



## Changes in Cardiovascular Biomarkers in Subjects Switching from Ritonavir-Boosted Protease Inhibitors to Raltegravir: The SPIRAL Study

E Martinez, P Monteiro, JM Llibre, F Gutierrez, D Podzamczar, A Antela, J Berenguer, I Perez, J Pich, JM Gatell, and the SPIRAL Study Group

Abstract #834



### Objectives

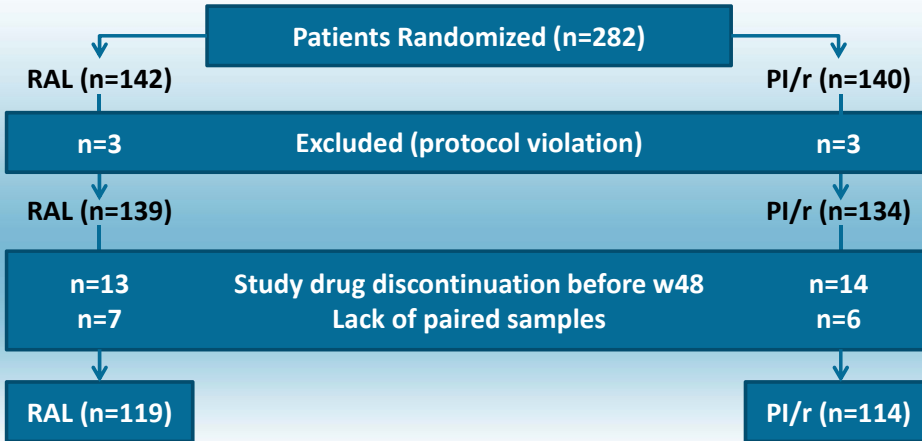
- We aimed to assess whether switching from the PI/r component to raltegraver in HIV-infected adults treated with combination therapy containing PI/r and sustained virological suppression in plasma HIV-1 RNA below 50 copies/mL induced significant changes in cardiovascular biomarkers
- Secondly, we aimed to know whether there was any correlation between changes in plasma lipids and changes in cardiovascular biomarkers



# SPIRAL Cardiovascular Biomarkers Sub-study: Participants



- Stable HIV-infected adults (≥18 years)
- HIV-RNA <50c/mL for ≥6 months
- PI/r plus ≥2 non-PI antiretrovirals
- No prior RAL use



Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.



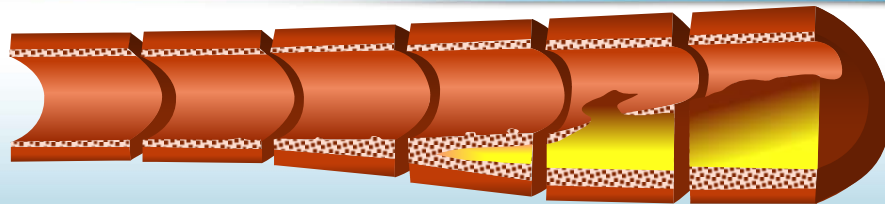
# Characteristic of Participants



	RAL (n=119)	PI/r (n=114)
<b>Age, years (IQR)</b>	43 (40-49)	44 (40-50)
<b>Men (n, %)</b>	94 (79)	83 (73)
<b>NRTI Backbone at Entry (n, %)</b>		
3TC/FTC plus TDF	69 (58)	64 (54)
3TC/FTC plus ABC	24 (20)	23 (20)
3TC/FTC plus AZT	9 (8)	10 (9)
Other	17 (14)	17 (15)
<b>PI/r at Entry (n, %)</b>		
LPV/r	52 (44)	54 (47)
ATV/r	45 (38)	40 (35)
Other	22 (18)	20 (18)
<b>Patients on 1<sup>st</sup> ART (n,%)</b>	15 (13)	14 (12)
<b>ART Exposure, Years (Median, Range)</b>	10 (5-12)	10 (6-12)
<b>PI Exposure, Months (Median, Range)</b>	31 (19-45)	30 (17-50)
<b>Previous Suboptimal ART or Virological Failure (n, %)</b>	68 (55)	55 (48)
<b>Patients with AIDS (n, %)</b>	43 (36)	42 (37)

Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.

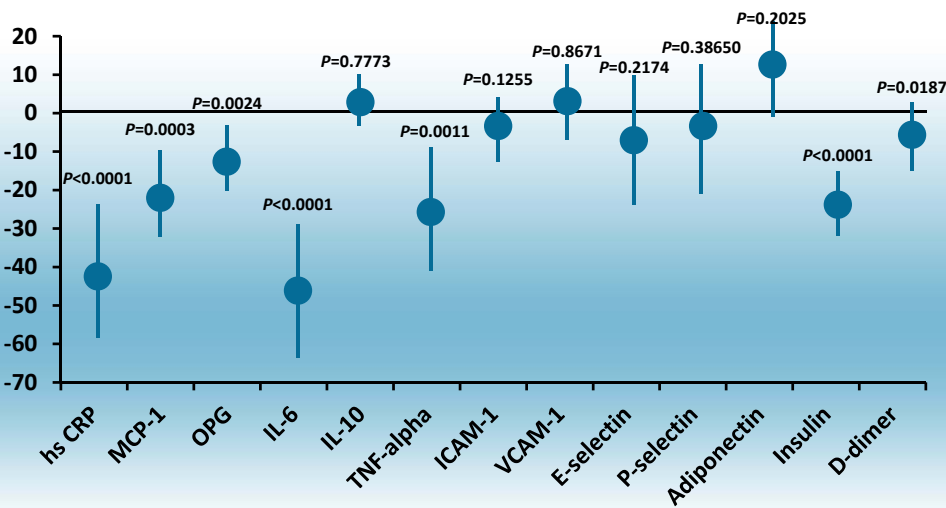
# Biomarkers and Lipids Measured at Baseline and 48 Weeks



Initiation	Progression	Complication
<b>Inflammation</b>	<b>Endothelial dysfunction Insulin Resistance</b>	<b>Hypercoagulability</b>
hsCRP, MCP-1 OPG, IL-6 TNF-alpha, IL-10	ICAM-1, VCAM-1 E-Selectin, P-Selectin Insulin, Adiponectin	D-dimer
<b>Lipids (Fasting)</b> Triglycerides, total Cholesterol, LDL Cholesterol, HDL Cholesterol		

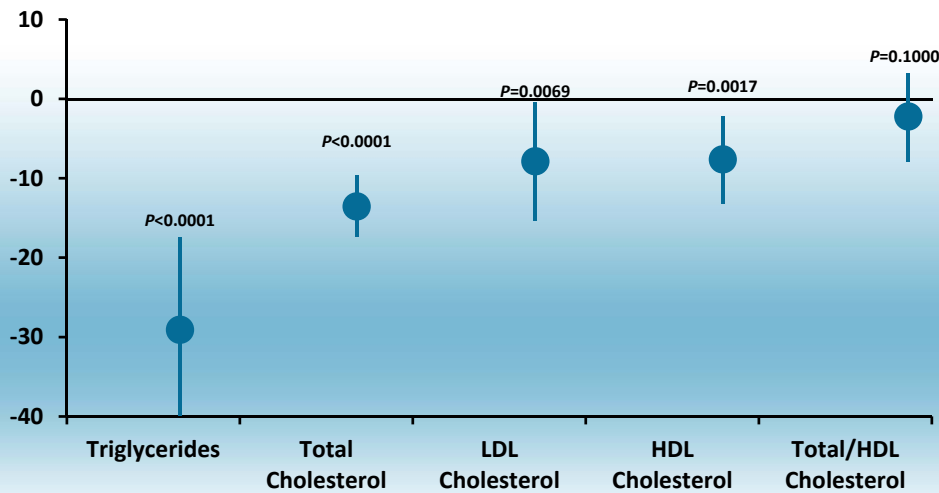
Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.

# Biomarkers: Median Difference of Percent Change RAL Minus PI/r (95% CI)



Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.

## Lipids: Median Difference of Percent Change RAL Minus PI/r (95% CI)



Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.

## Correlations Between $\Delta$ Biomarkers and $\Delta$ Lipids

	Spearman's rho			
	$\Delta$ Triglycerides	$\Delta$ Total Cholesterol	$\Delta$ LDL Cholesterol	$\Delta$ HDL Cholesterol
$\Delta$ hsCRP	-	-	0.24 ( $P=0.0016$ )	-
$\Delta$ MCP-1	-	0.16 ( $P=0.032$ )	-	0.18 ( $P=0.020$ )
$\Delta$ OPG	-	-	-	-
$\Delta$ IL-6	-	-	-	-
$\Delta$ IL-10	-	-	-	-
$\Delta$ TNF-alpha	-	-	-	-
$\Delta$ ICAM-1	-	-	-	-
$\Delta$ VCAM-1	-	-	-	-
$\Delta$ E-selectin	-	-	-	-
$\Delta$ P-selectin	-	-	-	-
$\Delta$ adiponectin	-	-	-	-
$\Delta$ Insulin	0.28 ( $P=0.0001$ )	0.2125 ( $P=0.004$ )	-	-
$\Delta$ D-dimer	-	-	-	-

Only correlations showing a P value of  $< 0.05$  are shown

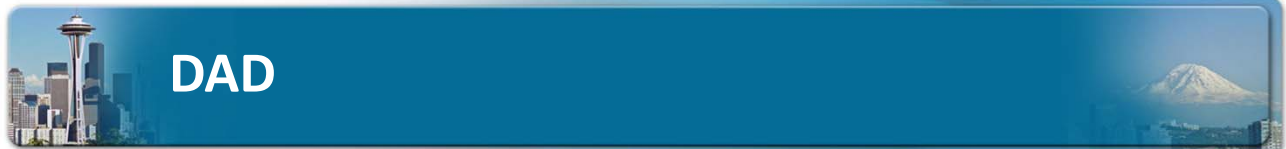
Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.



## Conclusions

- Switching from PI/r to RAL in SPIRAL study led not only to significant changes in plasma lipids but also to significant changes in several cardiovascular biomarkers associated with inflammation, insulin resistance and hypercoagulability, although not in those associated with endothelial dysfunction
- There were few and weak significant correlations between changes in lipids and changes in biomarkers suggesting that decreases in inflammation, insulin resistance, and hypercoagulability biomarkers were rather independent of lipid changes

Martinez E et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 834.



## DAD

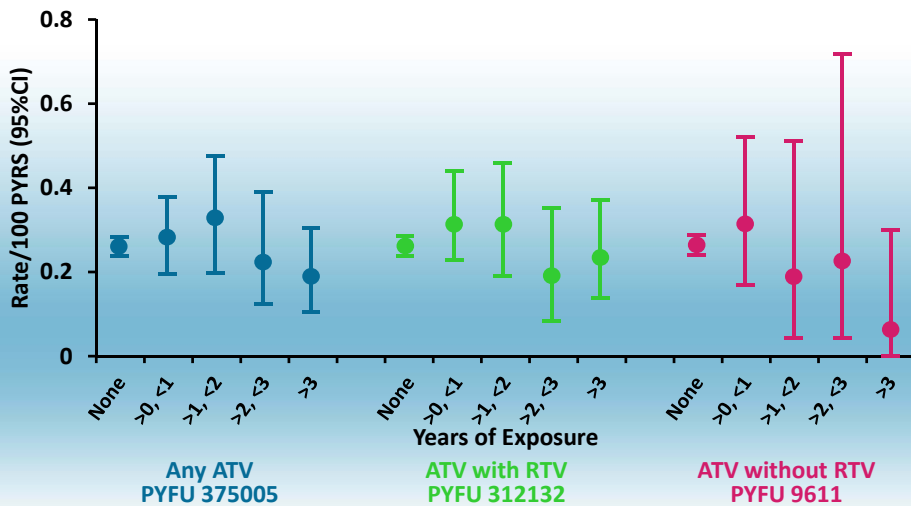
- Previous analysis found PIs associated with increase CV risk
- Did not include ATV or ATV/r
- Now has sufficient numbers
- Includes over 49,000 patients, with 37,000 person-years follow-up on ATV
- Results: no association of ATV or ATV/r with increase risk of MI or stroke, contrasting with IPV/r and IDV/r
- (No reduced risk found with increase Bilirubin)

Montefore A et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 823.





**MI Rate Stratified by Cumulative Exposure to (i) and any ATV, (ii) ATV with Ritonavir, and (iii) ATV Without Ritonavir**



Montefore A et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 823.

**Online Expert Poster Review and Discussion**  
**ARV Therapies and Therapeutic Strategies**  
*Reporting From*  
**The 19th Conference on Retroviruses and Opportunistic Infections (CROI)**  
JOINTLY SPONSORED BY THE POSTGRADUATE INSTITUTE FOR MEDICINE AND VIRALÉD, LLC

**Effect of Statin Therapy on Reducing the Risk of Serious Non-AIDS-Defining Events and Non-Accidental Death in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) Cohort**

Edgar Turner Overton<sup>1</sup>, Doug Kitch<sup>2</sup>, Pablo Tebas<sup>3</sup>, Peter W. Hunt<sup>4</sup>,  
 Heather Ribaud<sup>2</sup>, Marlene Smurzynski<sup>2</sup>, James H. Stein<sup>5</sup>, Constance A. Benson<sup>6</sup>

<sup>1</sup>University of Alabama, Birmingham, AL; <sup>2</sup>Harvard School of Public Health, Boston, MA;  
<sup>3</sup>Hospital of the University of Pennsylvania, Philadelphia, PA; <sup>4</sup>UCSF HIV/AIDS Division, San Francisco, CA;  
<sup>5</sup>University of Wisconsin School of Medicine and Public Health, Madison, WI; <sup>6</sup>UCSD Antiviral Research Center, San Diego, CA

Abstract #124



## Statins in Diseases of Aberrant T-cell Activation



- Rheumatoid Arthritis (2 RCTs)
  - Reduced Disease Activity Score
  - Mediated by Reduction in inflammatory parameters (IL-6, TNF- $\alpha$ , CRP)
- Kaiser Permanente Case-Control Study
  - 259 cases of lymphoma
  - 1295 matched controls
  - 45% reduction in NHL with statin use  
aHR 0.55 (95% CI: 0.31-0.95)
- Johns Hopkins HIV Clinical Cohort
  - 1538 person on suppressive HAART
  - 85 deaths
  - 3-fold reduction in mortality with statin use  
Adjusted relative hazard 0.33 (95% CI: 0.14-0.76)

McCarey et al. Lancet 2001; 363:2015-21; E. Barcary et al. Journal of Rheum, 2011;38:229-235



## Analysis Plan: Marginal Structural Model Methodology

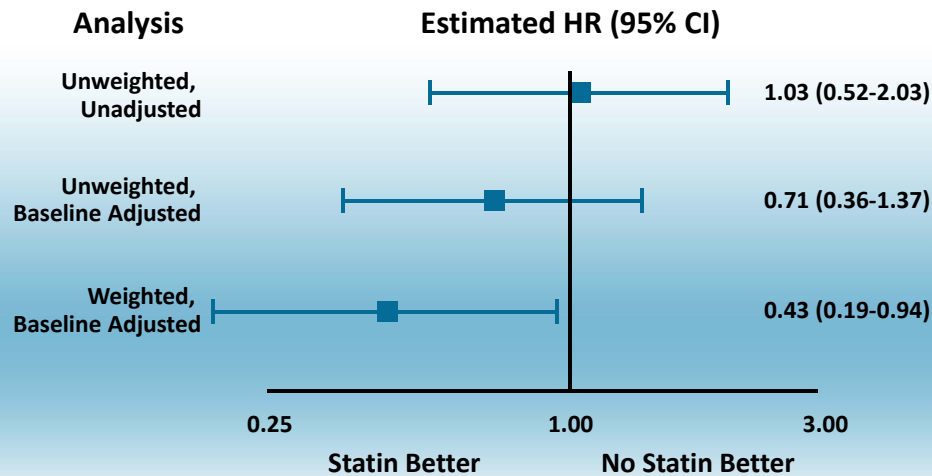


- Observational studies are fraught with bias due to confounding
- Time-dependent covariates, particularly those that are related to both the exposure and the outcome may confound results
  - Examples: Age, LDL Cholesterol, Blood Pressure
- IPTW and IPCW were used to create a *pseudopopulation* in which this confounding is not present

Overton TE et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 124.



# Malignancy Endpoint Analysis Effect of Statins (89 Events)



Overton TE et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 124.

# Conclusion

- Statin therapy was associated with a non-significant reduction in time to first non-AIDS events or death
  - 19% if early events excluded; 12% if early events included
- Suggestion of benefit in malignancies
  - Effect was attenuated by inclusion of early events
- Although not statistically significant, the observed effect increased with age and was influenced by nadir CD4 counts
- Additional studies are needed to evaluate the potential benefit for HIV-infected patients
  - Focus on persons of older age with LDLc <130
  - Consider CD4 nadir as a stratification parameter

Overton TE et al. 19<sup>th</sup> CROI; Seattle, WA; March 5-8, 2012; Abst. 124.