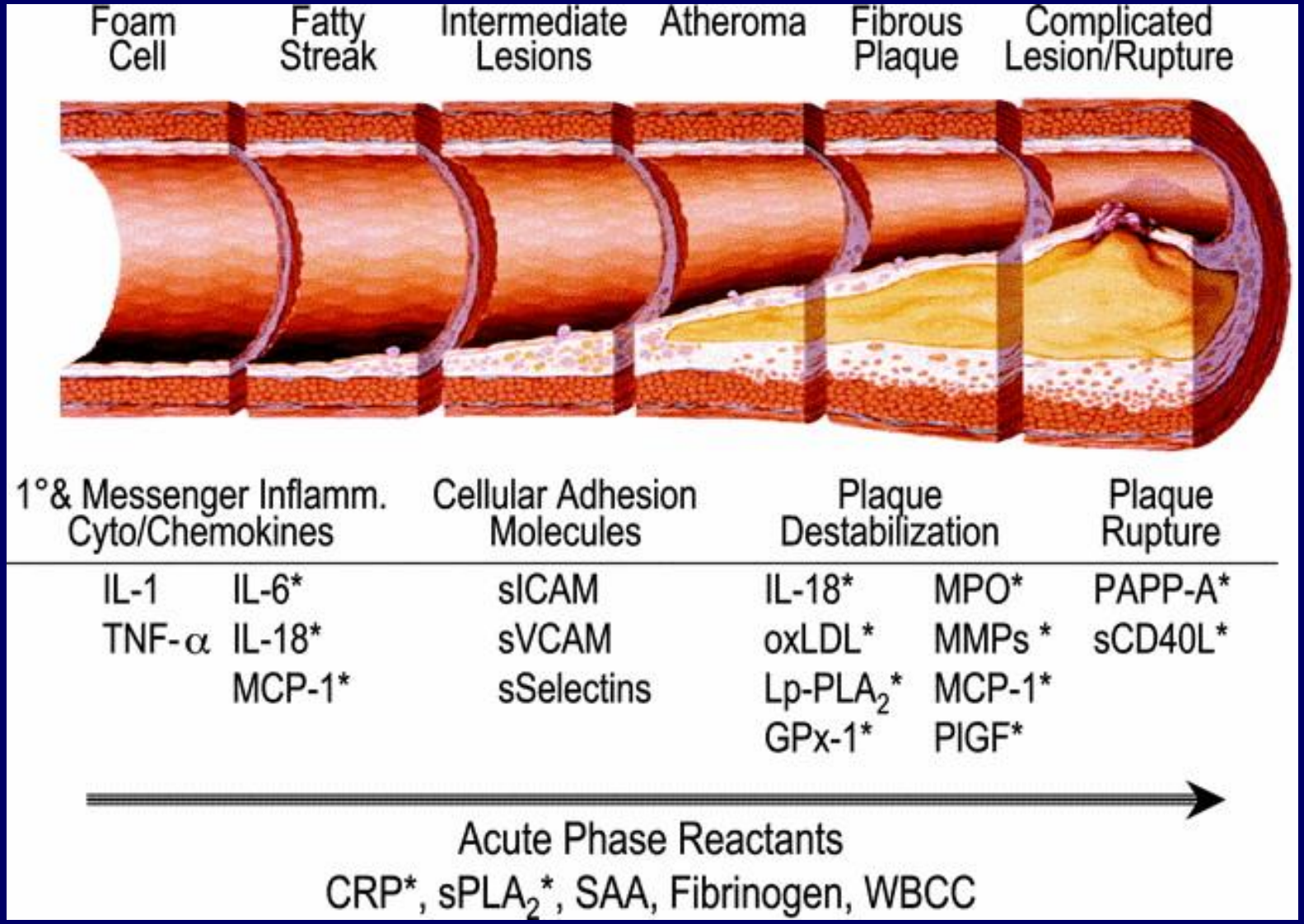
Potential Mechanisms of Increased Atherogenesis in HIV

Roger Bedimo, MD

- Cholesterol Metabolism
- Inflammation and Endothelial Dysfunction
- Flow Mediated Vasodilation
- Intima-Media Thickness

Atherogenesis: Biomarkers of plaque instability and rupture



Koenig W, Khuseyinova N. *Arterioscler Thromb Vasc Biol* 2007;1:15-26.

Potential Atherogenic Effects of HIV and HAART: 3 Stages of Atherogenesis

3

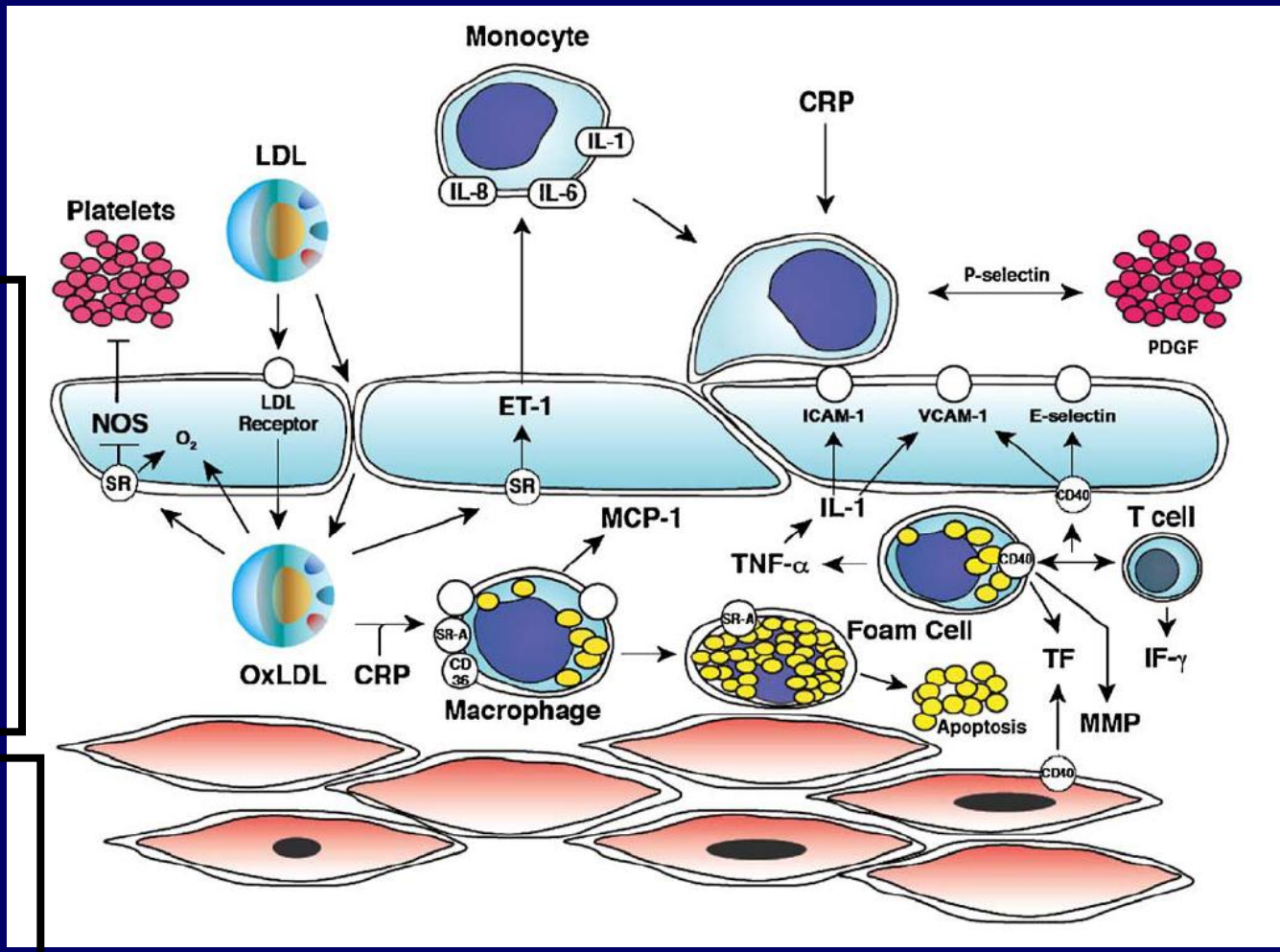
Thrombosis (Coagulation):
-D-dimer
-PAI-I

2

Plaque Instability and Rupture:
-Endothelial activation (adhesion molecules: VCAM-1)
-Inflammation (hsCRP, IL6, TNFα)

1

Atheroma Formation and Growth
-Inflammation



Sudano et al., AHJ. 2006 Jun;151(6):1147; Seminari, Atherosclerosis 2002;162:433 -8.
Mujawar et al., PLoS Biol. 2006;4; Blanco et al., JAC. 2006 Jul;58(1):133-9

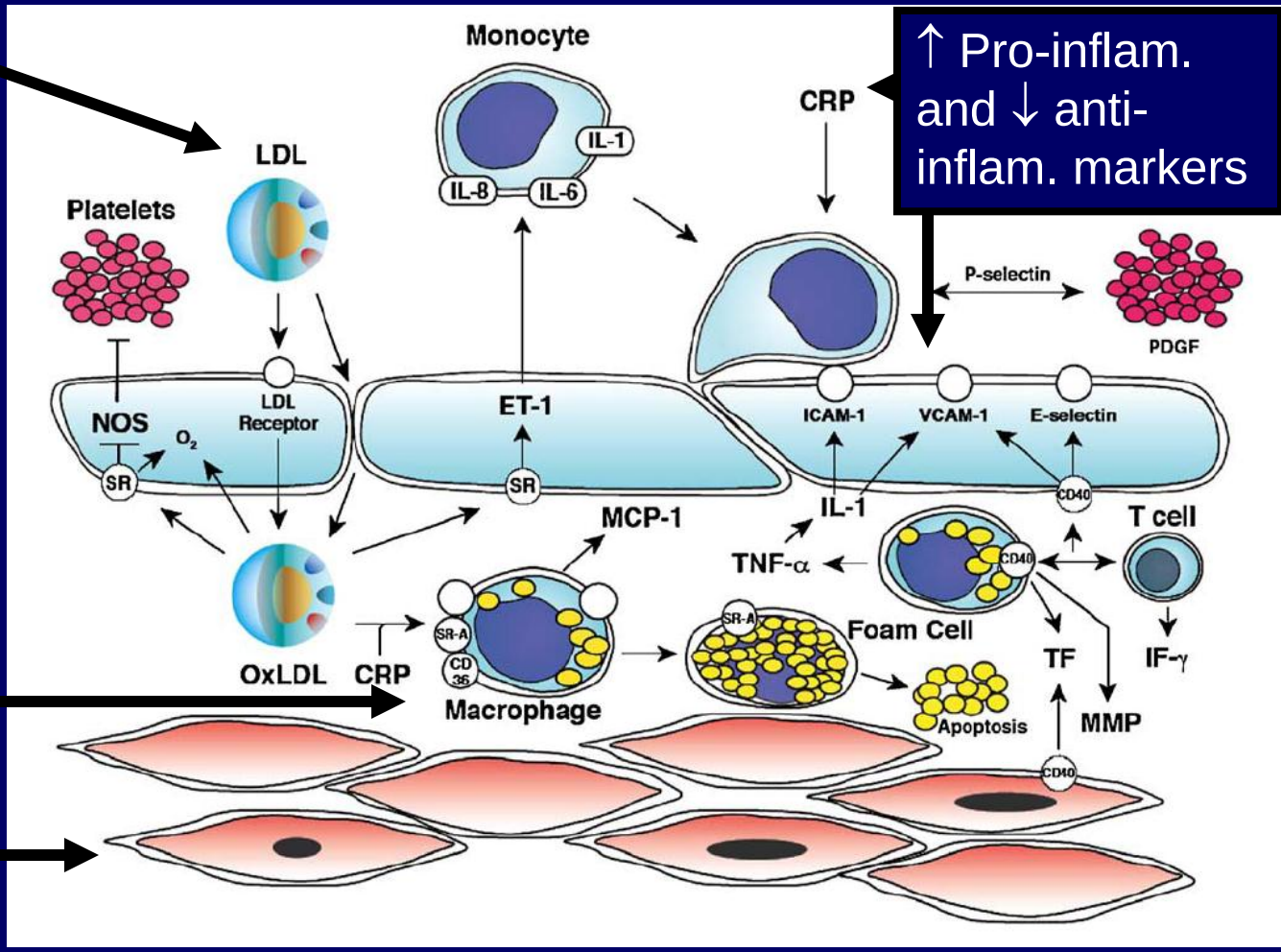
Potential Atherogenic Effects of HIV Infection and HAART

Atherogenic liporotein profile:

Endothelial dysfunction:
-Impaired FMD
- ↑ Activation markers

Impairment of cholesterol efflux from macrophages

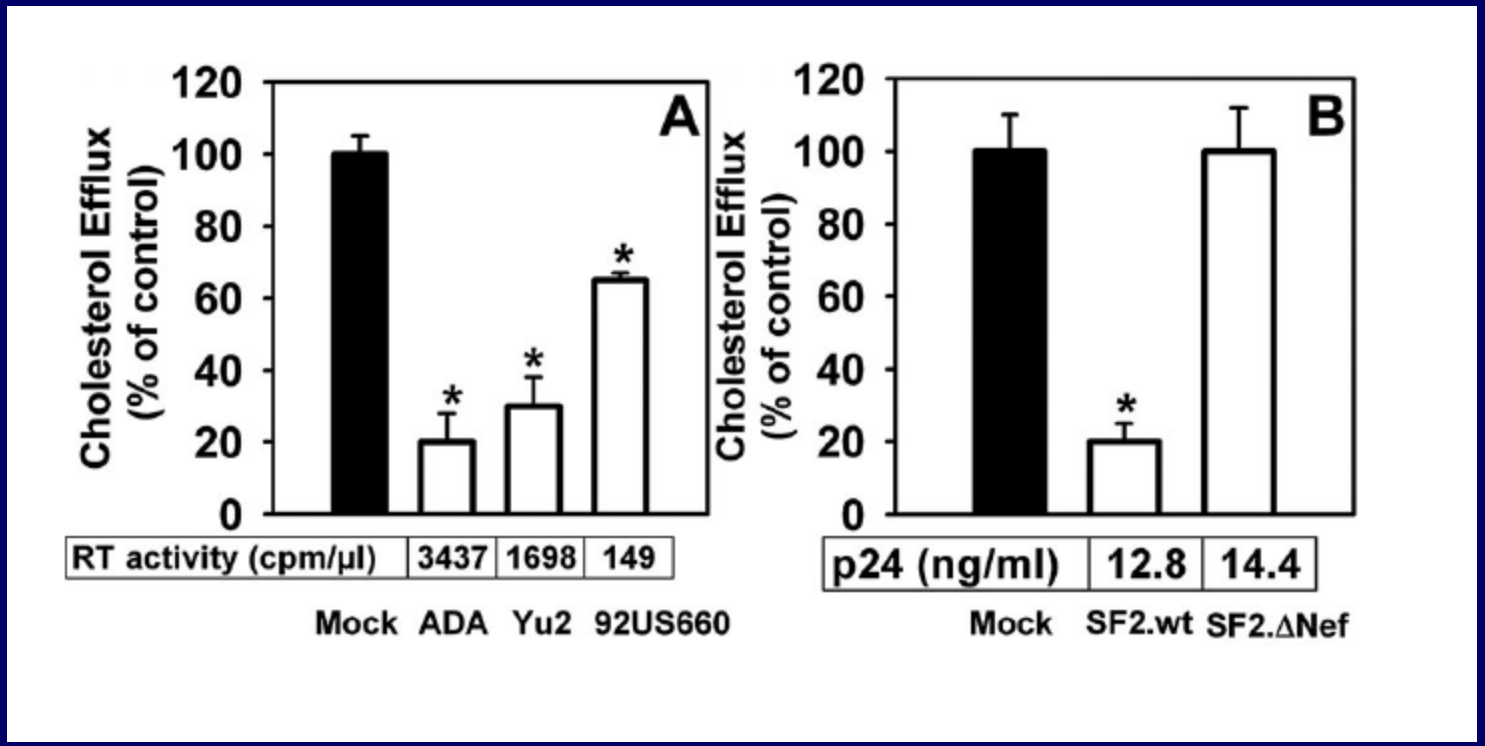
Increased intima-media thickness



Sudano et al., AHJ. 2006 Jun;151(6):1147; Seminari, Atherosclerosis 2002;162:433 -8. Mujawar et al., PLoS Biol. 2006;4; Blanco et al., JAC. 2006 Jul;58(1):133-9

HIV Impairs Cholesterol Efflux from Macrophages

Impairment of cholesterol efflux is highly atherogenic



Impairment of cholesterol efflux is function of reverse transcriptase activity and is Nef-dependent

Mujawar et al., PLoS Biol. 2006 Oct 31;4(11)

Untreated HIV Infection Associated With Increased Endothelial Activation and Inflammation

- Markers of endothelial activity significantly increased in HIV-infected ART-naive patients vs HIV-uninfected controls
  - Similar activity observed between treated patients with low HIV-1 RNA (<1000 copies/mL) and HIV-uninfected patients
- Inflammatory markers (sTNFRII) expressed at significantly higher levels in HIV-infected vs HIV-uninfected patients
  - Among infected patients, markers higher in therapy-naive vs therapy-experienced patients
- In HIV-infected patients, inflammation significantly correlated with endothelial activation markers (sICAM, sVCAM, vWF) and with marker of CVD (MPO)
  - No correlation between lipoatrophy and endothelial markers

Ross AC, Armentrout R, O'Riordan M, et al ; 15th CROI; Abstract 954

Reductions in Increased Markers of Endothelial Activation Observed After HAART Initiation

Endothelial Activation Markers, Mean (± SEM)	***HIV Infected (n = 115)***		***HIV Uninfected (n = 30)***
	Baseline	***Month 3***	
sICAM-1, ng/mL	296 (24)*	248 (12)†	144 (12)
sVCAM-1, ng/mL	957 (40)	766 (33)‡	876 (39)
tPAI-1, pg/mL	18,473 (1399)*	18,065 (1208)	5490 (576)
hsCRP, ng/mL	28,060 (5530)*	14,708 (2358)‡	6665 (2,063)
E-selectin, ng/mL	17.9 (1.1)	15.1 (0.8)‡	15.8 (1.2)

sVCAM, soluble vascular cell adhesion molecule.
*$P < .001$ vs control.; †$P < .05$ vs naive.; ‡$P < .001$ vs naive.

Sloth Kristoffersen U, Kofoed K, Kronborg G; 15th CROI; Abstract 953

Similar Declines in Biomarkers of Inflammation & Endothelial Dysfunction with ABC/3TC vs. TDF/FTC

- HAART-naïve: Similar Reductions in Biomarker Concentrations with at week 48 & 96 between ABC/3TC and TDF/FTC (HEAT Trial)[1]
  - sVCAM-1 (-49% vs. -48%), IL-6 (-23% vs. -26%), hsCRP
- HAART-experienced: No Difference in Biomarker Concentrations 48 weeks after Switch to ABC/3TC vs. TDF/FTC; all changes modest (BICOMBO Trial) [2]
  - CRP, MCP-1, IL-6, IL-10, TNF-alpha, ICAM-1, VCAM-1 (0.02 vs. -0.01%), selectin E, selectin P, and D-dimer.

[1]McComsey et al., CROI 2009; Abstract #732
[2] Martinez et al., AIDS. 2010 Jan 28;24(3):F1-9.

SMART Study: Non-AIDS Events

Endpoint, n	*Viral Suppression Arm (n = 2752)*	*Treatment Interruption Arm (n = 2720)*	*HR (95% CI)**	*P Value*
Major cardiovascular, renal, or hepatic disease	39	65	1.7 (1.1-2.5)	.009
• **Fatal/nonfatal cardiovascular disease**	**31**	**48**	**1.6 (1.0-2.5)**	**.05**
• Fatal/nonfatal renal disease	2	9	4.5 (1.0-20.9)	.05
• Fatal/nonfatal liver disease	7	10	1.4 (0.6-3.8)	.46

El-Sadr WM, Lundgren JD, Neaton JD, et al.
N Engl J Med. 2006;355:2283-2296.

Correlation Between Increased IL-6 and D-Dimer Levels and HIV-1 RNA in Treatment Interruption Patients

*Change in Plasma Marker From Baseline to Month 1**	*Month 1 HIV-1 RNA ≤ 400 copies/mL*	*Month 1 HIV-1 RNA 401-10,000 copies/mL*	*Month 1 HIV-1 RNA 10,000-50,000 copies/mL*	*Month 1 HIV-1 RNA > 50,000 copies/mL*	*P Value for Trend*
D-dimer, µg/mL	0	0.04	0.11	0.28	.0005
IL-6, $\log_{10}$ pg/mL	0.08	0.14	0.20	0.33	.0003

*Patients in TI arm on HAART at baseline and with HIV-1 RNA levels ≤ 400 copies/mL.

Kuller L, SMART study group. 15th CROI; February 3-6, 2008;. Abstract 139.

Levels of inflamm. and coagulation correlated with ↑ risk of death

Plasma Marker	*Adjusted OR* for Baseline Levels*	*P Value*	*Adjusted OR† for Change From Baseline*	*P Value*
hsCRP	2.8	.03	5.5	.003
Amyloid A	2.6	.09	2.2	.09
Amyloid P	1.1	.84	0.32	.04
IL-6	11.8	< .0001	5.3	.006
D-dimer	26.5	< .0001	5.0	.02
Prothrombin fragments 1 & 2	1.2	.66	1.2	.77

*Comparison of all-cause mortality between first and fourth quartile.
†Per average difference between first and fourth quartile.

Kuller L, SMART study group. 15th CROI; February 3-6, 2008;. Abstract 139.

HIV ↑ the Risk of Atherosclerosis as Much as Traditional Risk Factors

Cross-sectional study comparing carotid IMT in 433 HIV+ patients from FRAM study and HIV- patients from CARDIA and MESA studies.
At baseline, compared to HIV-, FRAM participants (> 90% on HAART) were:
-younger (median 49 vs. 60 years), and had lower rate of diabetes.
-but were more likely to be men (70% vs 47), to smokers and have dyslipidemia.

	Internal carotid bulb			Common carotid		
	Unadjusted	Model 1	Model 2	Unadjusted	Model 1	Model 2
Difference (HIV+ to HIV-)	0.11	0.19	0.15	0.02	0.04	0.03
P value	<0.0001	<0.0001	0.0001	0.017	0.0004	0.005

Effect on internal carotid bulb IMT (difference in mm) in multivariate analysis:
HIV infection: 0.15 mm; Male sex: 0.13 mm; Current smoking: 0.17 mm;
Diabetes: 0.12 mm; Older age (per 10 years): 0.16 mm.
HIV effect greater than hypertension and dyslipidemia

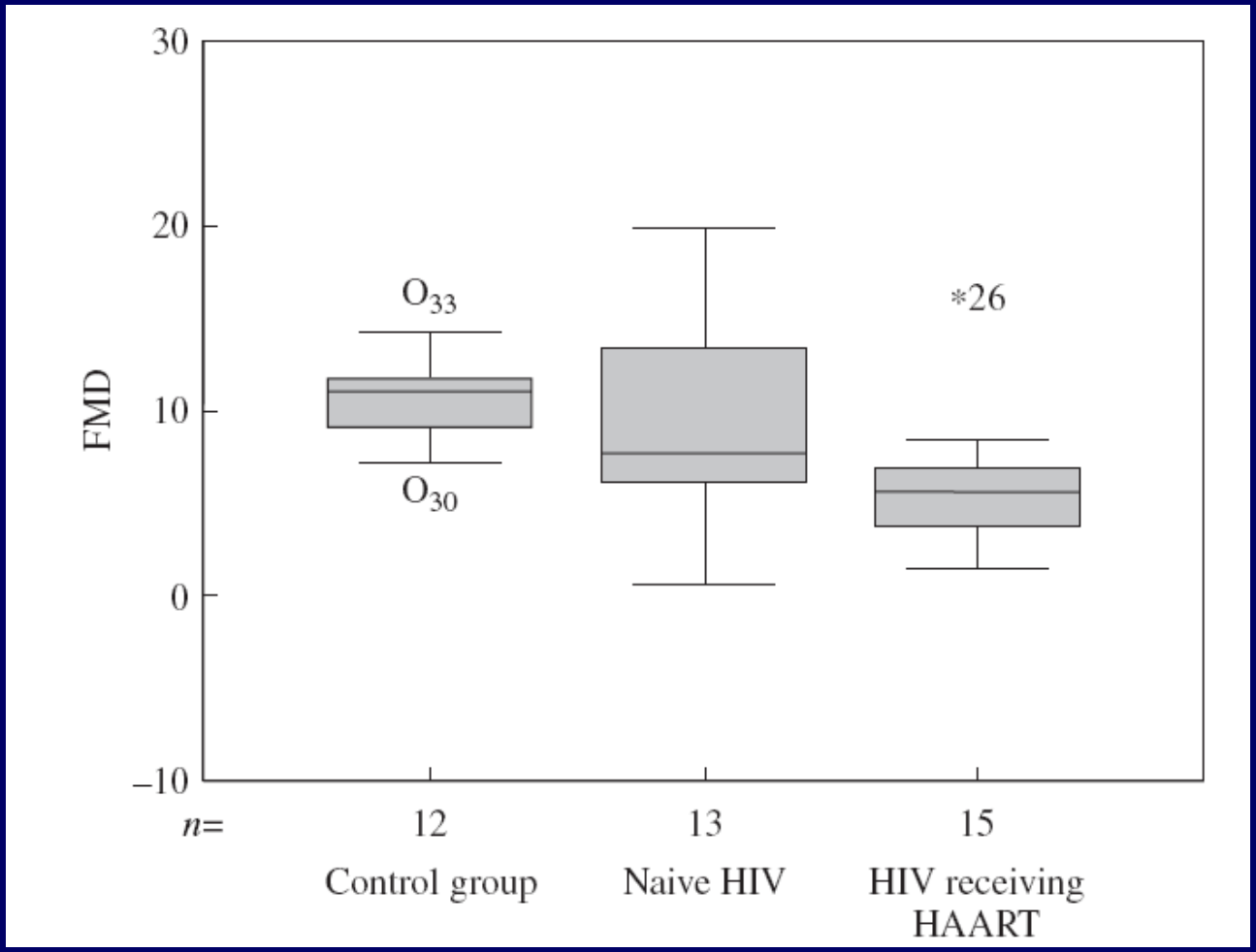
Grunfeld. CROI 2009; Abstract 146

FMD in HIV Patients on HAART

Cross-sectional study: Patients with low or mild coronary risk and lipid levels within the normal range.

Subjects with DM, HTN, CVD, obesity, high cholesterol or high triglyceride levels were excluded.

*FMD (% change) of HIV+ on HAART (5.93 ± 3.56) vs. Controls (10.64 – 3.08, P = 0.008)



O_{33}, O_{30} and 26 are outliers

No difference b/w arms after adjusting for age, sex, smoking, total cholesterol, pulse pressure and basal brachial artery diameter.

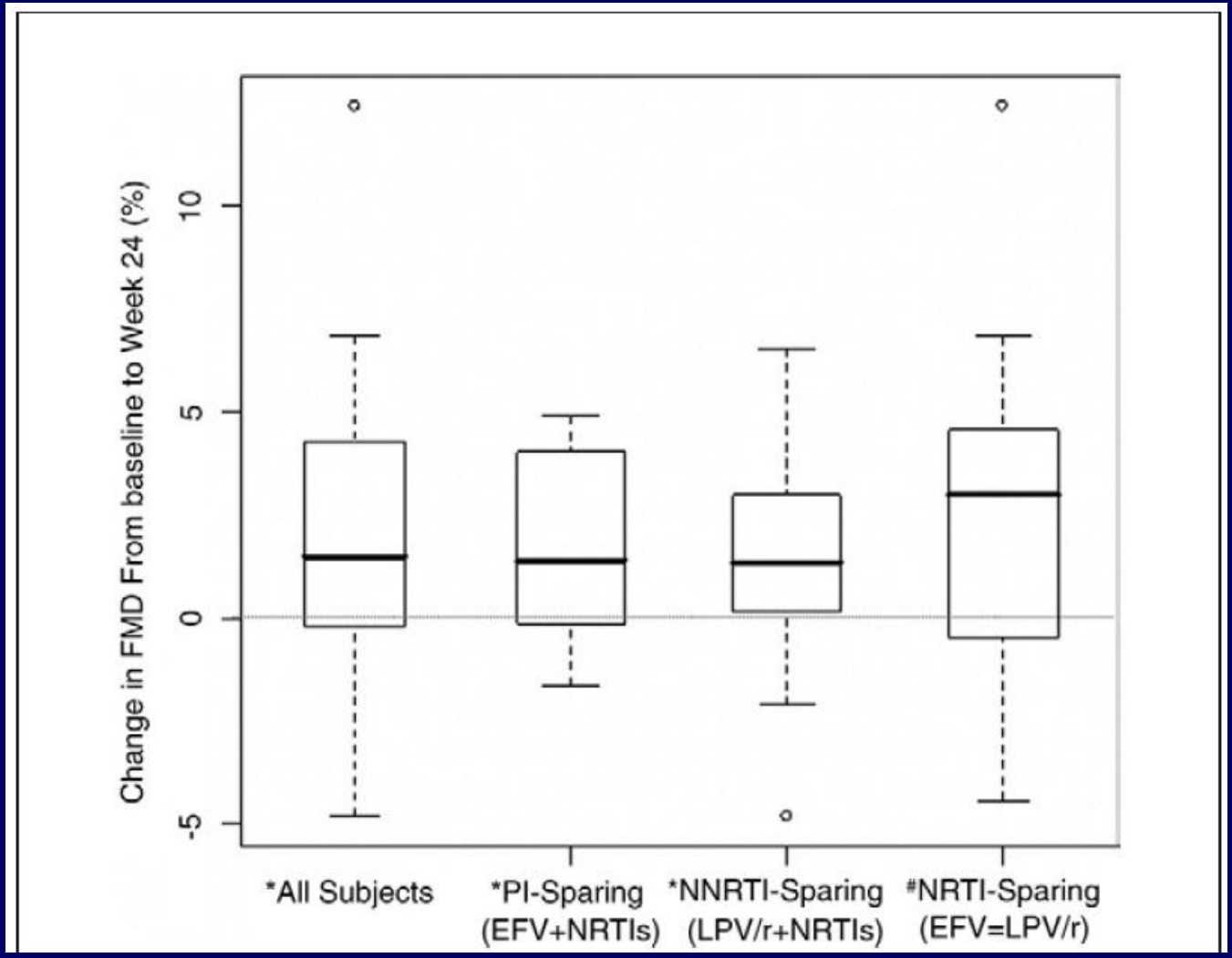
Blanco et al., J Antimicrob Chemother. 2006 Jul;58(1):133-9.

Changes in FMD from Baseline to Week 24 of HAART (A5152s Study)

Exclusion: Prior use of ART, known CVD, DM, and current (within 6 wks) use of lipid-lowering Rx

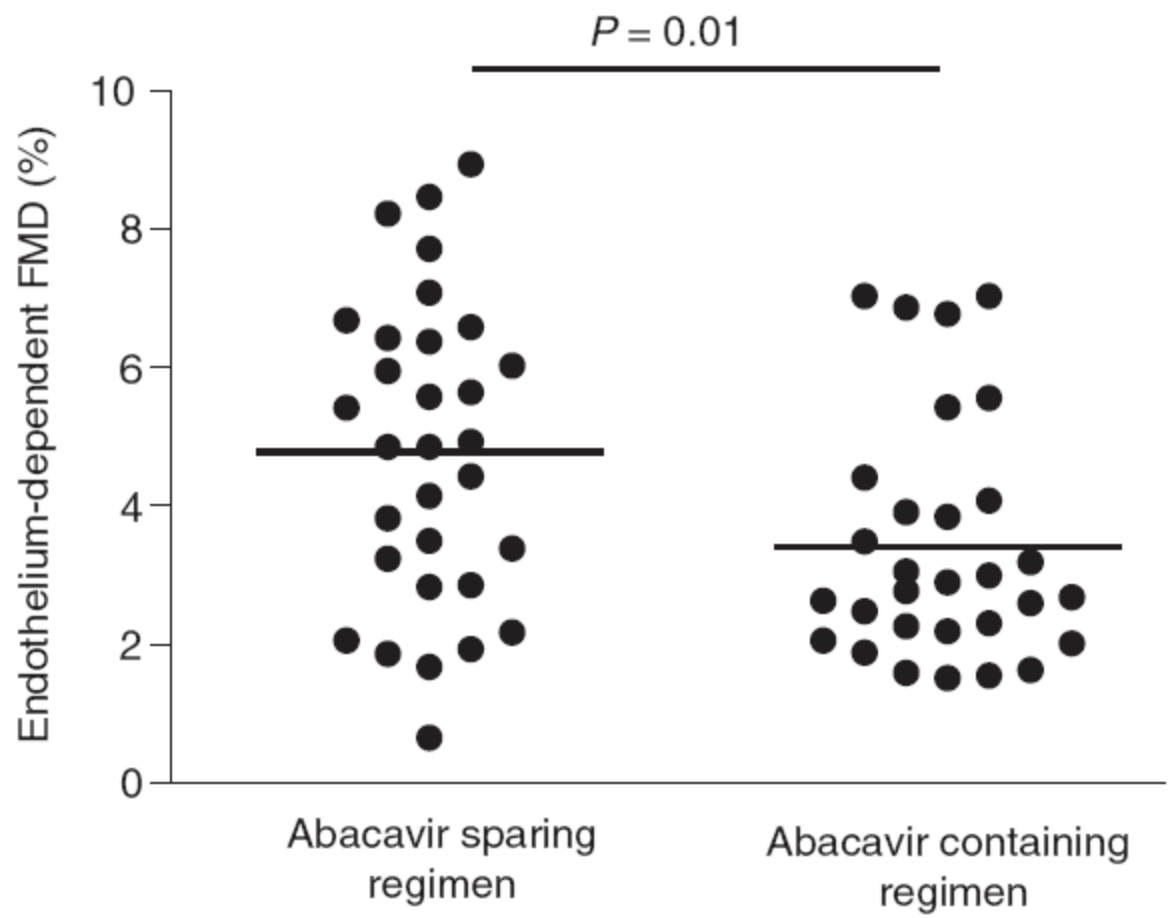
Thick bars=medians; Box edges =25th & 75th percentiles; Error bars=95% CI.

*p≤0.005, #p=0.015 within arm, compared to baseline (between groups p=0.828)



Torriani et al., J Am Coll Cardiol. 2008 Aug 12;52(7):569-76.

Flow-Mediated Vasodilation in HIV Patients on Abacavir (SCOPE)



The % of endothelium-dependent flow mediated Vasodilation:
1: Patients currently on ABC (n=30): 2.8% (IQR: 2.2–4.1),
2: Patients not on ABC (n=31): 4.9% (IQR: 2.9–6.4,).

Difference persists after adjusting for age, sex, traditional risk factors, nadir & current CD4)

Hsue et al., AIDS. 2009 Sep 24;23(15):2021-7

Concluding Remarks

- HIV likely promotes all three stages of atherogenesis:
  - atheroma formation (↑ dyslipidemia, ↑ carotid intima thickness and decreased FMD); plaque instability and rupture: endothelial activation (↑ adehsion molecules: eg VCAM-1; ↑ inflammation (hsCRP, IL-6, TNF-alpha) and thrombosis (↑D-Dimer, PAI-1).
- HAART use moderately (and probably transiently) ↓ markers of inflammation and endothelial dysfunction, (FMD as well?).
  - Specific antiretroviral drugs might differ in their impact on those biomarkers.

Concluding Remarks

- CKD and HCV are significant CVD risks factors in HIV
- The positive impact of HAART on markers of inflammation and endothelial dysfunction (and by extension, on incidence of CVD) might be mitigated or exacerbated by co-morbidities
- The comparative atherogenic potential of specific antiretroviral drugs or regimens is still unclear.