEGY-PI did not lead to lower lipids

Change From Baseline in Fasting Lipids at Week 48

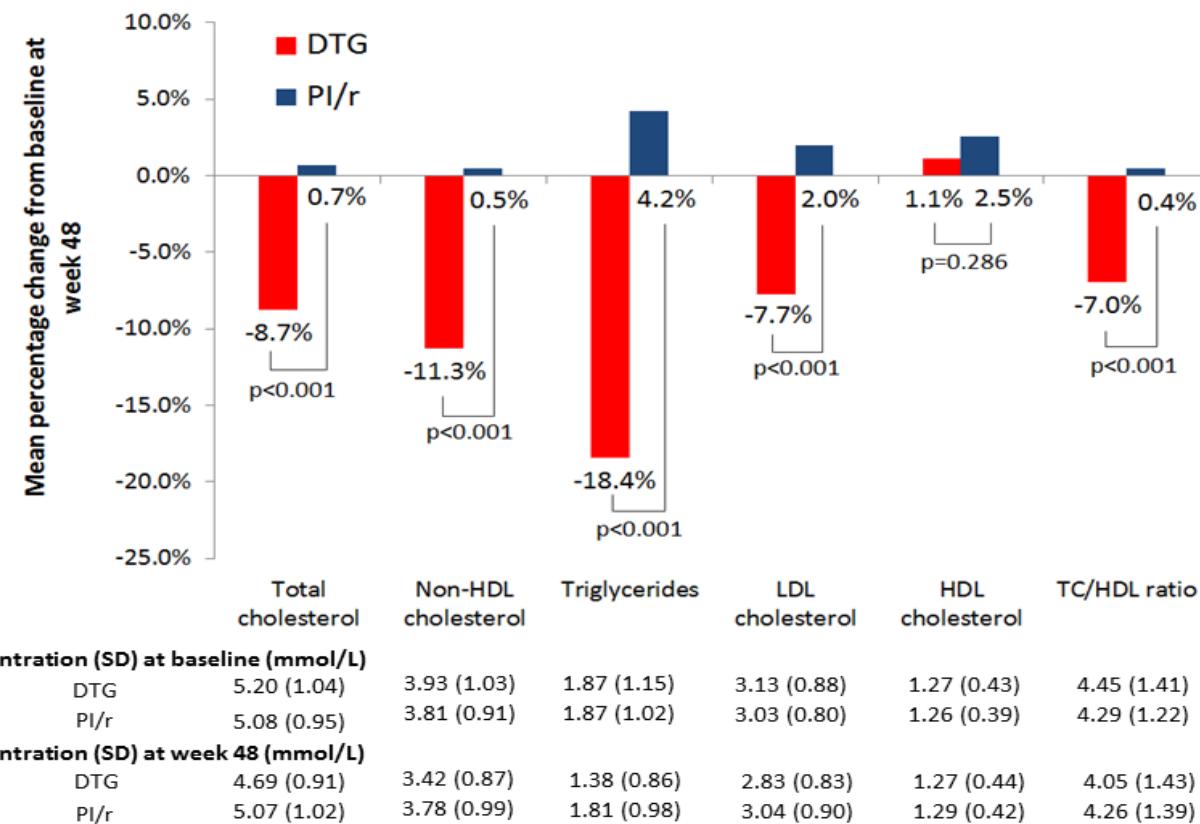
STRATEGY-PI: Darunavir Subgroup

	Total-c	LDL-c	Triglycerides	HDL-c
Baseline: median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=107)	182 (160, 206)	115 (96, 139)	111 (89, 157)	48 (42, 56)
Darunavir (n=58)	193 (169, 219)	128 (105, 152)	112 (79, 180)	51 (43, 57)
Change at Week 48: median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=105)	0 (-13, 16)	0 (-13, 15)	-11 (-35, 16)	3 (-2, 9)
Darunavir (n=53)	0 (-20, 13)	0 (-14, 13)	-5 (-31, 26)	0 (-5, 5)
P value †	0.43	0.56	0.32	0.03

†Comparison between treatment group using the Wilcoxon Rank Sum test.

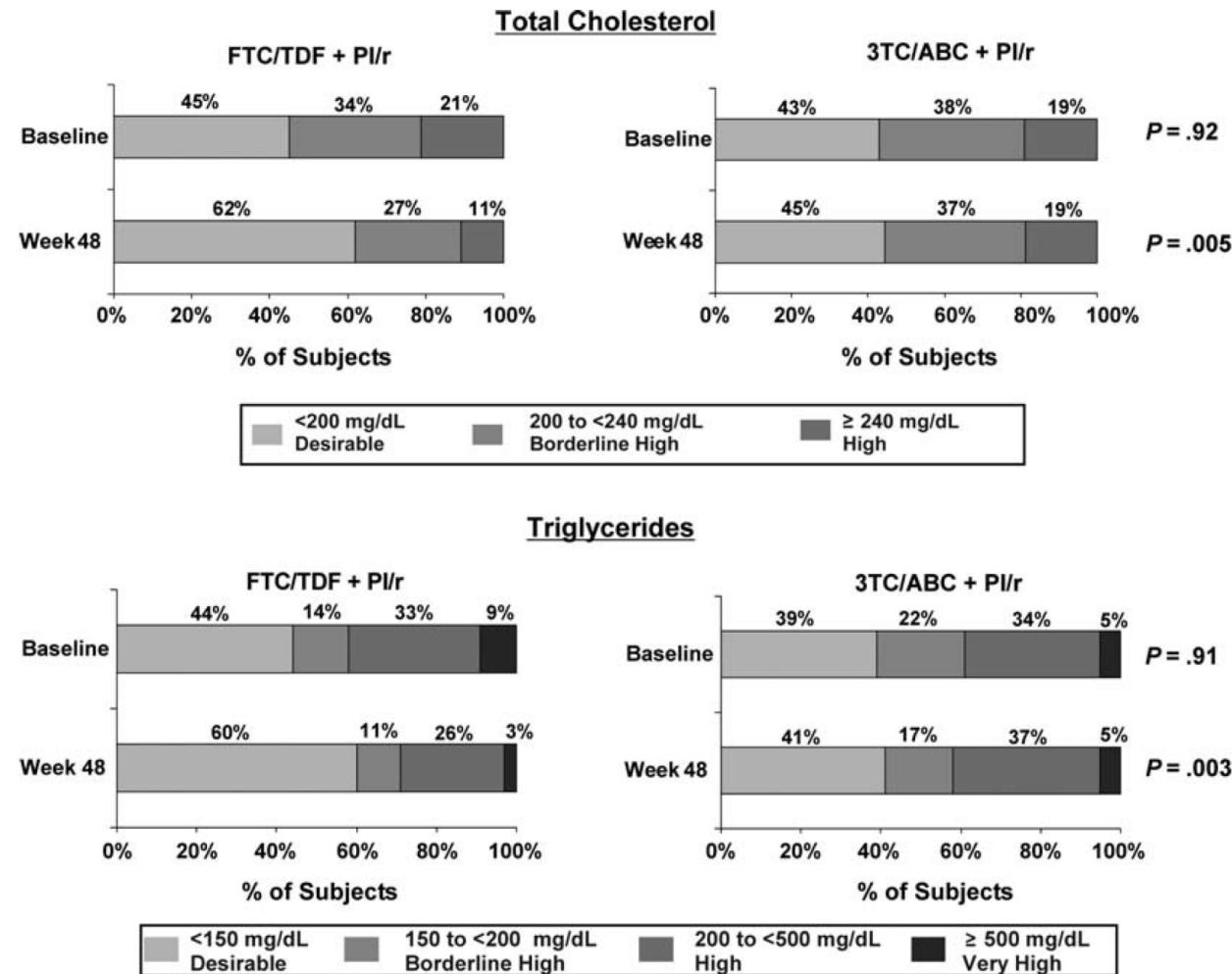
Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

Switch to DTG in NEAT022 led to ↓total-to-HDL cholesterol ratio



No changes in the utilization of lipid lowering agents (30% in each arm, both at baseline and week 48).

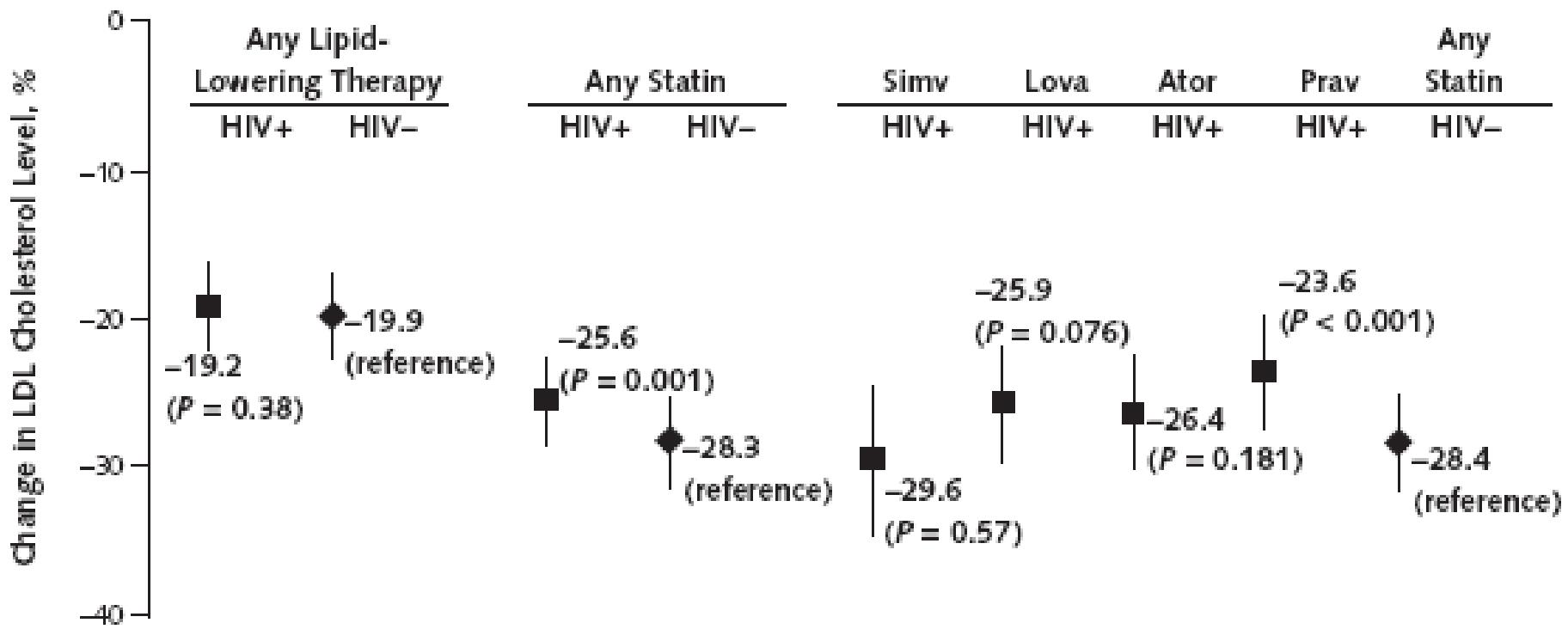
Switching from ABC to TDF decreased plasma lipids



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

Actually Quite Good!

■ HIV-infected
◆ HIV-uninfected





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 ($\frac{1}{2}$ and 1 doubling, respectively).

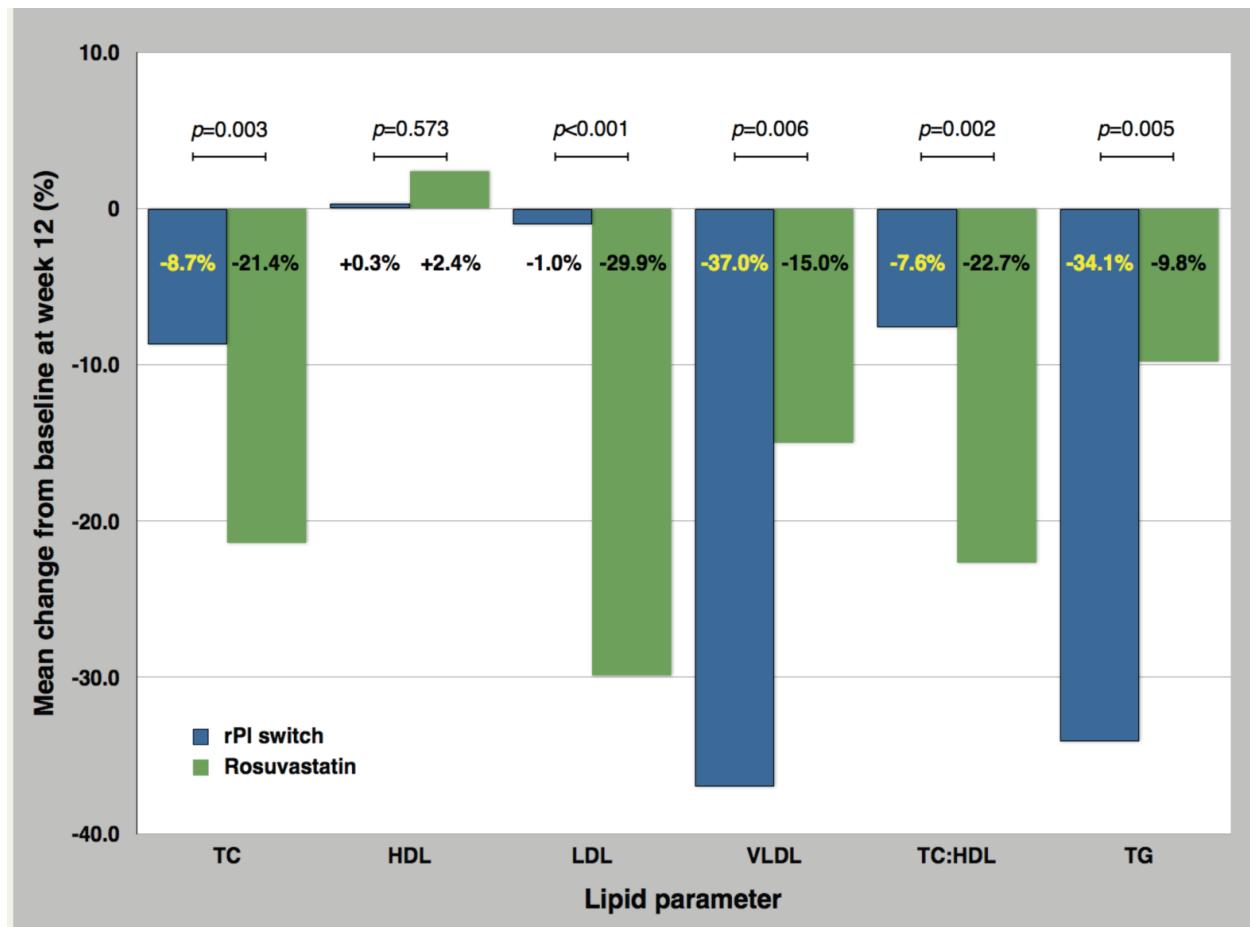
[†]Most commonly used dose in United States.

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.

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

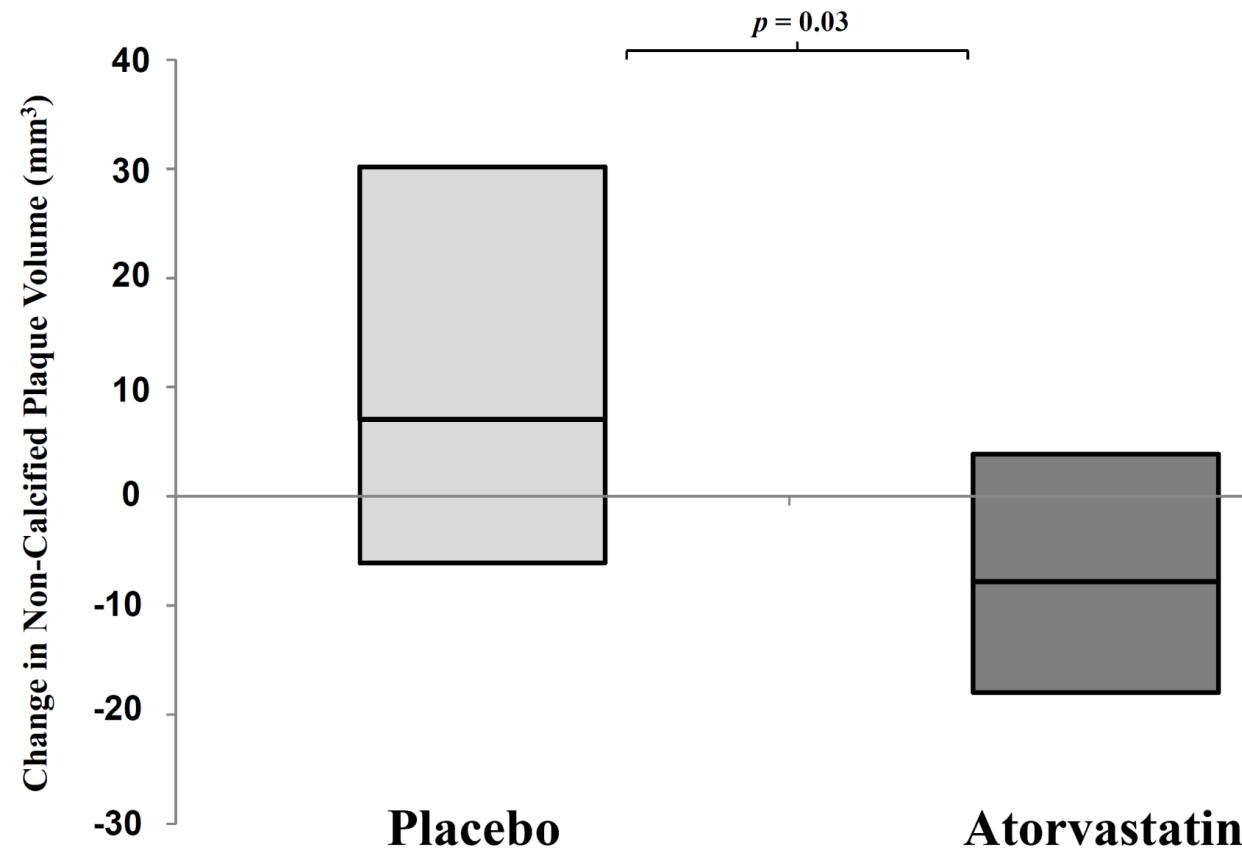




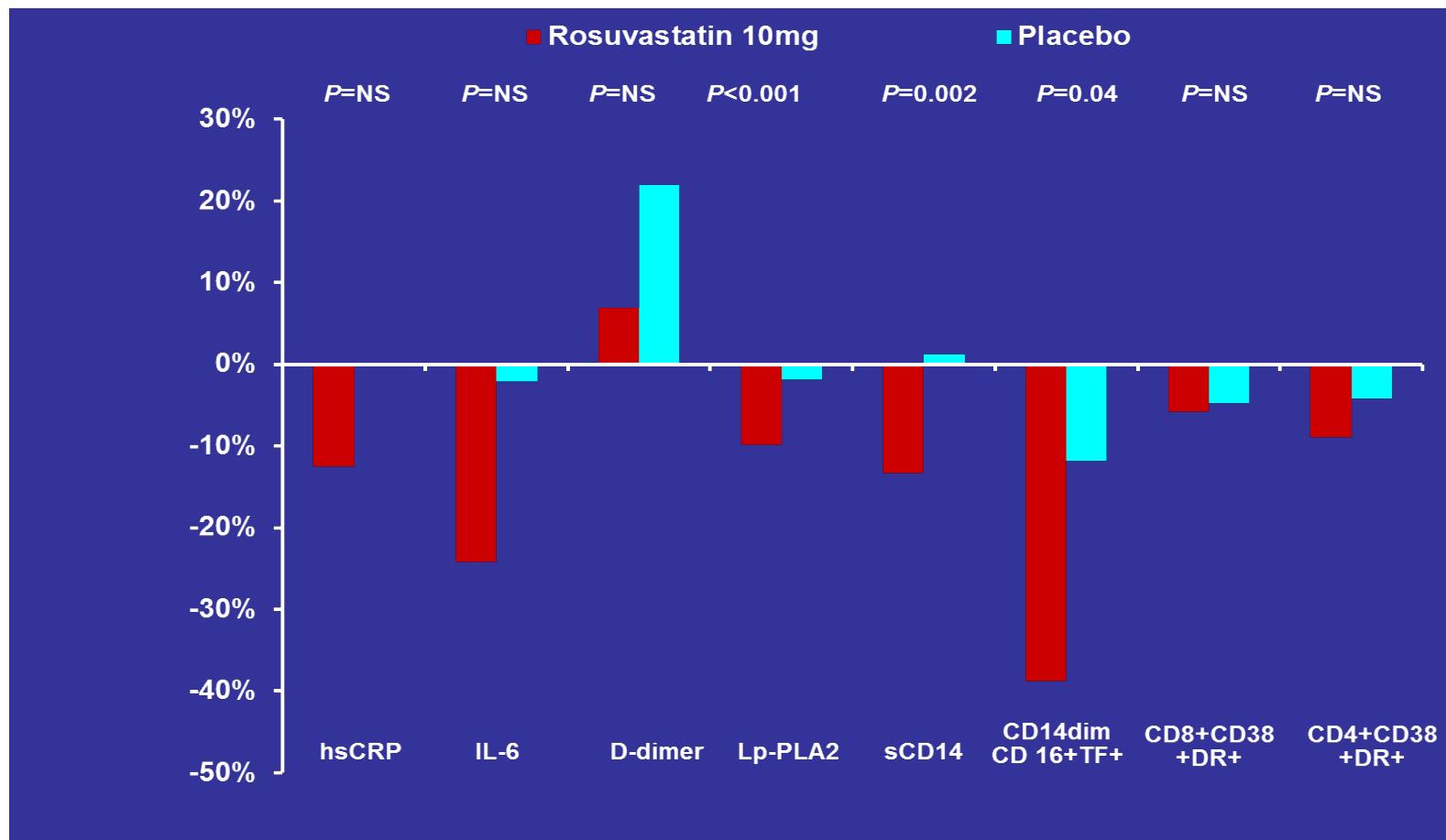
And, statin is better tolerated than PI/r switch !

	Rosuvastatin	rPI switch
One or more events, n (%)	14 (61)	14 (70)
Study drug-related events, n (%)	1 (4)	10 (50)
nausea	1 (4)	4 (20)
diarrhoea	0 (0)	4 (20)
fatigue	0 (0)	2 (10)
myalgia/myopathy	0 (0)	0 (0)
rash	0 (0)	1 (5)
other	1 (4)	6 (30)
SAEs - all, n %	1 (4)	1 (5)
SAEs - study drug-related, n (%)	0 (0)	0 (0)
Discontinuation due to adverse event, n (%)	0 (0)	0 (0)

1- year change in non-calcified plaque volume in HIV-patients randomized to atorvastatin vs placebo

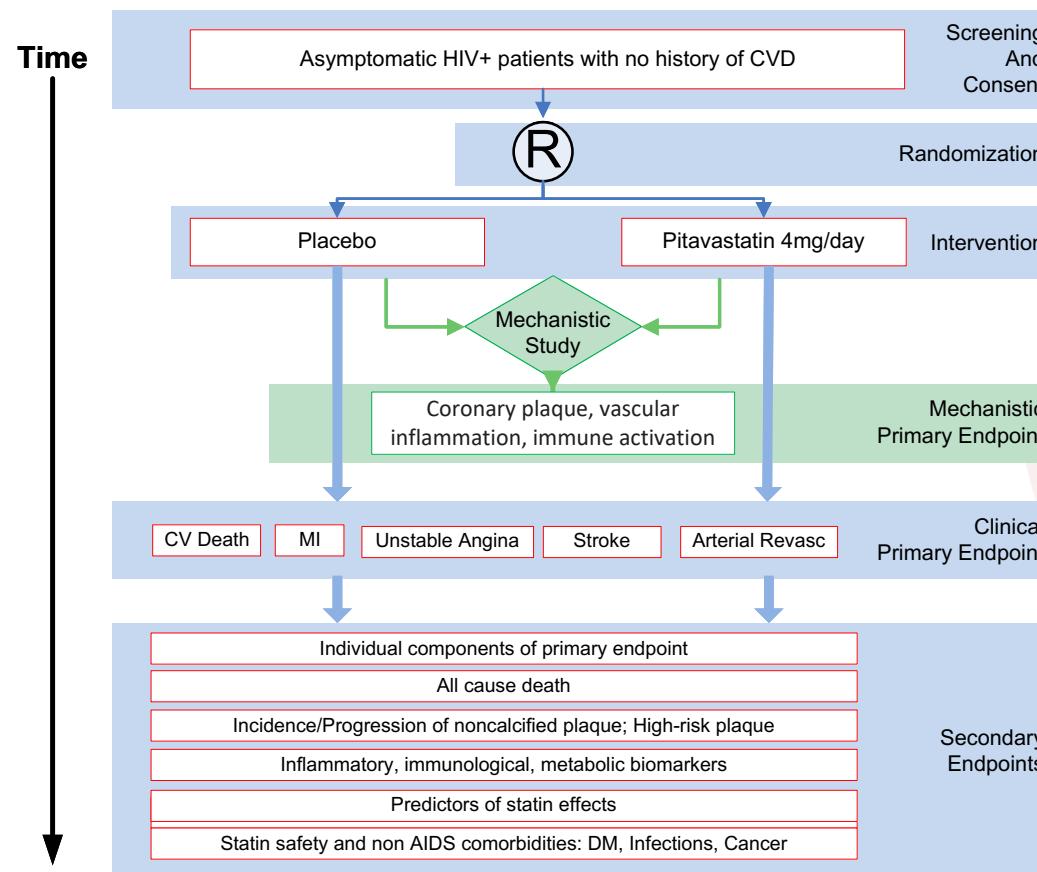


Statins also decrease inflammation and immune activation in HIV+ patients on cART





Randomized trial to prevent CV events in HIV: REPRIEVE (ACTG 5332)



Principal Investigators:
Steven Grinspoon, MD
Pamela S Douglas, MD
Udo Hoffmann, MD,
MPH
Heather Ribaudo, PhD

Decisions made

Smoker 10 cigarettes per day

- Smoking cessation considered.

No illicit drugs

- Healthy lifestyle (food, exercise).

Blood pressure 140/80 mmHg

- Boosted darunavir discontinued.

No hypertension, no diabetes

- ABC/3TC discontinued.

BMI 25 kg/m²

- Unboosted integrase inhibitor (RAL or DTG) considered.

Total cholesterol 240 mg/dL

- Tenofovir considered.

HDL cholesterol 40 mg/dL

- Atorvastatin 20 mg initiated.

LDL cholesterol 180 mg/dL

MDRD GFR 80 mL/min/1.73m²

No proteinuria

