

The Treatment Experienced Patient Cardiovascular Disease and Dyslipidemia

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NEW Learning Objectives

- At the conclusion of this interactive session, participants should be able to:
 - 1 Modify clinical strategies to address both traditional and additional risk factors for cardiovascular disease in HIV-infected patients.
 - 2 Utilize an understanding of the basic pathophysiology of lipids in cardiovascular disease to improve clinical care.

W.P. 60 yo white male

1/1/91 HIV+ CD4=545 (30.9%)
10/20/95 CD4 = 554 (27%) VL = 86,051 copies/ml BP = 126/80
4/15/96 CD4 = 404 (21.8%) VL = 114,000 copies/ml
Rx: 3TC, d4T, IDV
8/23/99 Clinical lipoatrophy
7/20/00 CD4 = 707 (31.0%) VL = 96 copies/ml TC = 216 HDL-C = 37
LDL-C = 127 TG = 260 Switch to boosted indinavir
12/28/01 CD4 = 815 (31.3%) VL = ND TC = 257 HDL-C = 45
LDL-C = 157 TG = 273 BP = 118/84
4/24/03 D/C IDV/RTV. Start NVP. BP = 122/90
2/7/04 CD4 = 932 (31.2%) VL = 236 copies/ml TC = 198
HDL-C = 45 LDL-C = 128 TG = 125 BP = 141/99
10/28/04 Shortness of breath while walking dog. ER: elevated
troponins. ST segment dep. Cardiac cath: LAD lesion. Stent
1/18/05 Simvastatin 40 mg PO daily BP = 108/72
3/18/05 D/C d4T/3TC Start FTC/TDF with NVP Lisinopril 2.5 daily
6/16/08 CD4 = 698 (45.5%) VL = ND TC = 118 HDL-C = 51
LDL-C = 55 TG = 62 BP = 112/72

Why did he have a myocardial infarction?

1. Older age
2. HIV infection
3. Dyslipidemia
4. Use of IDV, RTV, and/or d4T
5. 1 and 3
6. 1, 3, and 4
7. 1, 2, 3, and 4
8. We don't know for sure
7. (*#%@ happens)

Do You Use the Framingham 10-year Cardiovascular Risk Algorithm in Your Patients?

1. No. I am unfamiliar with it.
2. No. It doesn't apply to HIV-infected patients.
3. Yes. In all patients.
4. Yes. In select patients.

Major Risk Factors per NCEP (2001)*

- Cigarette smoking
- Hypertension (BP \geq 140/90 mmHg or on anti-hypertensive medication)
- Low HDL cholesterol**
 - $<$ 40 mg/dL in males
 - $<$ 50 mg/dL in females
- Family history of premature CHD
 - CHD in male first degree relative $<$ 55 years
 - CHD in female first degree relative $<$ 65 years
- Age (men \geq 45 years; women \geq 55 years)
- Waist $>$ 40" male, $>$ 35" female

* Factors are weighted

** HDL cholesterol \geq 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Assessment of 10-year CHD Risk

- Lower Risk (LR)
 - ≤1 Risk Factors
- Moderate Risk (MR)
 - ≥2 Risk Factors
 - Framingham 10 year CV Risk <10%
- Moderately High Risk (MHR)
 - ≥2 Risk Factors
 - Framingham 10 year CV Risk 10-20%
- High Risk (HR)
 - ≥2 Risk Factors
 - Framingham 10 year CV Risk >20%
 - Coronary Risk Equivalent (Prior CV event, DM, Met. Synd.)

Determine Risk Category

- Establish LDL-C goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine LDL-C level for drug consideration
- HDL-C is a secondary NCEP goal

LDL Cholesterol Goals (Triglycerides <200 mg/dL)

Risk Category	LDL Goal	LDL Level - Initiate TLC*	LDL Level - Consider Drug TX
LR 0-1 Risk Factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL
MR and MHR ≥2 Risk Factors (10 yr risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-20%: ≥ 130 mg/dL <10%: ≥ 160 mg/dL
HR ≥2 Risk Factors or CRE (10 yr risk >20%)	<100 mg/dL (Optional <70)	≥100 mg/dL	≥ 130 mg/dL

Persell D, et al. J Gen Intern Med 21:171-76, 2006

*Therapeutic lifestyle changes

Non-HDL Cholesterol Goals (Triglycerides >200 mg/dL)

Risk Category	N-HDL-C Goal	N-HDL-C Initiate TLC*	N-HDL-C Consider Drug TX
LR 0-1 Risk Factor	<190 mg/dL	≥190 mg/dL	≥190 mg/dL
MR and MHR ≥2 Risk Factors (10 yr risk ≤20%)	<160 mg/dL	≥160 mg/dL	10-20%: ≥ 160 mg/dL <10%: ≥ 190 mg/dL
HR ≥2 Risk Factors or CRE (10 yr risk >20%)	<130 mg/dL (Optional <100)	≥130 mg/dL	≥ 160 mg/dL

Persell D, et al. J Gen Intern Med 21:171-76, 2006

*Therapeutic lifestyle changes

Framingham 10-year Cardiovascular Risk in W.P.

- Age – 60 yo (55 yo at time of coronary event)
- Male
- Not treated for hypertension – BP normal except once
- Family history negative for early CVD
- Fasting glucose = 84 mg/dL
- BMI = 22.2 kg/m² Waist = 34"
- Never smoker
- No diabetes

10-year Cardiovascular Risk Prior to Stent: <10%
Low Risk

10-year Cardiovascular Risk Currently: 20%
Highest Risk (Coronary Risk Equivalent)

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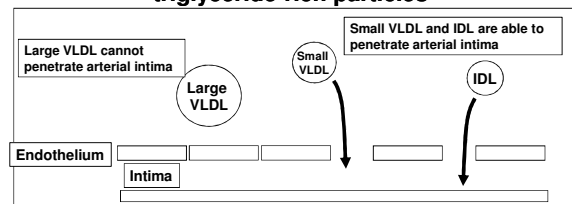
How Important are Elevated Triglycerides in Our Patients?

1. Very important. They increase the risk of CVD in my patients.
2. Somewhat important. It depends on the level.
3. Not important. It is LDL-cholesterol that is most important.
4. Triglycerides influence metabolism of LDL-cholesterol.
5. 1 and 4.
6. 2 and 4.
7. 3 and 4.

At What Level Do You Treat Triglycerides with Fibrates &/or Omega-3 Fatty Acids?

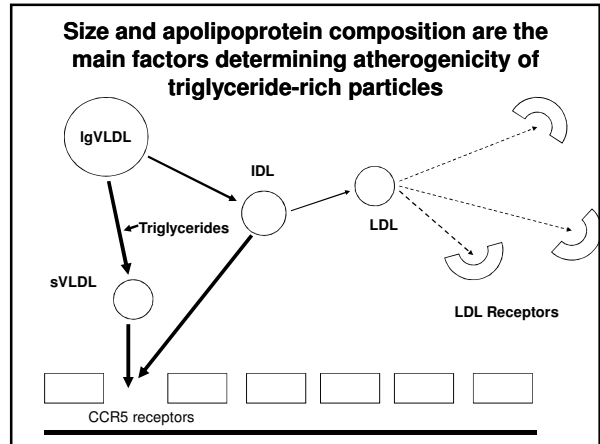
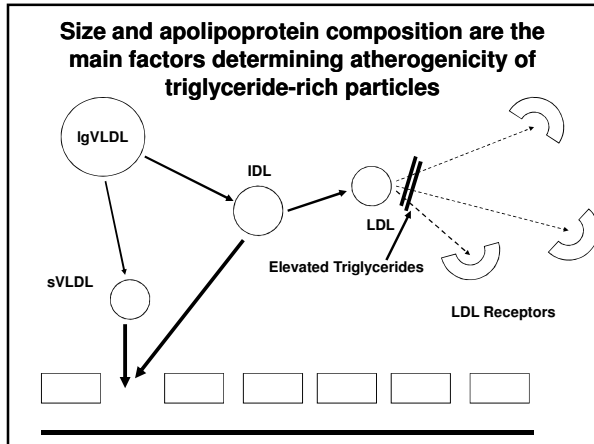
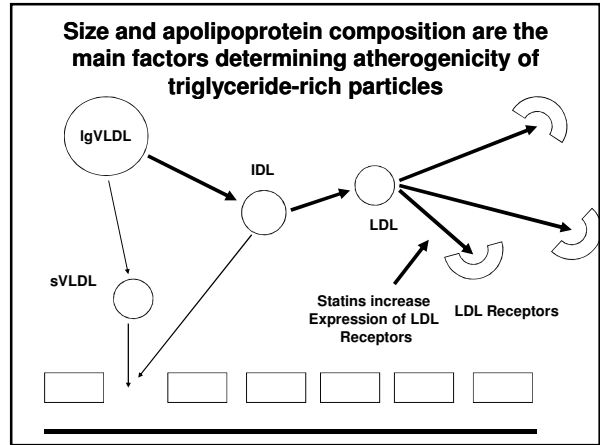
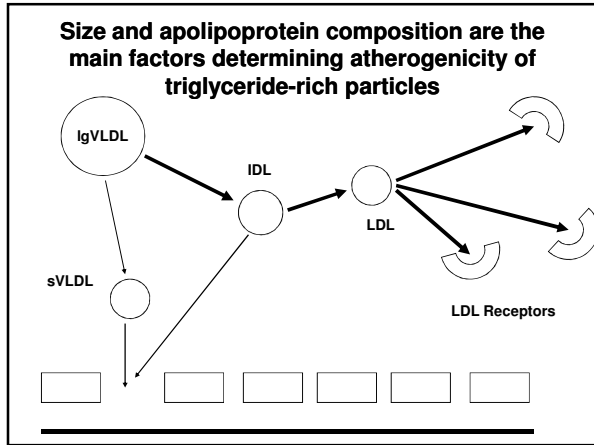
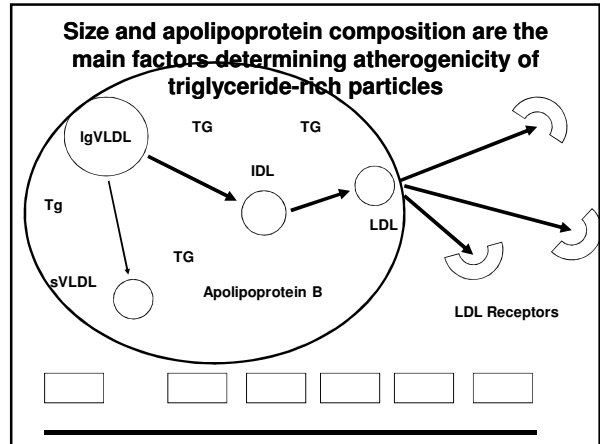
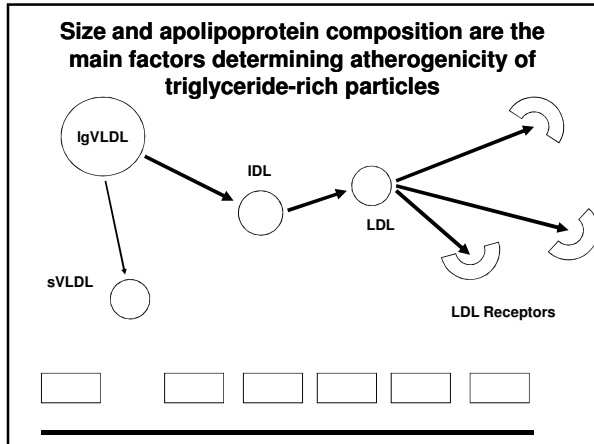
1. >150 mg/dL
2. >200 mg/dL
3. >400 mg/dL
4. >500 mg/dL
5. None of the above

Size and apolipoprotein composition are the main factors determining atherogenicity of triglyceride-rich particles



- Some triglyceride-rich lipoproteins are atherogenic¹
 - Small very-low-density lipoproteins (VLDL)
 - Intermediate-density lipoproteins (IDL)
- Ratio of VLDL TG to VLDL TG-apolipoprotein B can be used to determine VLDL composition and estimate CVD risk in patients with hypertriglyceridemia

NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults



To What Degree Do Antiretroviral Agents Increase Cardiovascular Risk?

1. Not at all
2. To a small degree due to alterations of lipids and glucose metabolism.
3. To a moderate degree due to alterations of lipids and glucose metabolism.
4. To a large degree due to alterations of lipids and glucose metabolism.
5. We don't really know.

Inconsistent Results: From major studies on CVD risk in HIV-infected and HAART-treated patients

Study	N	Study	Event	ARV	Effect	Traditional risk factors
VA ¹	36,766	R	1,207 CHD	HAART or PI	No	Not evaluated
HOPS ²	1807	P	84 CV events	specific ARVs	No	Age >40 y, diabetes, HTN
SMART ³	5472	P	63 CHD	intermittent HAART	No – stopping therapy led to complication	Age
Kaiser ⁴	4408	R	86 MI	PIs	Risk of HIV+ vs. HIV- No risk on PI	Not evaluated
Medi-Cal ⁵	28,513	R	NA	ART	Risk with ART in 18–33 year olds	Not evaluated
DAD ⁶	23,490	P	345 MI	cART and PI	Yes	Smoking, age, gender, HTN, DM
French ⁷	34,976	R	49 MI	PI	Yes	Age
Johns Hopkins ⁸	2671	Case control	43 CHD	HIV+ vs. HIV-	Yes	Age, HTN, DM
Frankfurt ⁹	4993	R	29 MI	HAART	Yes	Age >40

1. Bozzette SA, *New Eng J Med*. 2003;348:702–10
 2. Finkelstein N, *N Eng J Med*. 2007;356:1729–35
 3. Klein D, et al. *J AIDS*. 2002;30:471–7
 4. Currier JS, *J AIDS*. 2003;33:506–12
 5. Mary-Krause N, *AIDS*. 2003;21:2479–86
 6. Moore RD, *Ann CROI*. Boston 2003, #132
 7. Ricketts V, *Eur J Med Res*. 2000;5:329–33
 8. Lichtenstein K, *Ann CROI*. Denver 2006, #735
 9. El-Saie W, et al. *N Eng J Med*. 2006;355:2263–69

KLEAN Study: Fosamprenavir (FPV) + RTV Versus. Lopinavir/r SGC (+ Abacavir [ABC]/Lamivudine [3TC]): No Differences in Lipid Levels Between Study Arms

- Open-label, non-inferiority study: 878 ART-naïve, HIV+ patients randomized to FPV + RTV (n=436) 700 mg/100 mg BID or LPV/r (SGC) 400 mg/100 mg BID (n=443)
 - Primary end points: proportion of patients achieving HIV-1 RNA <400 c/mL at Week 48 and treatment discontinuations because of an adverse event
- Fasting Lipid Levels at Week 48

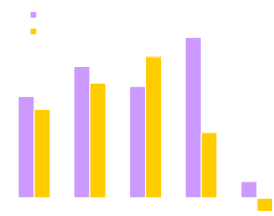


Eron R, et al. *Lancet*. 2006;368:476–482.

2NN Study: Lipid Effects of NNRTIs Efavirenz Versus Nevirapine

- 2NN Study
 - Prospective analysis in treatment-naïve patients
 - Lipid profiles
- Randomized treatments
 - Efavirenz (n=289)
 - Nevirapine (n=417)
 - All patients: 3TC + d4T

Lipid Changes at Week 48



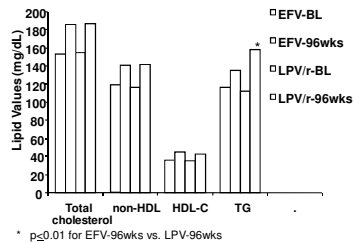
*Patients fasted for 3 hours prior

*P<0.05 and †P<0.001 versus NVP arm.

van Leth, et al. *PLoS Med*. 2004;1:64–74.

ACTG 5142: Baseline and 96 wk lipid values

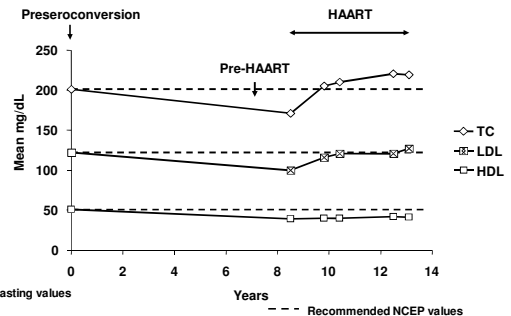
- Randomized to 3 arms:
 - Efavirenz + 3TC + (AZT or TDF or d4TXR)
 - LPV/r + 3TC + (AZT or TDF or d4TXR)
 - Efavirenz + LPV/r
- n=753; median F/U 112 weeks
 - NRTI selection: ZDV, 42%; d4T XR, 24%; TDF, 34%
- No differences in BL characteristics:
 - Median CD4+: 182 cells/mm³; HIV RNA: 5 log₁₀ c/mL
- By week 96, 10% and 12% of EFV and LPV subjects used a lipid lowering agent



* p<0.01 for EFV-96wks vs. LPV-96wks

Haustrup R, et al., *CROI*. Los Angeles 2007

MACS Cohort: Mean Lipid Values Before and After HIV Infection (Treated and Untreated)



Riddler SA, et al. *JAMA*. 2003;289:2978–2982.

Increased Risk of MI or CV Events and Association with ABC or TDF

	Case Ascertainment	N	Age	Increased MI Risk?	
				ABC	TDF
D:A:D	Prospective	33,308	~44	Yes (RR: 1.68)	No
FHDH	Prospective	1,173	47	Yes (OR: 1.97)	No
SMART	Prospective	5,472	44	Yes (RR: 4.3)	No
STEAL	Prospective	357	45	Yes* (HR: 7.7)	No
ALLRT	Prospective	3205	37	No	NR
GSK analysis	Retrospective	9582	37	No	NR

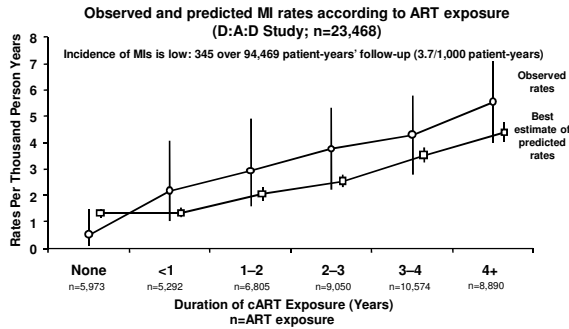
*Increased risk of CV events
NR=Not Reported

Adapted from Reiss P, CROI 2009; 152

To What Degree Does HIV Infection or the Inflammation Resulting From HIV Increase Cardiovascular Risk?

1. It is not a factor.
2. HIV-infected patients have more modifiable CV risk factors than the general population.
3. Cardiovascular disease is an inflammatory disorder that is exacerbated by chronic inflammatory diseases such as SLE and HIV infection.
4. CCR5 is an inflammatory mediator of destabilization of atherosclerotic plaques.
5. HIV invades and damages vascular tissue.
6. 2 & 3
7. 2, 3, & 4
8. 2 & 5

D:A:D Study: Is the Framingham Risk Estimation Valid in HIV-Infected Patients?



Law MG, et al. HIV Med. 2006;7:218-230.

Higher Incidence of CHD in HIV-Infected vs HIV-Uninfected Patients

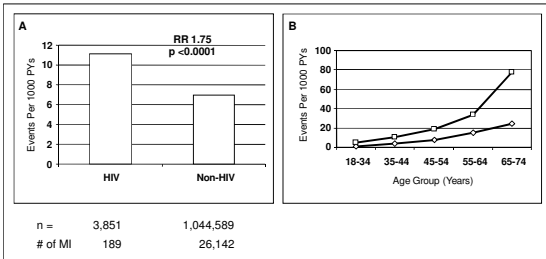
- 5000 HIV-infected men followed for 10.5 years compared with 43,000 age-matched HIV-uninfected men
- HIV-infected men had significantly higher rates of CHD ($P < .002$) and MI ($P < .002$) vs HIV-uninfected men
 - Trend for HIV-infected men on PI-based regimens to be at higher risk of CHD ($P = .11$) and MI ($P = .14$) vs those not taking PIs

Age-Adjusted Rates* From 1996-2004, Events per 1000 Person-Yrs (95% CI)	All HIV-Infected Patients	HIV-Infected Patients on Any PI	HIV-Infected Patients Not on PI	HIV-Uninfected Comparator Group
CHD	6.1 (4.9-7.3)	6.9 (5.3-8.6)	4.9 (3.1-6.8)	2.9 (2.7-3.1)
MI	3.8 (2.8-4.7)	4.4 (3.1-5.8)	2.9 (1.5-4.4)	2.2 (2.0-2.4)

*Rates adjusted to 1990 US population, 5-year age groups.

Klein D, et al. CROI 2007. Abstract 807.

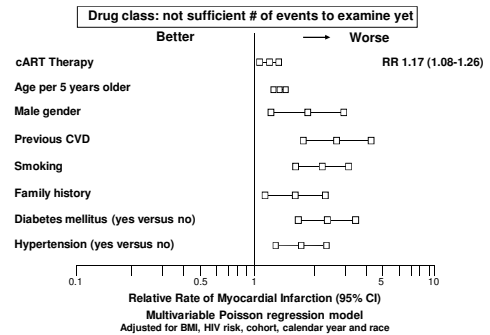
Risk of MI While Admitted to Either of Two Hospitals in Boston According to HIV Status



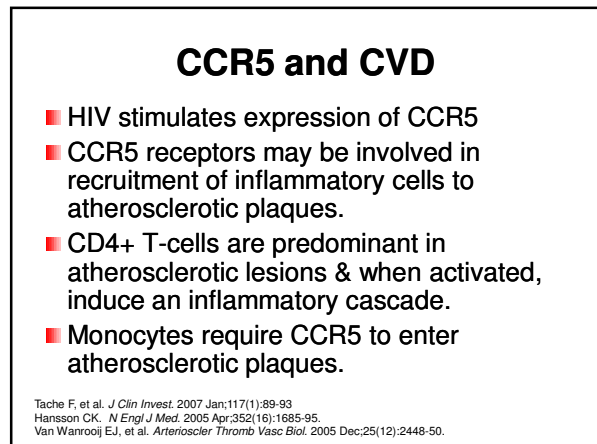
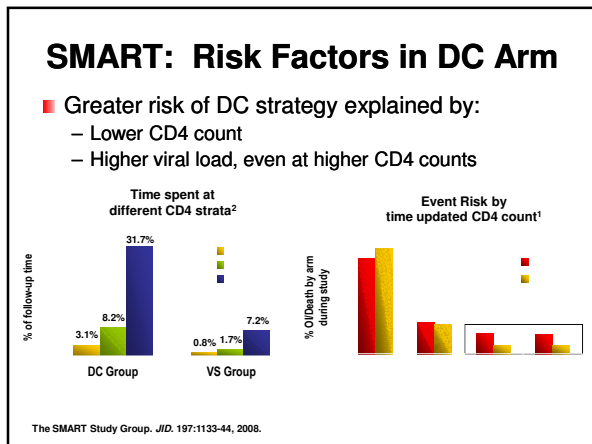
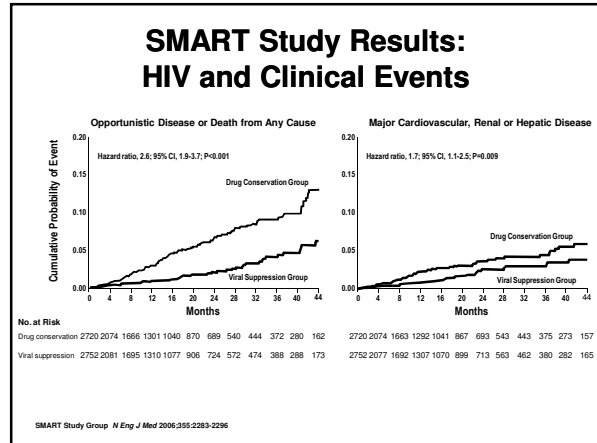
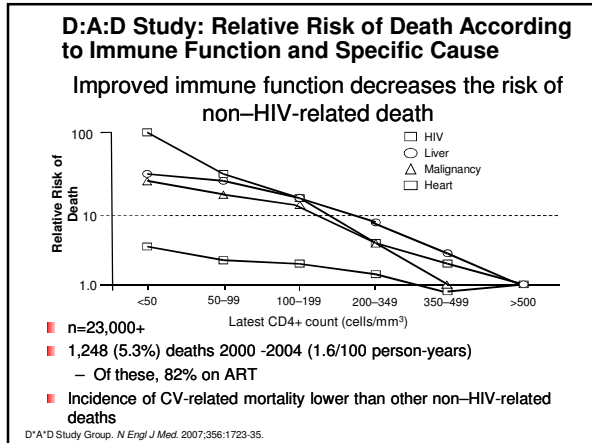
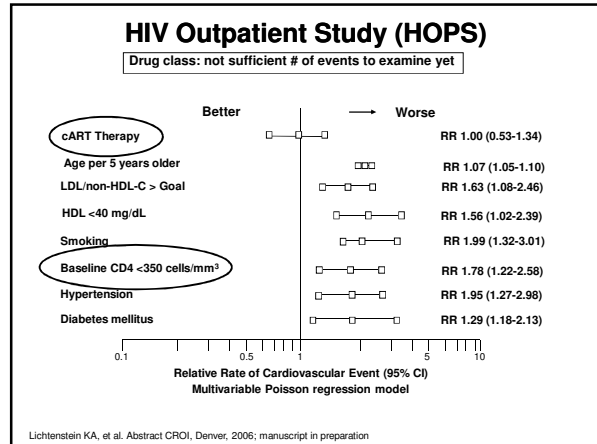
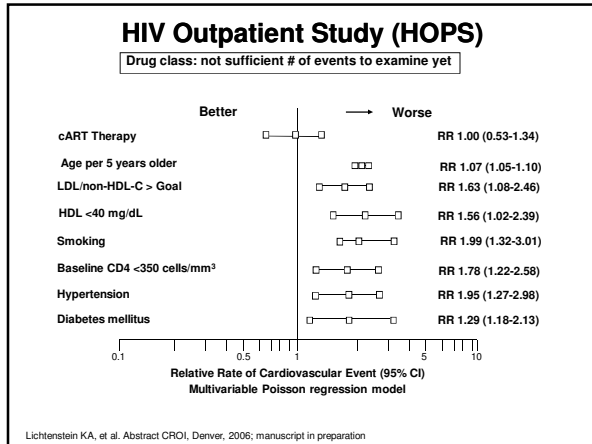
*Adjusted for age, gender, race, hypertension, diabetes and dyslipidemia.

Triant et al., JCEM. 2007.

D:A:D Study: Risk Factors for CHD in an HIV+ Population



D'A'D Study Group. N Engl J Med. 356:1723-35, 2007.



HIV Patients Have Accelerated Atherosclerotic Progression as Assessed by IMT

- 148 HIV-infected adults and 63 age- and gender-matched HIV- controls studied
- At baseline, HIV patients had greater IMT compared with controls
- HIV infection was an independent predictor of higher IMT

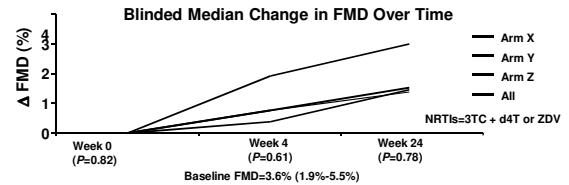
Hsue PY, et al. *Circulation*. 2004;109:1603-1608.

ACTG 5152s: ART Rapidly Improves Endothelial Function in Treatment-Naïve HIV+ Individuals on LPV, EFV, and/or AZT + 3TC

- Endothelial cell function measured by brachial artery flow-mediated dilation (FMD) in 82 patients receiving: PI-sparing (EFV + NRTIs), NNRTI-sparing (LPV/r + NRTIs), and NRTI-sparing (LPV/r + EFV) regimens

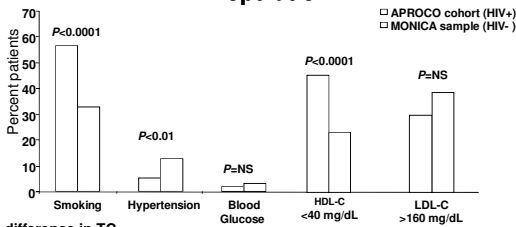
Conclusions:

- All 3 regimens rapidly improved endothelial function in treatment-naïve HIV+ patients
- Benefits similar for all 3 regimens, appearing after 4 weeks and persisting at 24 weeks
- Improved vascular reactivity may signify decreased short-term CVD risk



Torriani FJ, et al. ACTG 5152s, a substudy of ACTG 5142. *Antivir Ther*. 2007;12 (suppl2):L15

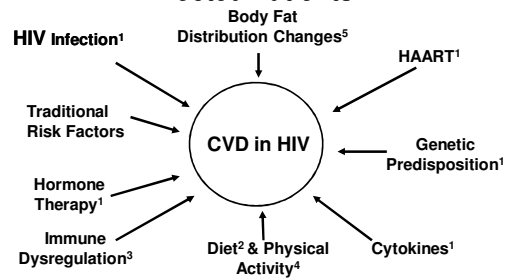
Incidence of Smoking Is Increased Among HIV-Infected Individuals Versus the General Population



- HIV+ men and women (n=223) on PI-based regimens versus 527 HIV- male subjects
- HIV+ patients have lower HDL and higher TG
- Predicted risk of CHD > in HIV+ men (RR=1.2) and women (RR=1.6); P<0.0001

Savès M, et al. *Clin Infect Dis*. 2003;37:292-298.

Multiple Host, Viral, Immunologic, and Drug Factors Contribute to CVD in HIV-Infected Patients



1. Grinspoon S, Carr A. *N Engl J Med*. 2005 Jan 6;352(1):48-62.
2. Manfredi R, et al. *J Acquir Immune Defic Syndr*. 2004 Jul 1;36(3):878-80.
3. Majumder Z, et al. *PLoS Biol*. 2006 Oct;4(11):e165.
4. Robinson FP, et al. *Biol Res Nurs*. 2007 Jan;8(3):177-85.
5. van Wijk JP, et al. *J Clin Endocrinol Metab*. 2005 Jun;90(6):3575-82.

Is cardiovascular disease in HIV a simple drug toxicity, mate, or is it a wee-bit more complicated than that?



NEW Learning Objectives

- At the conclusion of this interactive session, participants should be able to:
 - 1 Modify clinical strategies to address both traditional and additional risk factors for cardiovascular disease in HIV-infected patients.
 - 2 Utilize an understanding of the basic pathophysiology of lipids in cardiovascular disease to improve clinical care.