



**Cardiovascular Issues and HIV Drug
Development**

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Cardiovascular Disease in HIV

CVD Risk in HIV (Atherosclerosis)

- Overall Risk in HIV Populations
- Role of HIV
- Role of Antiretroviral Therapy
- Considerations for HIV drug development

Conduction System and HIV

Autopsy Studies pre-HAART era

- *Joshi et al.*¹ (1987)
 - Autopsy study of 6 children with HIV. 3/6 had coronary artery pathology, others had pathologic features in other arteries
- *Paton P et al.*² (1993)
 - 8 heart lung specimens, 6/8 had major eccentric atherosclerotic lesions in proximal coronary arteries with underlying risk factors.
 - Age 23-32

Summary of Studies Evaluating Risk of MI in HIV

Study	Event	N	Comment
VA ¹	1,207 CHD	36,766	↔ risk of MI with HAART or PI
DAD ²	126 MI	23,490	↑ with longer cART
Kaiser ³	65 MI	4408	↑ risk of MI HIV+ vs HIV-
Medi-Cal ⁴	N/A	20,742	↑ risk of CHD with ART in (18 to 33 year olds only)
French ⁵	49 MI	34,976	↑ risk of MI on PI vs HIV-
Johns Hopkins ⁶	43 CHD	2671	↑ risk of CHD HIV+ vs HIV-
HOPS ⁸	21 MI	5672	↑ risk of MI PI vs no PI

¹Bozzette SA, et al. *N Engl J Med.* 2003;348:702-710.

²Friis-Moller N, et al. *N Engl J Med.* 2003;349:1993-2003.

³Klein D, et al. *JAIDS.* 2002;30:471-477.

⁴Currier JS, et al. *JAIDS.* 2003;33:506-512.

⁵Mary-Krause M, et al. *AIDS.* 2003;21:2479-2486.

⁶Moore RD, et al. 10th CROI. Boston. 2003. Abstract 132.

⁸Homberg SD, et al. *Lancet.* 2002;360:1747-1748.

ART Exposure Is Associated With Increased Risk of MI—D:A:D Study

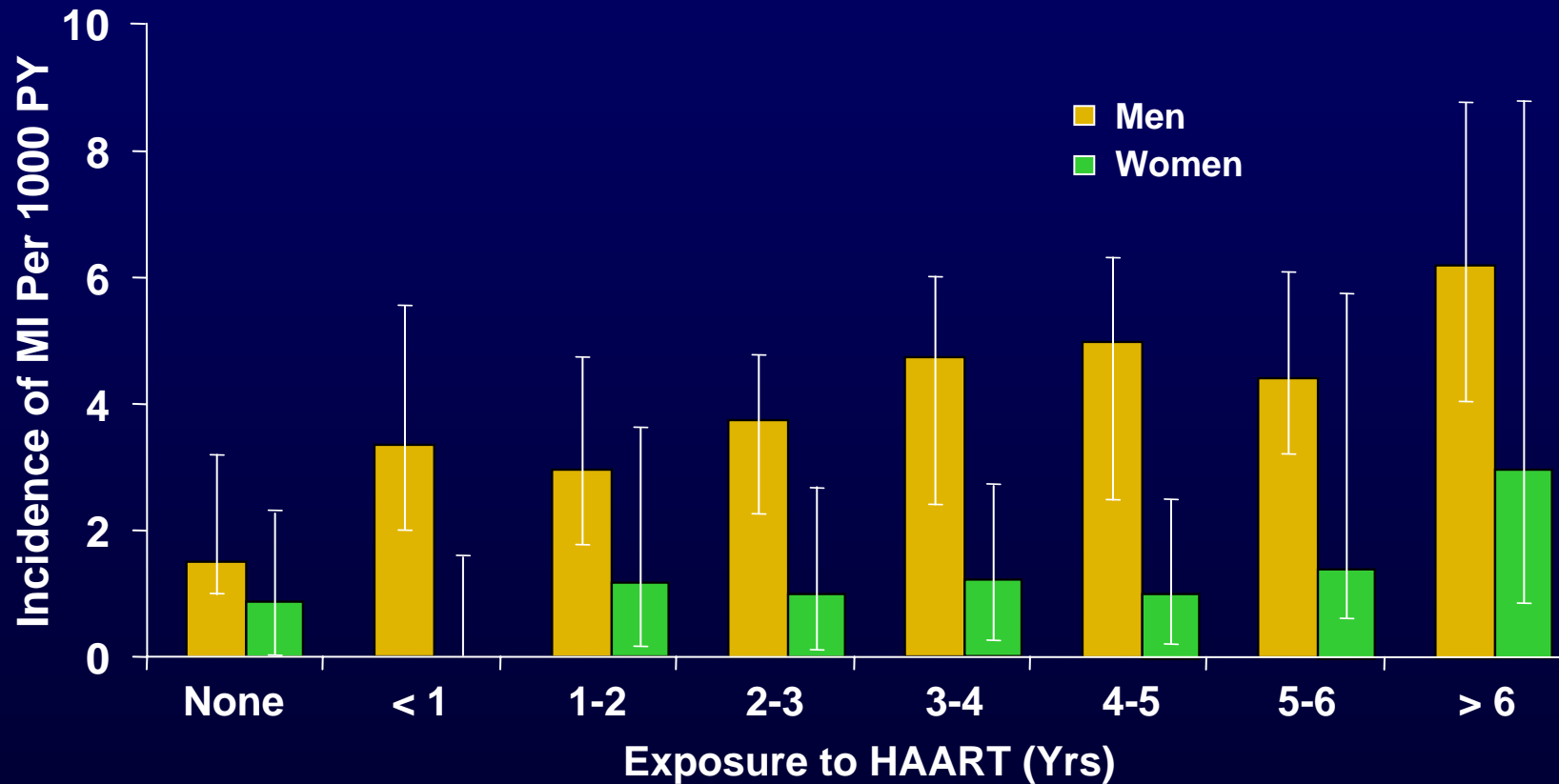
- 23,468 patients from 11 cohorts
- Median CD4 count 418 cells/ μ L; 55% undetectable viral load
- PIs 67%; NNRTIs 34%; NRTIs 81%; treatment naive 19%
- During 36,199 patient-years, 126 patients with MI (31% fatal; 6% of fatalities due to MI)
- Each year of ART exposure associated with a 26%* \uparrow MI adjusted RR

*Adjusted for other risk factors.

Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. NEJM 2003;349:1993-2003.

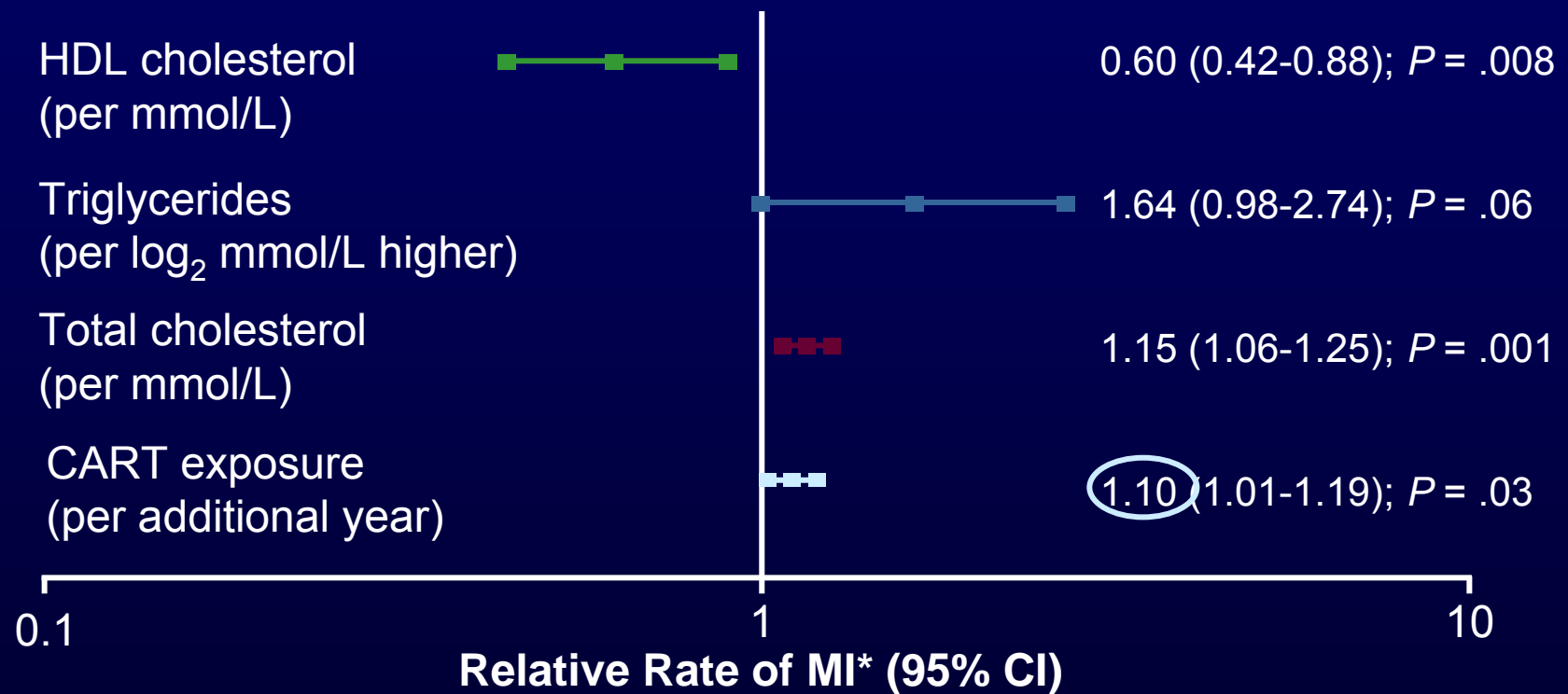
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D:A:D—Prolonged Antiretroviral Exposure and Myocardial Infarction



Events	11 / 3	16 / 0	19 / 3	31 / 3	52 / 4	52 / 3	35 / 4	37 / 4
PYFU	6633	4396	5972	8124	10106	9703	7341	5659
	3470	1928	2193	2722	1954	2551	1732	1093

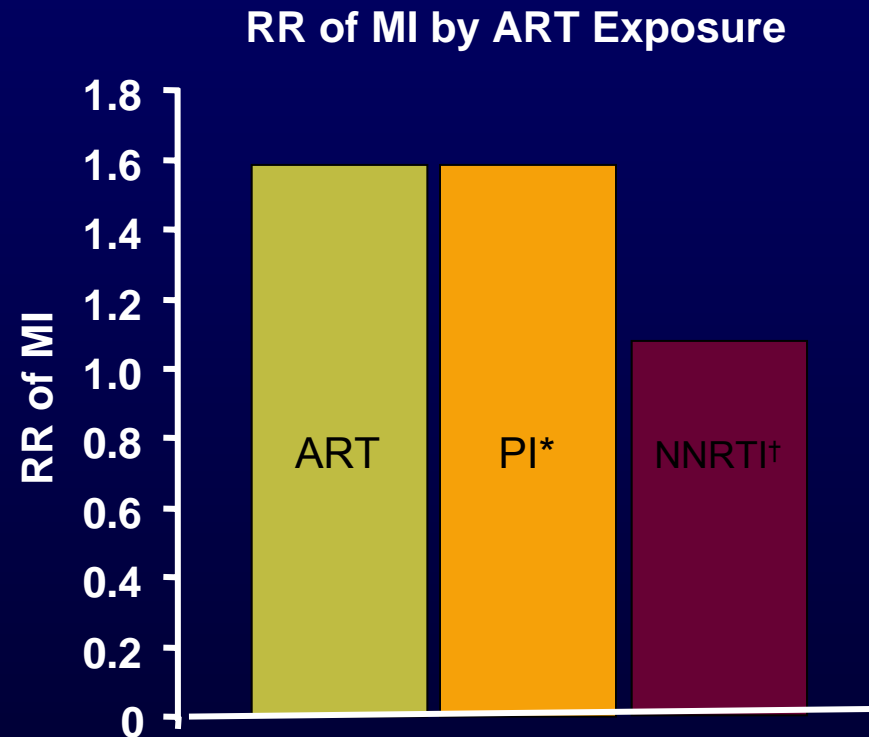
Contribution of Dyslipidemia to MI Risk



*Adjusted for conventional risk factors (age, sex, prior/family history of CVD, smoking) not influenced by CART.

HAART and the Risk of Myocardial Infarction: Updated Data From D:A:D

- Exposure to elements of HAART
 - NNRTI: 6.3 years (3.8-8.3)
 - PI: 3.0 (0.5-5.4)
 - NNRTI: 0.9 (0-3.2)
- PI exposure associated with similar increased risk as CART exposure
- NNRTI exposure not associated with increased risk of MI
- Adjustment for NRTI exposure did not change risk
- Suggests that increased risk previously reported with CART largely driven by PIs

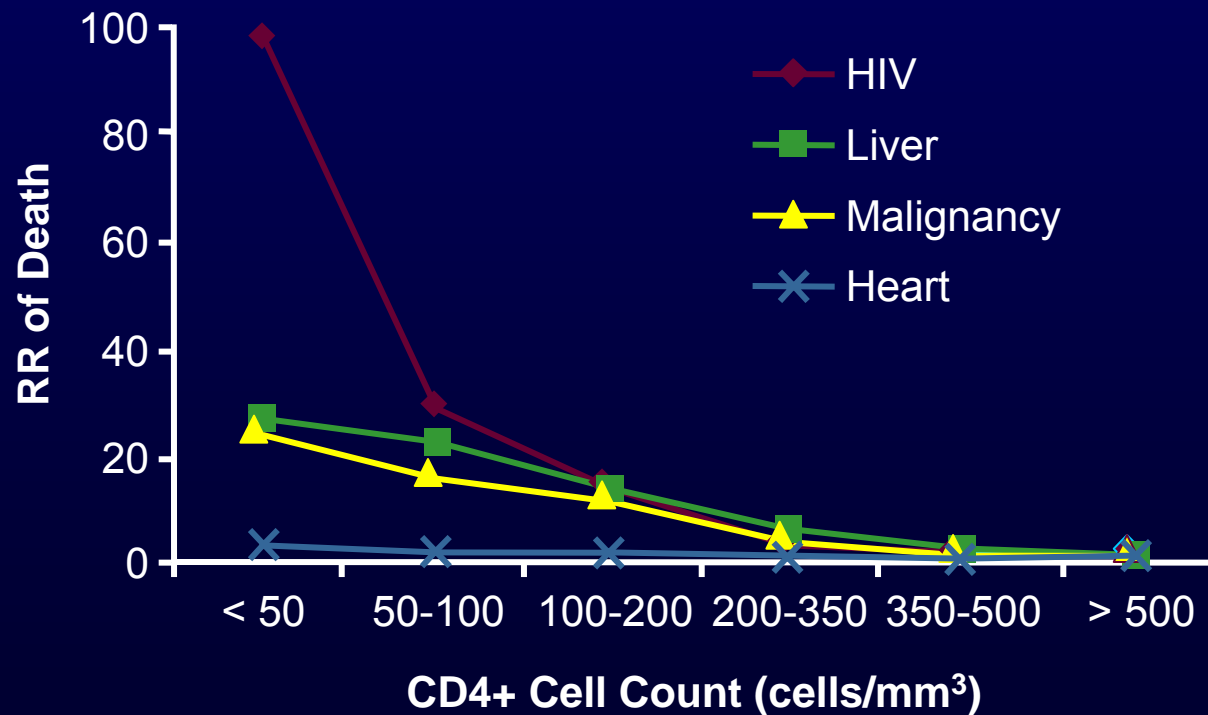


*Adjusted for NNRTI exposure.
†Adjusted for PI exposure.

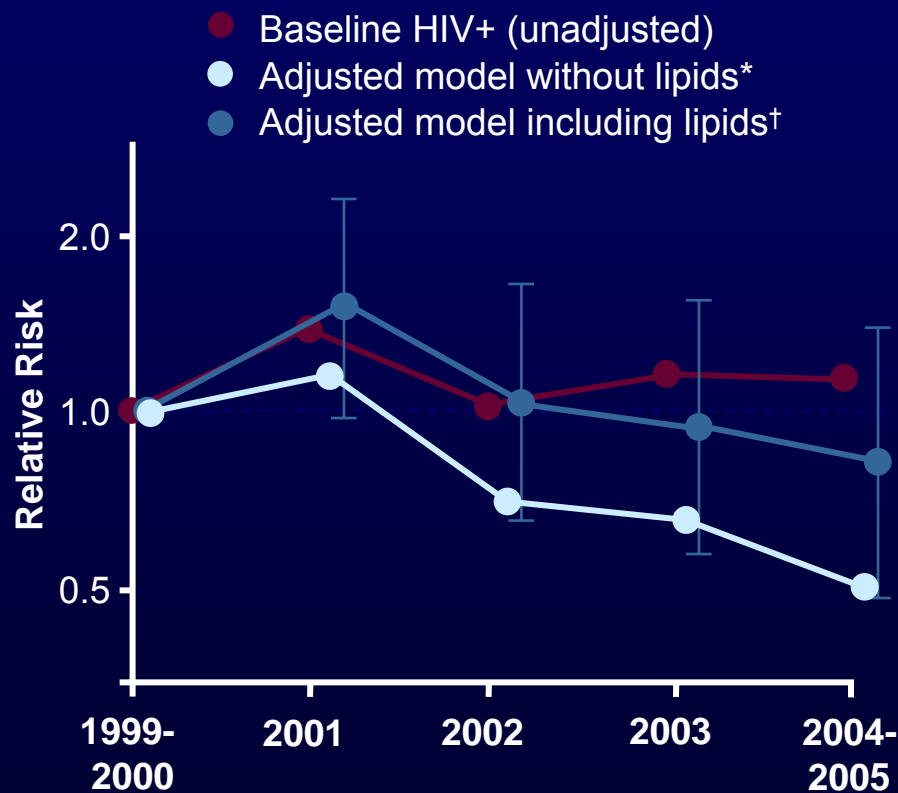
HIV and ART: Risk vs Benefit

D:A:D Study

Risk of HIV-Related Death and Comorbidities in Immunosuppressed Patients



D:A:D Study: MI Incidence Stable or Decreasing Over Time



- Incidence of MIs was 3.7/1000 patient-years (345 events in 94,469 patient-years)
- Increased PI exposure was associated with increased risk of MI (RR: 1.17/year of exposure; 95% CI: 1.12-1.23)
- No evidence of increased risk of MI with increased NNRTI exposure, although fewer years of experience (RR: 1.07/year of exposure; 95% CI: 1.00-1.14)

*Model adjusted for: sex, age, cohort, prior CVD, family CVD history, smoking, BMI, ART exposure.

†Above covariates plus serum lipids (total cholesterol, HDL-C, and triglycerides).

Friis-Moller, et al. CROI 2006. Abstract 144.

Slide adapted from Clinical Care Options online

Studies of HIV and Carotid Intima-Media Thickness (CIMT)

Study	Design	Results
<p>Stephan et al^[1] (N = 292) Follow-up: 5 years</p>	<ul style="list-style-type: none"> HIV patients compared with age- and sex-matched controls in 1:4 ratio CIMT, HIV status, and traditional risk factors assessed 	<ul style="list-style-type: none"> CIMT plaques more common at baseline in HIV-positive patients (12.3% vs 7.8%; $P = .03$) Common carotid IMT plaques 5% higher in HIV-positive subjects when adjusting for traditional risk factors ($P = .0002$) Carotid bifurcation IMT plaques 19% higher ($P < .0001$) in HIV-positive patients
<p>Hsue et al^[3] (N = 130) Follow-up: 1 year</p>	<ul style="list-style-type: none"> CIMT, CRP, T-cell activation measured in patients and controls CMV-specific responses monitored 	<ul style="list-style-type: none"> Baseline CIMT higher in HIV-positive patients compared with controls (0.95 mm vs 0.68 mm; $P < .001$) Difference persisted after correction for traditional risk factors hsCRP and CMV-specific T-cell responses also shown to independently correlate with CIMT

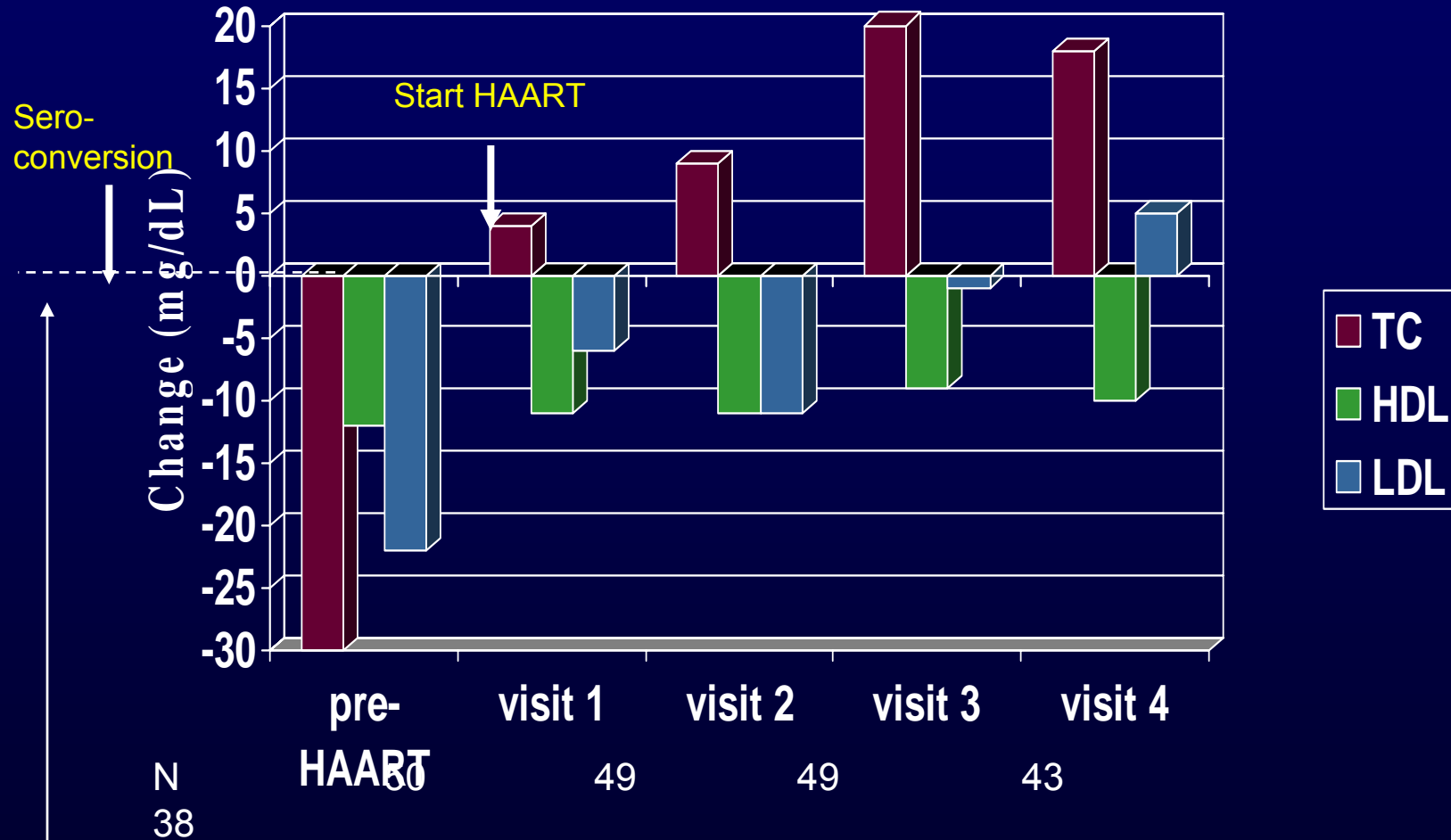
Surrogate Endpoints: Carotid IMT

- Study evaluated progression of IMT in matched groups
 - HIV+, continuous PI use ≥ 2 years (n = 44)
 - HIV+, PI naive (n = 45)
 - HIV- controls (n = 45)
- Neither HIV infection nor PI exposure significantly affected the rate of progression of carotid IMT over 3 years of follow-up
- No significant difference between
 - PI naive and PI treated ($P = .19$)
 - PI-naive and HIV+ antiretroviral therapy-naive group ($P = .78$)
 - Combined HIV+ groups and HIV- controls ($P = .71$)

Group	Mean IMT Rate (mm/yr)
PI treated	0.0102
PI naive	0.0047
HIV negative	0.0083

Does HIV infection play a role?

Change in Lipids Relative to Pre-Seroconversion Values: MACS



Pre-SC Means: TC 201, HDL 51, LDL 122

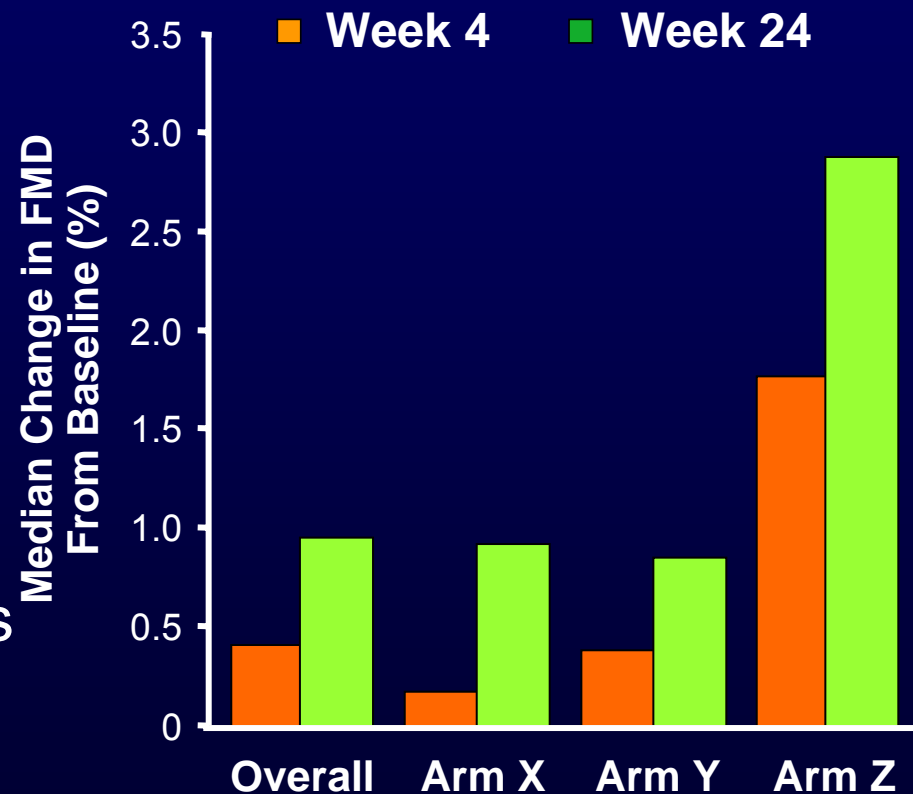
SMART Study: Fatal and Non-Fatal CVD Events

- Study population had median treatment duration of 6 yrs, median f/u time off ART of one year, during this follow-up CVD events greater in the DC arm
 - Viral Suppression arm (n=2752)
 - 0.8 per 100 pt yrs
 - Drug Conservation arm (n=2720)
 - 1.3 per 100 pt yrs
 - HR 1.6 (1.0 -2.5) p=0.05

CVD includes: non-fatal myocardial infarction (MI) requiring hospitalization or diagnosed by serial Q-wave change on electrocardiogram (ECG) (silent MI), non-fatal stroke, coronary artery disease requiring surgery, death from CVD,
NEJM 2006; 355:2283-2296,

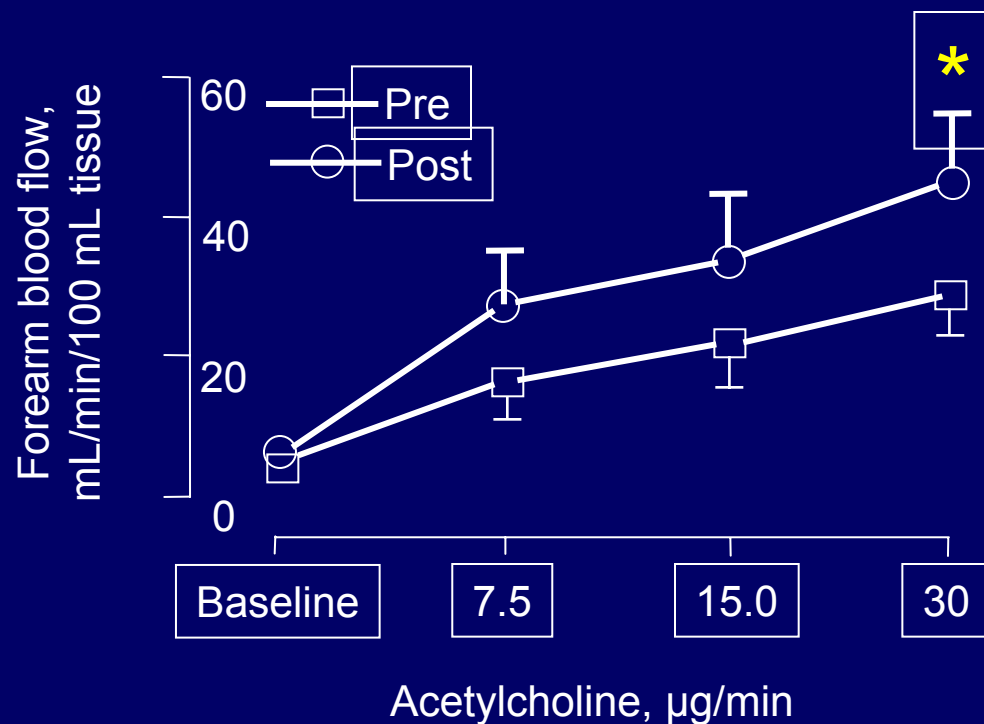
A5152s: Impact of HIV Infection and Treatment on Endothelial Function

- FMD improved during HIV treatment
 - Nonsignificant difference between blinded treatment groups
- HIV infection itself affected endothelial function
 - Baseline FMD: 3.6%
- No consistent correlations between changes in FMD and changes in any lipids



ART and Endothelial Function

Improved flow-mediated vasodilation associated with boosted PI in healthy volunteers



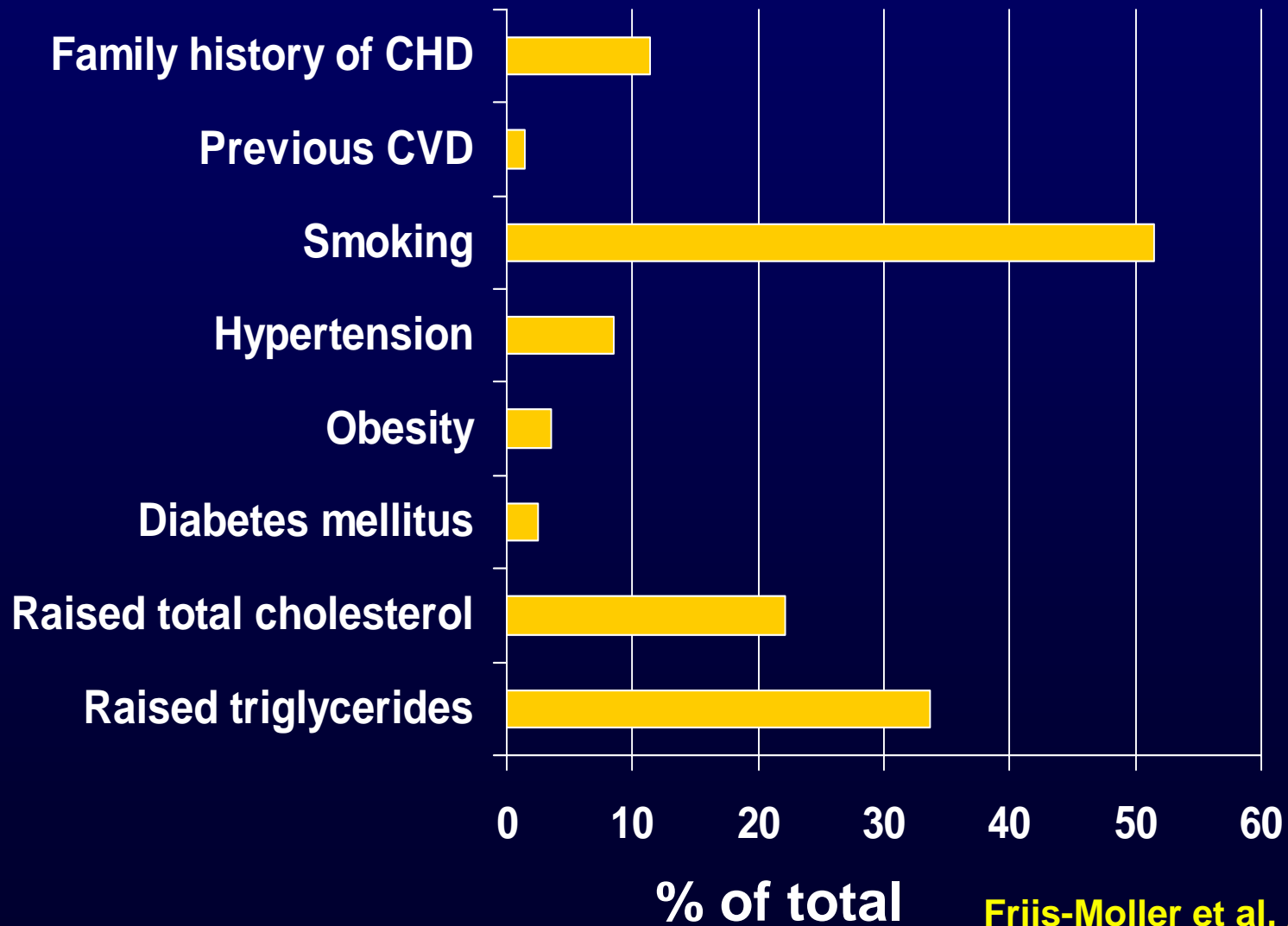
$P = 0.03$

- 6 healthy male and female HIV-seronegative
- mean age 25 yrs, nonsmokers
- Forearm blood flow (FBF) determined before and 1 month after treatment with LPV/r
- After 30 µg/min acetylcholine, the AUC of absolute FBF was significantly increased with LPV/r treatment ($P = 0.03$); for each dose, absolute or percentage increases over baseline were nonsignificant.

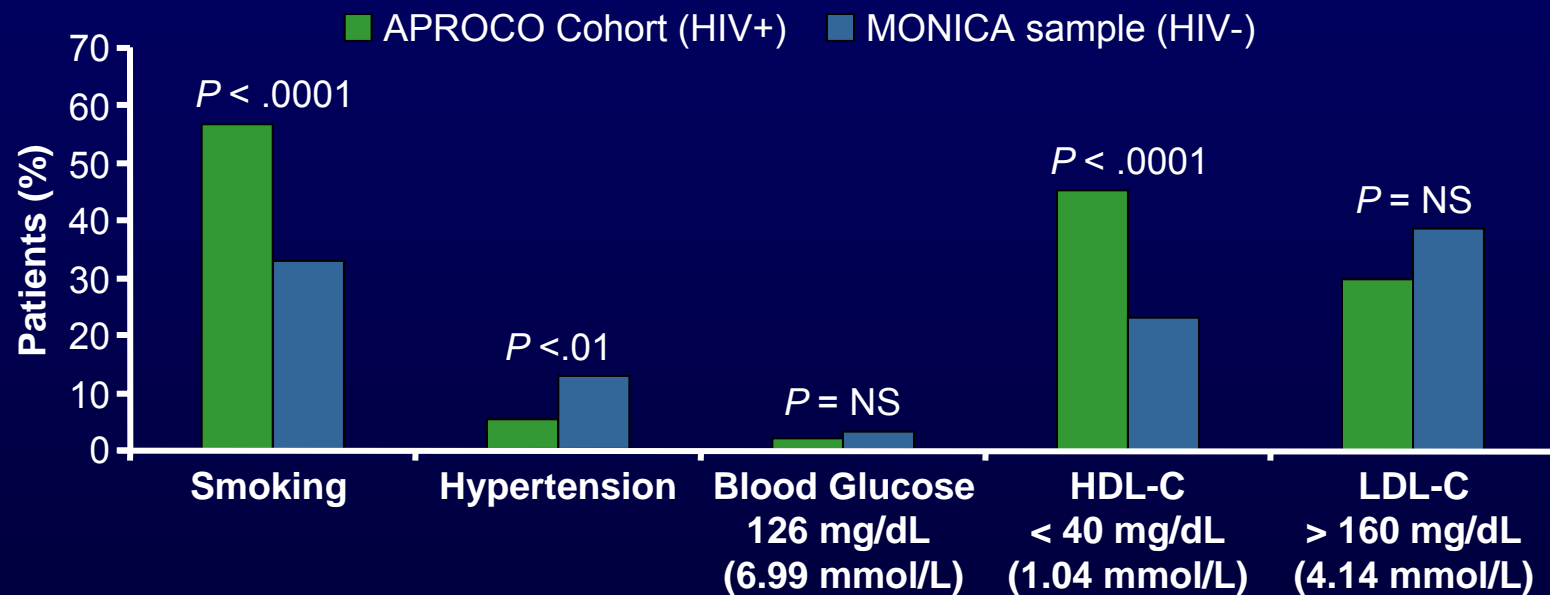
- Prevalence of CV Risk Factors in HIV Populations

HIV metabolic and cardiovascular disease

Myocardial infarction - risk factors



Smoking Incidence Is Increased in HIV-Infected Pts vs General Population



- 223 HIV+ men and women on PI-based regimens vs 527 HIV- male subjects
- Predicted risk of CHD > in HIV+ men (RR: 1.2) and women (RR: 1.6); $P < .0001$

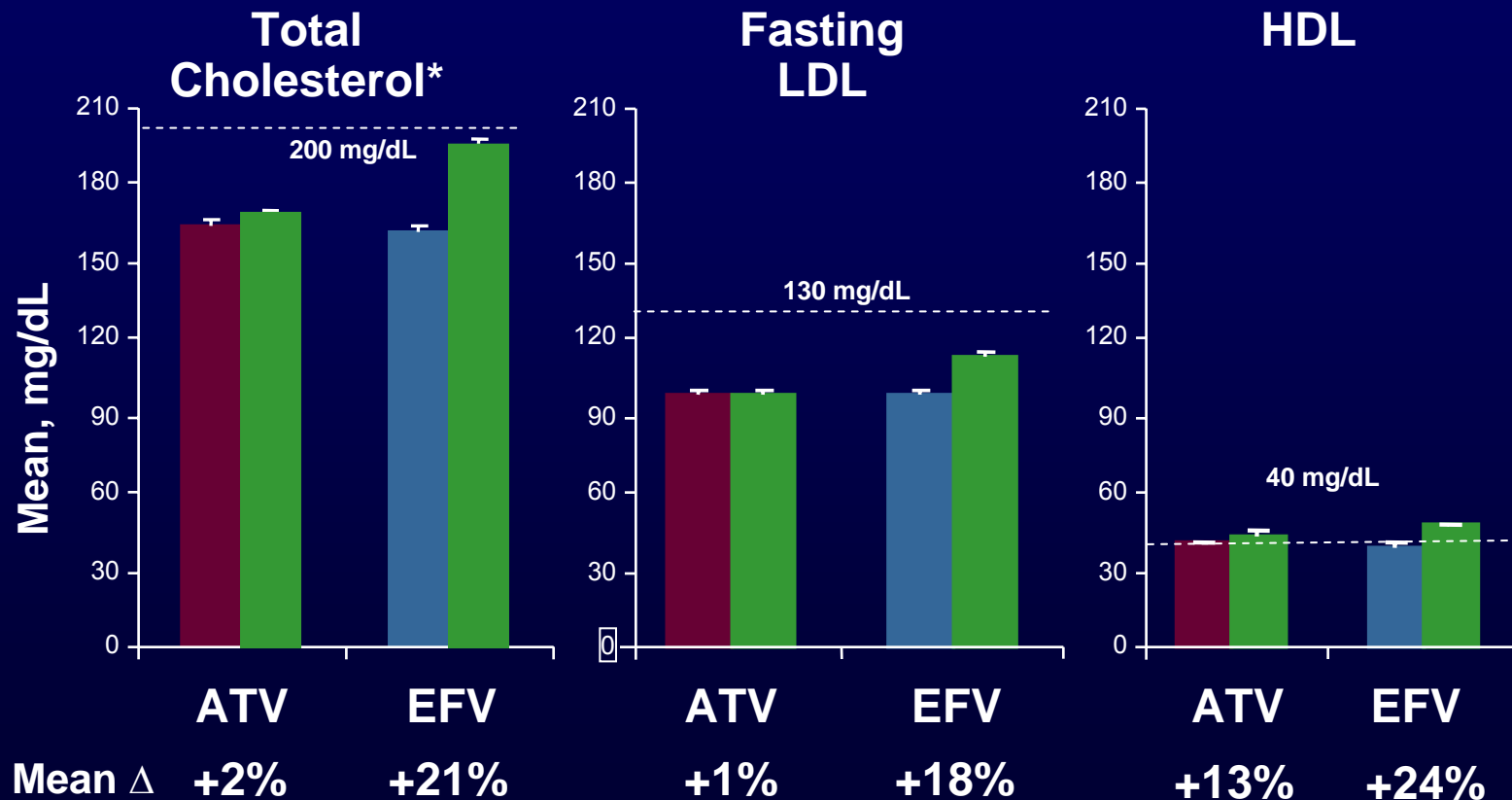
- Lipid Effects of Contemporary ARV Regimens

Prevalence of Dyslipidemia

	Cholesterol		
	Total	LDL	HDL
mmol/l	>6.2	>3.4	<0.9
(mg/dl)	(240)	(130)	(<35)
naive	7	31	23
NRTIs only	9	37	22
NRTI + PI	26	58	23
NRTI + NNRTI	22	54	16
NRTI + PI + NNRTI	43	68	22

- stable levels after 3-6 months ART
- also associated with increasing age and lipodystrophy

BMS-034: Effects of Atazanavir vs Efavirenz on Total, LDL, and HDL Cholesterol

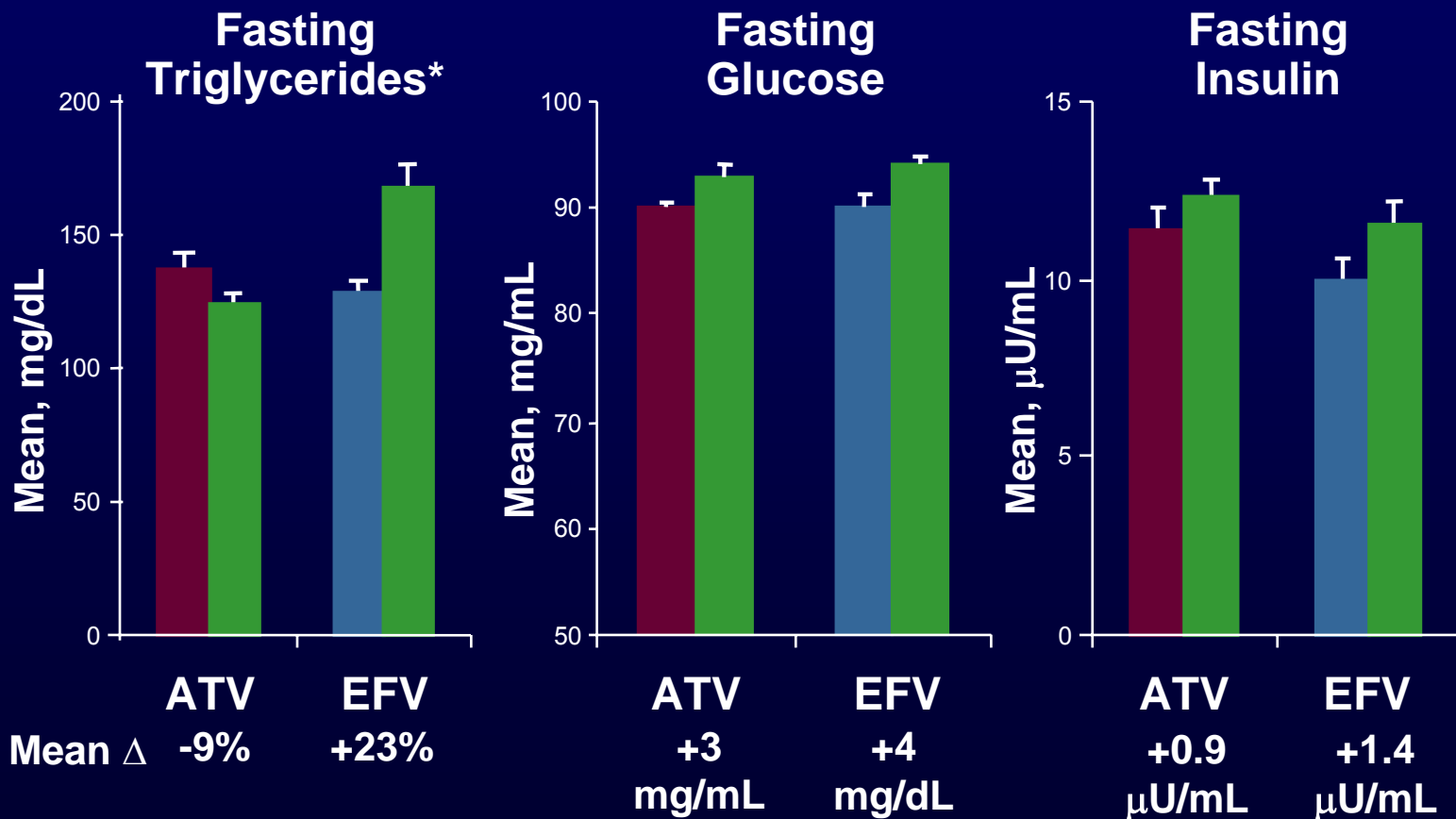


P < .0001, atazanavir vs efavirenz at 48 weeks, all comparisons

■ Baseline ■ Week 48

Squires et al. 42nd ICAAC, San Diego, 2002. Abstract H-1076.

BMS-034: Effects of Atazanavir vs Efavirenz on Triglycerides, Glucose, and Insulin



* $P < .0001$, atazanavir vs efavirenz

■ Baseline ■ Week 48

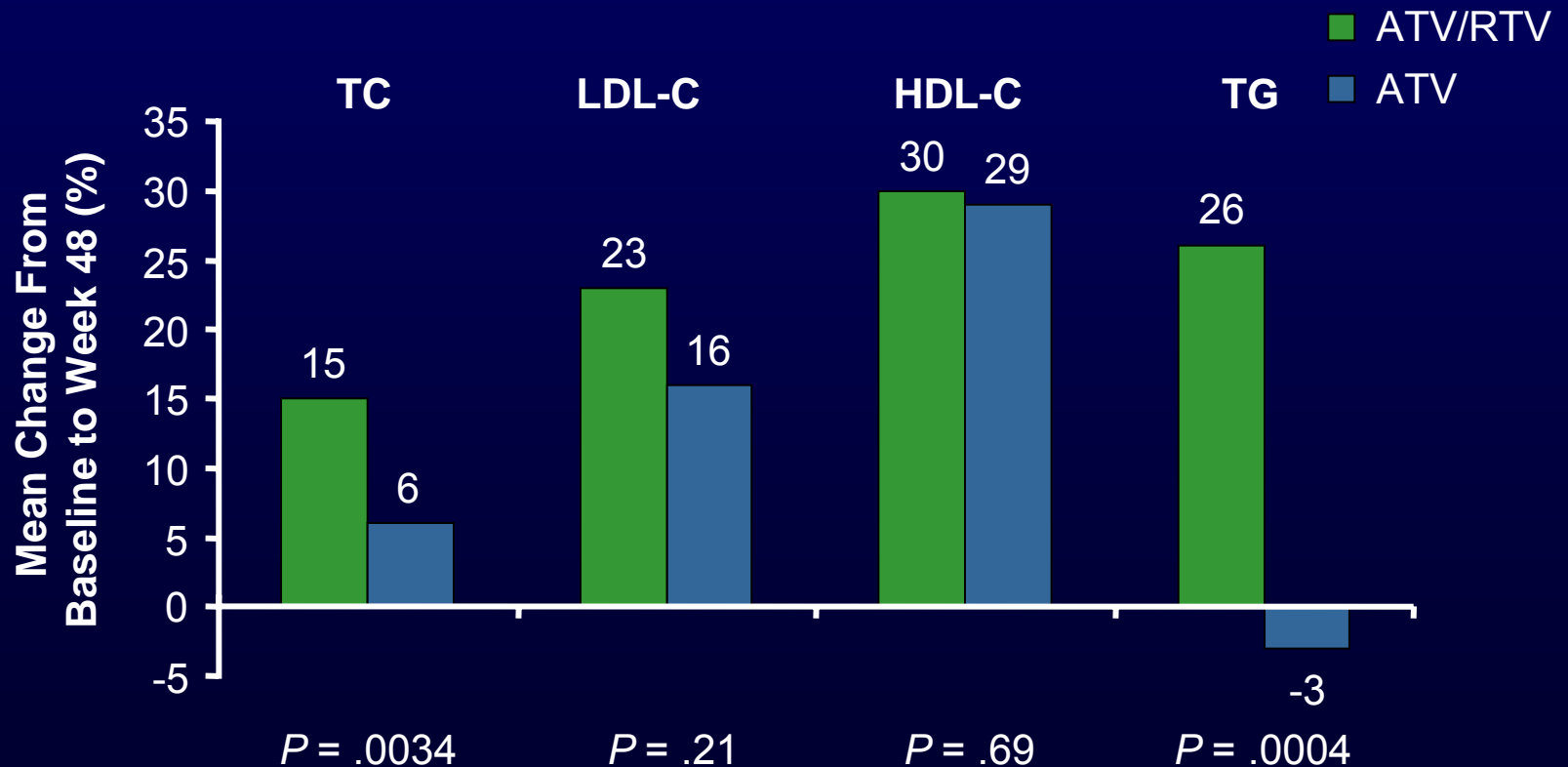
RTV Affects Lipids—Even at Low Doses

- RTV 100 mg BID or LPV/RTV 400/100 mg BID x 14 days in healthy volunteers

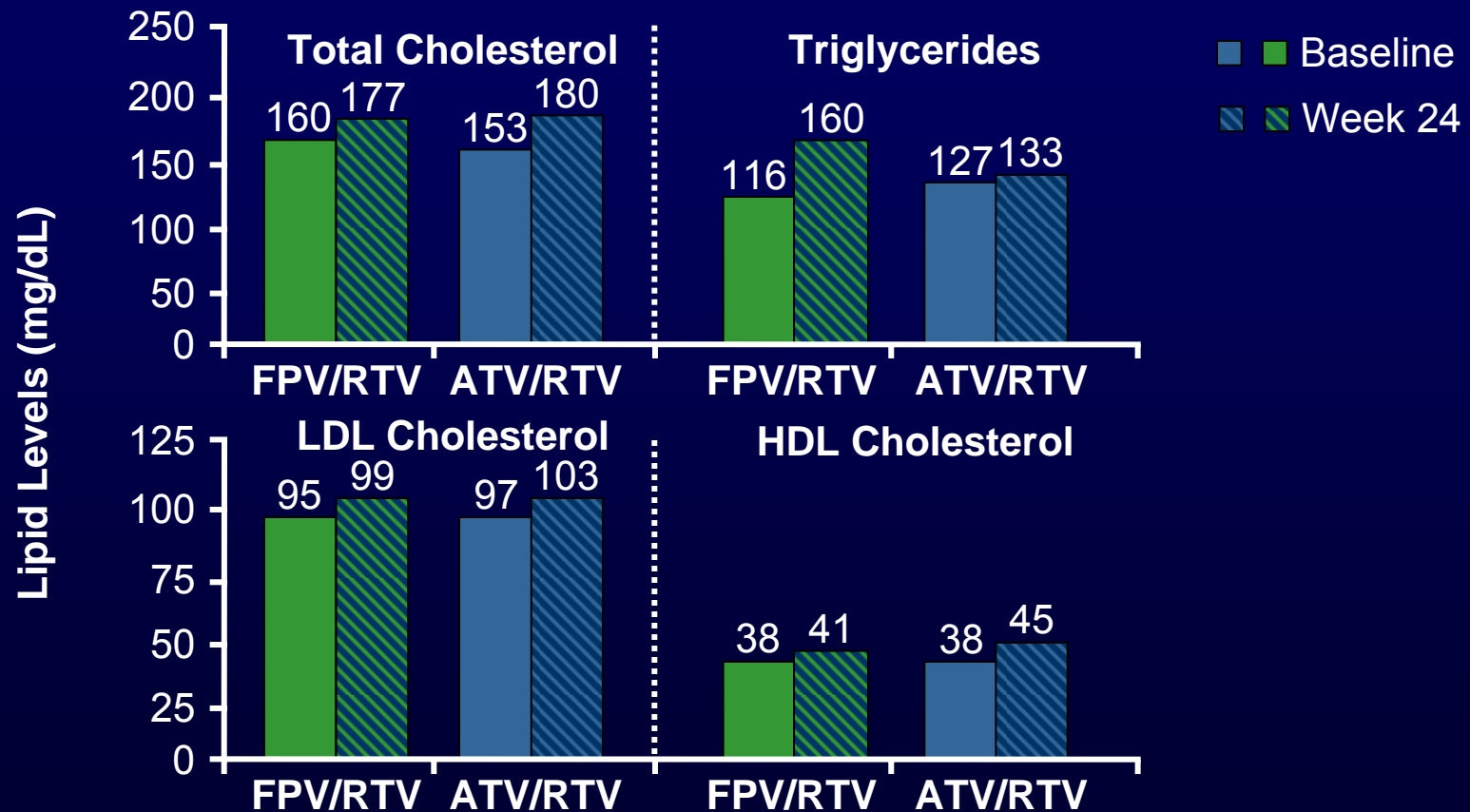
Parameter	Baseline	RTV (n = 20)	LPV/RTV (n = 20)
TC, mg/dL (mmol/L)	166 (4.30)	185* (4.79)	197* (5.10)
LDL-C, mg/dL (mmol/L)	97 (2.51)	113* (2.93)	120* (3.11)
HDL-C, mg/dL (mmol/L)	54 (1.40)	51* (1.32)	53* (1.37)
TG, mg/dL (mmol/L)	77 (0.87)	98* (1.11)	114* (1.30)

Effect of RTV Boosting on ATV: BMS-089 Study

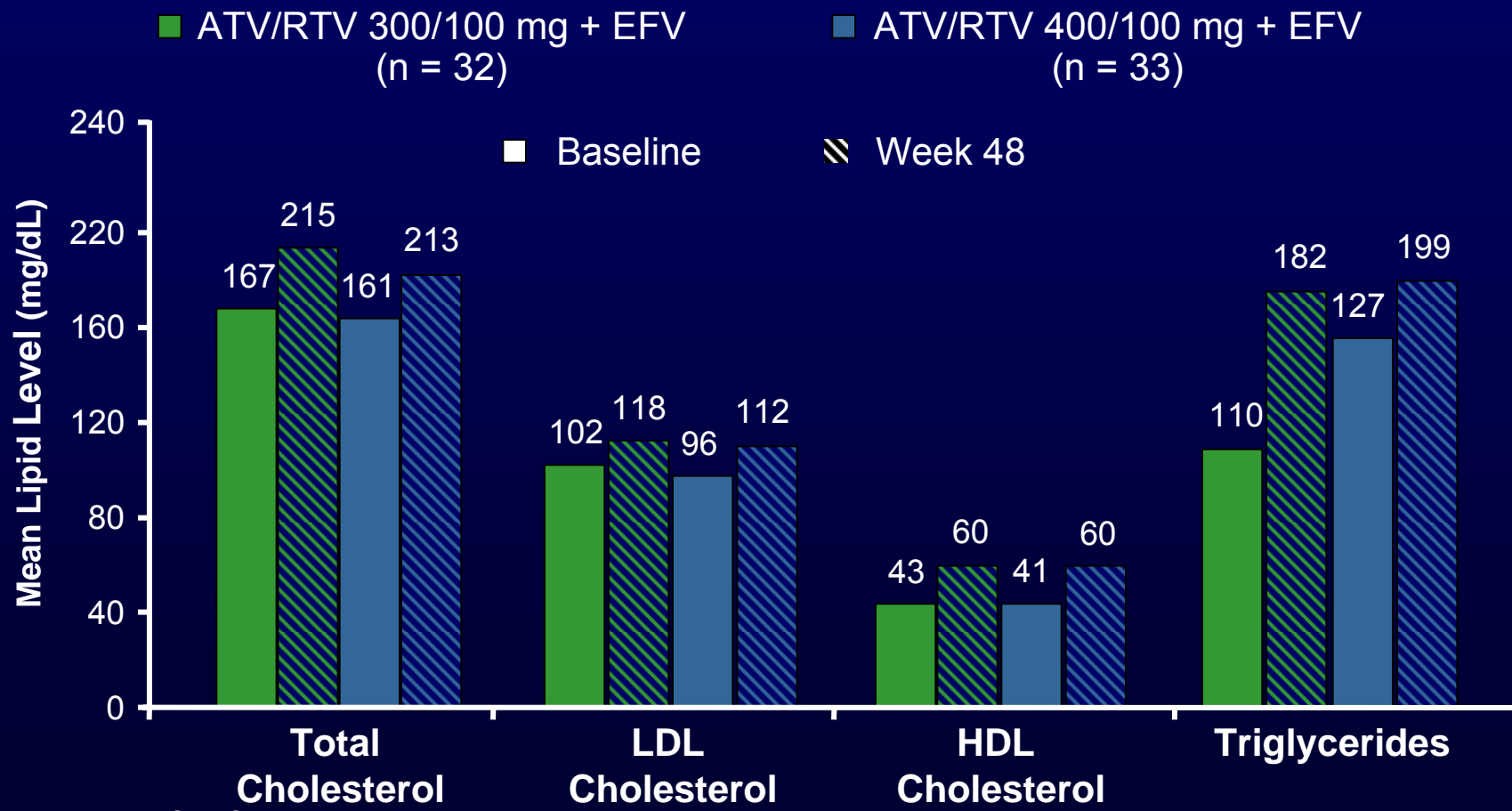
- BMS-089: randomized trial of 100 treatment-naive patients
- ATV/RTV 300/100 mg vs ATV 400 mg



ALERT: Median Fasting Lipids at Baseline and Week 24



BMS-121: Lipid Changes At Week 48

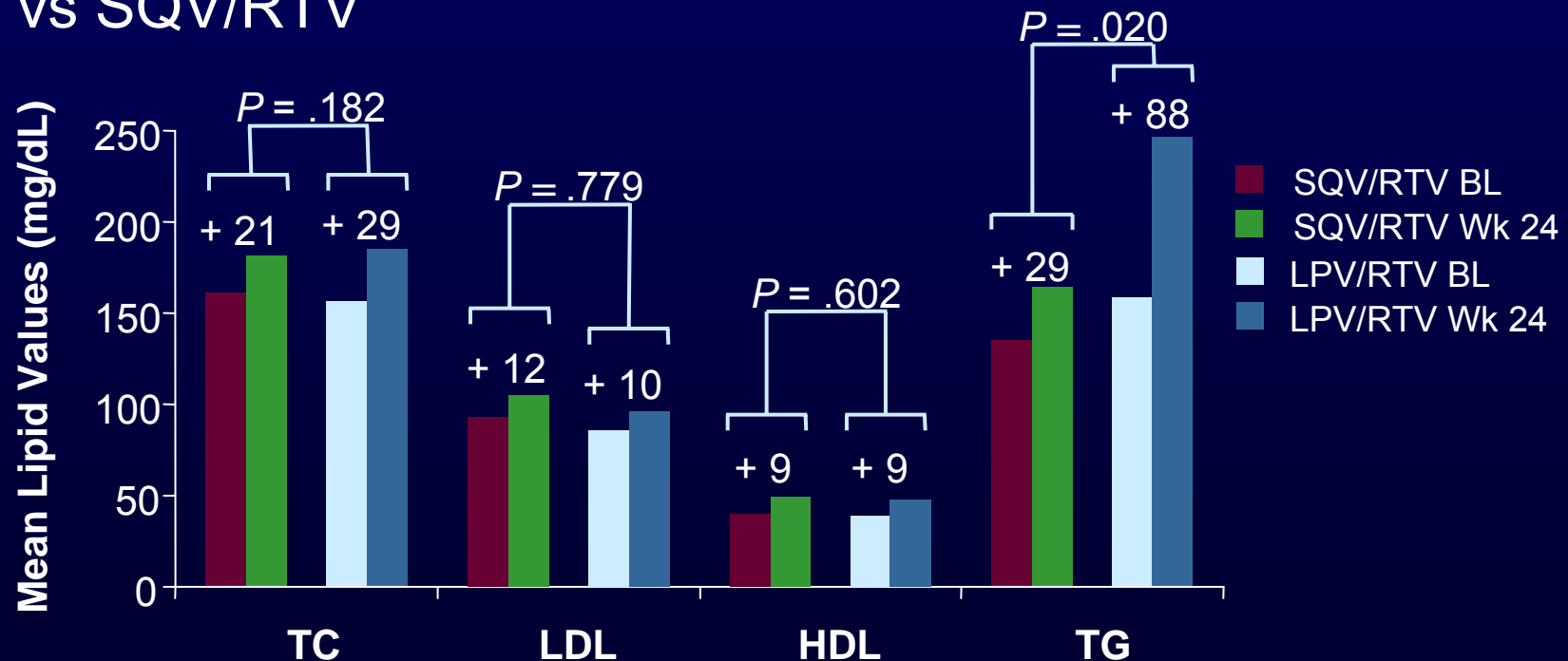


Ward D, et al. ICAAC 2006. Abstract H-1057.

Slide adapted from Clinical Care Options online

GEMINI: SQV/RTV vs LPV/RTV in Treatment-Naive Pts at Wk 24

- Prospective, phase IIIb, randomized, multicenter, open-label study (N = 337)
- Significantly greater risk of hyperlipidemia with LPV/RTV vs SQV/RTV



MK-0518: Serum Lipids at Week 24 in Naive Patients

Treatment Arm	Mean Baseline TC, mg/dL (mmol/L)	Change From Baseline at Wk 24, % (95% CI)	Mean Baseline TG, mg/dL (mmol/L)	Change From Baseline at Wk 24, % (95% CI)
MK-0518 100 mg BID (n = 39)	168 (4.35)	-7 (-14 to 0)*	129 (1.46)	+2 (-22 to 26)
MK-0518 200 mg BID (n = 34)	161 (4.17)	-2 (-11 to 8)*	110 (1.24)	-5 (-20 to 9)*
MK-0518 400 mg BID (n = 40)	168 (4.35)	-7 (-15 to 2)*	127 (1.44)	-2 (-23 to 18)*
MK-0518 600 mg BID (n = 35)	162 (4.19)	-4 (-12 to 5)*	155 (1.75)	-43 (-87 to 1)*
EFV 600 mg QD (n = 36)	170 (4.40)	+19 (8 to 30)	128 (1.45)	+47 (-1 to 96)

Teppler H, et al. ICAAC 2006. Abstract 256a.

*Significant difference vs EFV ($P < .05$).

MK-0518: Serum Lipids at Week 24 in Naive Patients

Treatment Arm	Mean Baseline TC, mg/dL (mmol/L)	Change From Baseline at Wk 24, % (95% CI)	Mean Baseline TG, mg/dL (mmol/L)	Change From Baseline at Wk 24, % (95% CI)
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Teppler H, et al. ICAAC 2006. Abstract 256a.

*Significant difference vs EFV ($P < .05$).

Effectiveness of Interventions to Reduce CV Risk

- Challenges
 - Drug Interactions
 - Cyp 3A4 inhibition and statins
 - Magnitude of lipid lowering effect in HIV pts
 - Polypharmacy

Lipid-Lowering Agents and PIs

- Low interaction potential
 - Fibrates¹
 - Fluvastatin²
 - Pravastatin¹
- Use cautiously^{3,4}
 - Statin-fibrate combinations
 - Atorvastatin
- Contraindicated⁵
 - Lovastatin
 - Simvastatin

¹Fitchenbaum CJ, et al. *AIDS*. 2002;16:569-577.

²Hsyu PH, et al. *Antimicrob Agents Chemother*. 2001;45:3445-3450.

³Carr RA, et al. 40th ICAAC. Toronto, 2000. Abstract 1644.

⁴Calza L, et al. *AIDS*. 2003;17:851-859.

⁵Doser N, *AIDS*. 2002;1:1982-1983.

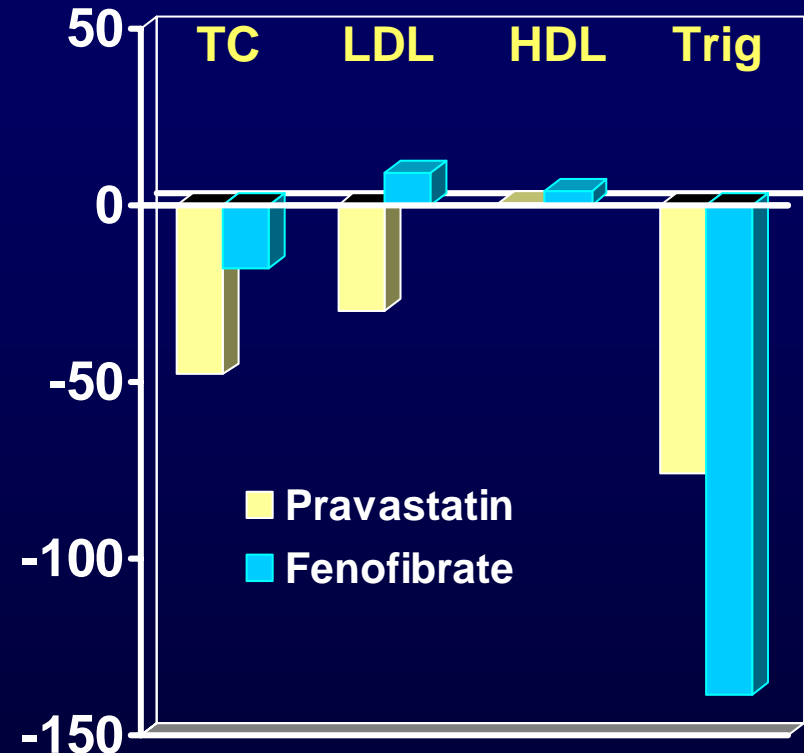
ACTG 5087: Treatment of HIV-Associated Hyperlipidemia

HIV+ patients with dyslipidemia:

- LDL cholesterol >130 mg/dL
and
- Triglycerides >200 mg/dL



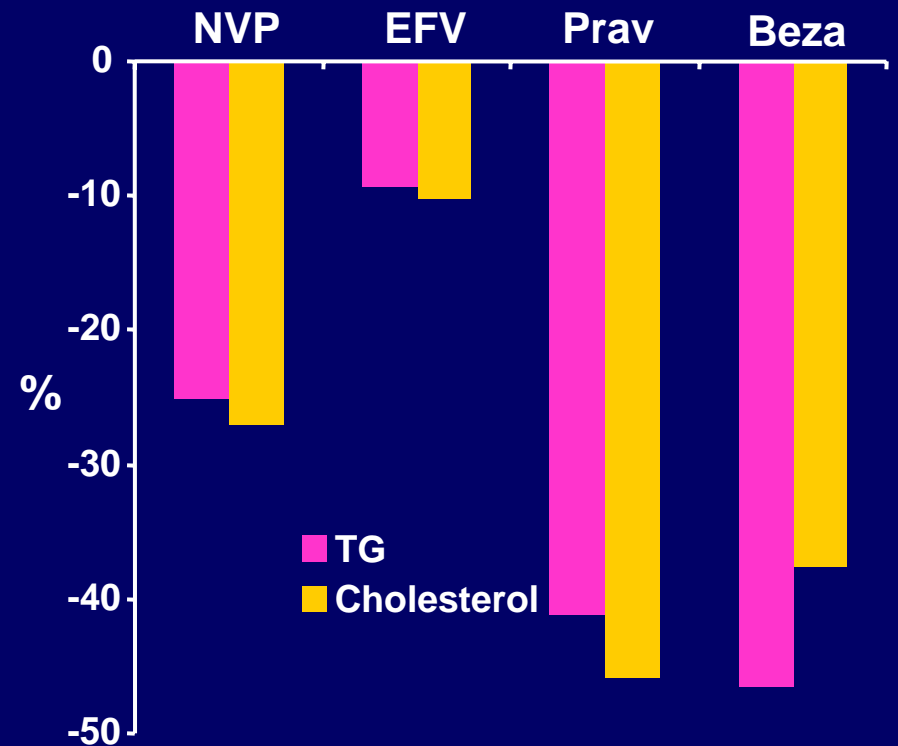
- **Endpoint: reaching NCEP goal (Composite for TG/LDL) by week 12.**



Only 1% of fenofibrate and 5% of pravastatin met NCEP goals

Dyslipidemia: Comparing the impact of switching to lipid-lowering agents

- 142 NNRTI-naïve patients on PI-based HAART ≥ 12 months
- HIV RNA < 50 c/mL
- CD4+ > 350 cells/mm³
- Diet-resistant hyperlipidemia
- Randomized to replace PI with NVP or EFV, or to add pravastatin or bezafibrate
- **Adding a lipid-lowering agent more effective than switching to NNRTI**



$p < 0.01$ for comparison of TG and cholesterol between any or both lipid-lowering drugs vs any or both NNRTIs

Where does this leave us?

- HIV Therapy will likely remain long term
- Traditional CV risk factors are common in HIV populations and increase risk of CVD and should be addressed
- HIV disease may contribute to CVD risk
- ART may be associated with a small increase in the absolute risk of CVD; although study results are inconsistent, and follow-up is still modest
- CVD risk should **not** influence the decision to initiate ART in most cases; however it should be considered when selecting ART options
- Current treatment options can be improved in terms of contribution to long term CV risk

Chemokines and Atherosclerosis

- Atherosclerosis is a chronic inflammatory disease involving the migration of leukocytes into subendothelial space.
- Chemokines facilitate cell migration.
- Experiments using LDL receptor knock-out mice have demonstrated a role chemokines in pathogenesis of atherosclerosis
 - CXCR2 (leukocyte adhesion to endothelium)¹
 - CX3CR1 (development of atherosclerotic lesions)²
 - CCR5⁻ (reduced inflammation within lesions)³
- CCR5 delta 32 adults- Reduced risk of early MI and severe CAD ^{4,5}

1. Boisvert WA. J. Clin Invest 1998;101:353-363.

2. Combadiere C. Circulation 2003;107:1009-1016

3. Potteaux S. Arterioscl Throm Vasc Biol 2006;26:1858-1863

4. Gonzalez P, Genes Immun. 2001;2:191-195.

5. Szalai C, Atherosclerosis 2001;158:233-239

Summary

- The absolute risk of CHD in the HIV population currently remains low
- Data is accumulating to suggest that patients with HIV infection on HAART may experience an increased relative risk of CHD with longer exposure to therapy
- **Modification of CHD risk and use of ARV agents less likely to cause metabolic disturbances** may be warranted when patients have many options, but fear of CHD should not preclude the use of effective HAART
- CV issues need to be considered early during new drug development
- Long term studies evaluating surrogate markers for CVD will help to establish the critical factors that contribute to CV risk in HIV