

## **Long-Term Metabolic Consequences of ARV Therapy**

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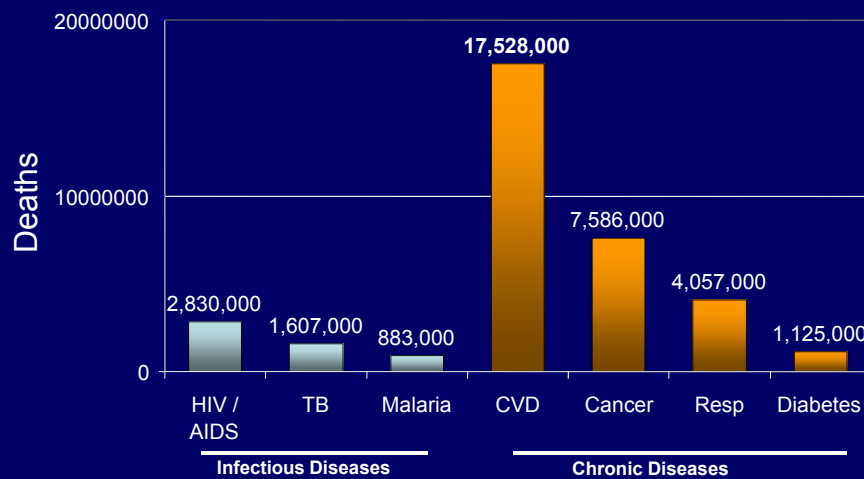
**Pfizer**

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

## Background

- CVD is common in general population and is associated with aging
- CV risk factors well established in general population and risk multiplies with additional risk factors
- CVD may go undetected for significant period

## Projected Global Deaths (All ages, 2005)

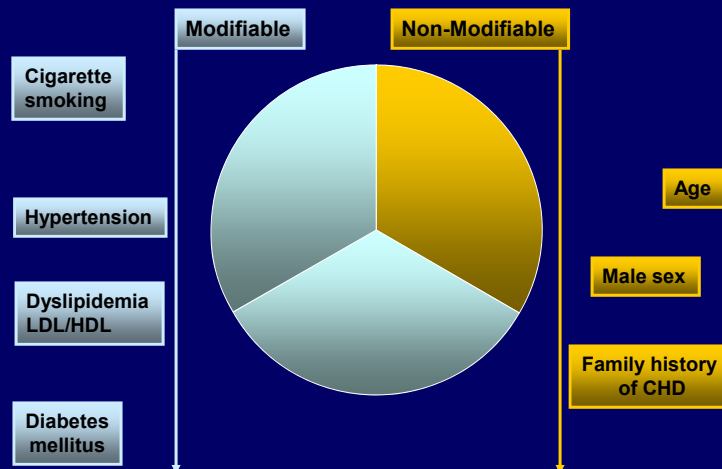


World Health Organization. Preventing Chronic Diseases 2005. Available at: [http://www.who.int/chp/chronic\\_disease\\_report](http://www.who.int/chp/chronic_disease_report)

## Background

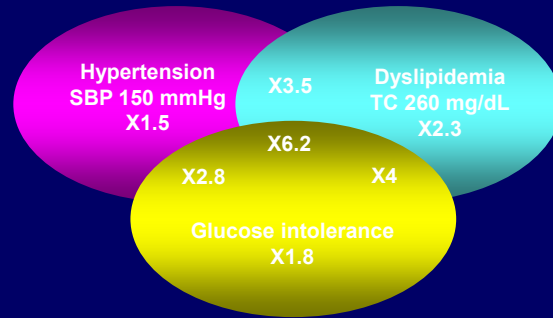
- CVD is common in general population and is associated with aging
- CV risk factors are well established in general population and risk multiplies with additional risk factors
- CVD may go undetected for significant period

## Risk Factors for CVD



Wood D, et al. *Eur Heart J* 1998;19:1434–1503.

## CHD: Risk multiplies with additional CV risk factors

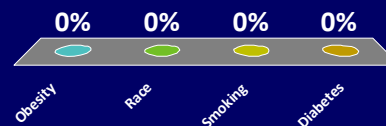


*Risk shown above is compared with baseline risk for a 40-year-old male non-smoker with TC 4.7 mmol/L (185 mg/dL), SBP 120 mmHg, and no glucose intolerance, who is ECG-LVH negative and whose probability of developing CVD is 15/1000 (1.5%) in 8 years*

Kannel WB. In: *Hypertension: Pathophysiology and Treatment* 1977:888-910.

## Which of the following is a Non-Modifiable CVD risk factor?

1. Obesity
2. Race
3. Smoking
4. Diabetes



## NCEP ATP III: The metabolic syndrome

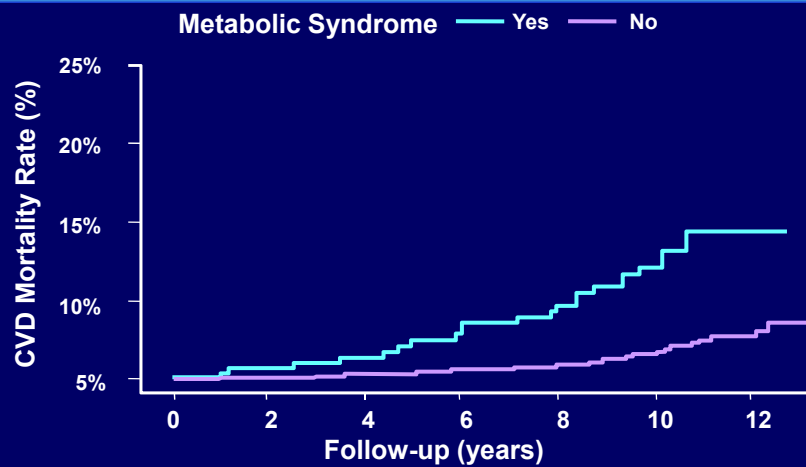
A syndrome overrepresented in CVD and diabetic populations

Diagnosis is established when  $\geq 3$  of the following risk factors are present

Risk factor	Defining level
<b>Abdominal obesity (waist circumference)</b>	
Men	>102 cm (>40 inches)
Women	>88 cm (>35 inches)
<b>TG</b>	$\geq 150$ mg/dL
<b>HDL-C</b>	
Men	<40 mg/dL
Women	<50 mg/dL
<b>Blood pressure</b>	$\geq 130/\geq 85$ mmHg
<b>Fasting glucose</b>	$\geq 110$ mg/dL

Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486–2497.

## CV mortality from metabolic syndrome

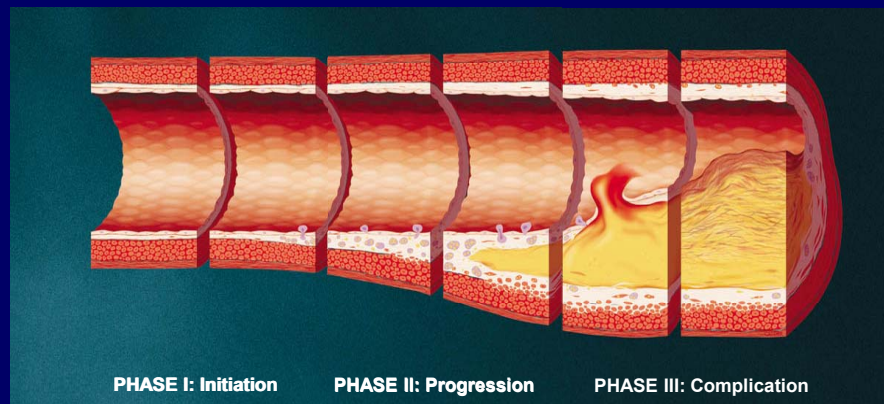


Lakka HM, et al. *JAMA* 2002;288: 2709

## Background

- CVD is common in general population and is associated with aging
- CV risk factors well established in general population and risk multiplies with additional risk factors
- CVD may go undetected for significant period

## Atherosclerosis is a chronic degenerative disease with LDL-C at the core



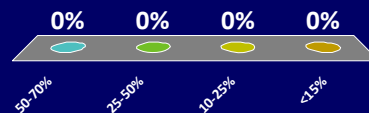
Adapted from Libby P, et al. *Circulation* 2001;104:365–372.

## Conventional CVD Risk Management

- Smoking Cessation
- Diet and Exercise, Weight loss
- Antihypertensives
- Lipid Lowering Therapy
- Anticoagulants (e.g. Aspirin)

## What percentage of HIV patients smoke cigarettes?

1. 50-70%
2. 25-50%
3. 10-25%
4. <15%



New York State Department of Health AIDS Institute, LIGHT UP YOUR LIFE A Leadership Forum on HIV and Smoking, HIV and Smoking: A Wake-Up Call for Action, May 2006, <http://www.nyhealth.gov/diseases/aids/docs/hivandsmoking.pdf>, accessed April 22, 2009

## Effects of Lipid-Lowering Drugs on Lipoproteins

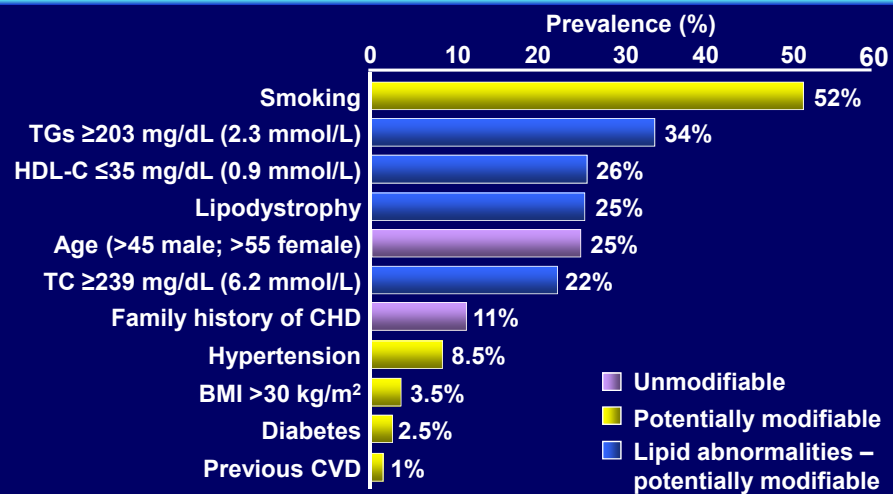
Drug	% Change			
	Total C	LDL C	HDL C	TG
Bile acid sequestrant	↓ 10–20%	↓ 15%–30%	↑ 3%–5%	↑ 0%–5%
Ezetimibe	↓ 18-20%	↓ 20-25%	↑ 4-5%	↓ 25-25%
Nicotinic acid	↓ 10%	↓ 15%–25%	↑ 10%–20%	↓ 20%–50%
Fibric acid derivatives	Variable	↓ 5%–25%	↑ 10%–30%	↓ 40%–50%
HMG-CoA reductase	↓ 25%–30%	↓ 30%–40%	↑ 10%–15%	↓ 25%
Fish oil (omega-3 fatty acids)	NC	NC	↑	↓ 30%–50%

## CVD in HIV

## Increased CV Risk in HIV

- HIV population older at diagnosis and surviving longer
- HIV populations have excess CVD risk factors
- ARV therapy and high prevalence of metabolic syndrome may exacerbate CVD risk
- HIV shown to have higher prevalence of CVD than general population

## Cardiovascular risk factors in an HIV-infected population: the D.A.D study



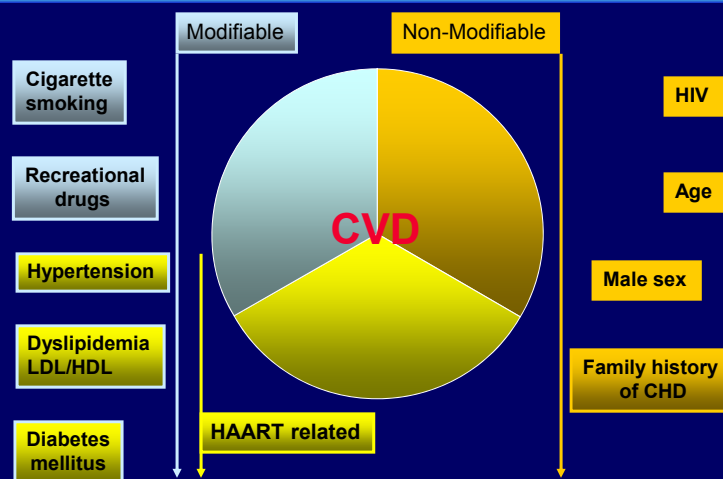
TC=total cholesterol

Friis-Moller N, et al. *AIDS* 2003;17:1179–1193.

## Increased CV Risk in HIV

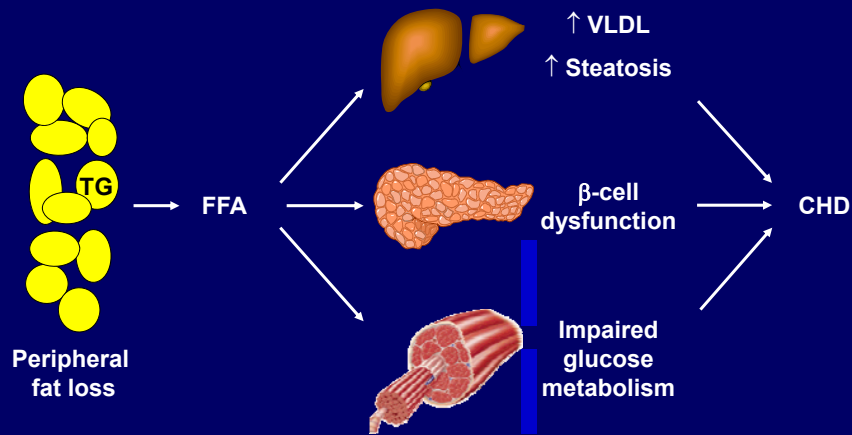
- HIV population older at diagnosis and surviving longer
- HIV populations have excess CVD risk factors
- ARV therapy and high prevalence of metabolic syndrome may exacerbate CVD risk
- HIV shown to have higher prevalence of CVD than general population

## Risk Factors for CVD in HIV patients



Wood D, et al. *Eur Heart J* 1998;19:1434–1503; Weber R, et al. 12th CROI (2005) #595

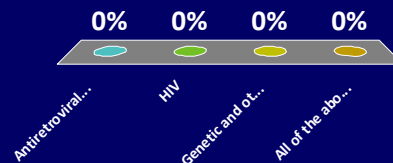
## HIV Lipodystrophy, Dyslipidemia, and Impaired Glucose Tolerance



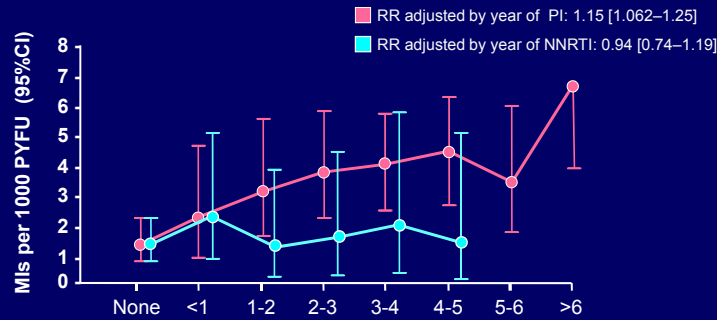
Van Wijk JP, et al. J Clin Endocrinol Metab. 2005;90:3575-3582.

## What is thought to contribute to Lipodystrophy?

1. Antiretroviral medications
2. HIV
3. Genetic and other host factors
4. All of the above



## ART effect on CV risk is driven by PIs (D:A:D study)

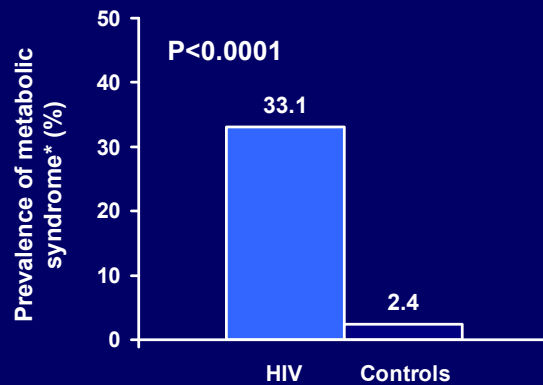


	Years of exposure to PI or NNRTI								Total
<b>PIs MI</b>	16	7	12	19	25	23	12	22	<b>136</b>
<b>PYFU</b>	11815	3108	3808	5144	6108	5199	3525	3306	<b>42013</b>
<b>NNRTIs MI</b>	16	6	3	3	3	2			<b>33</b>
<b>PYFU</b>	11815	2585	2294	1980	1525	1425			<b>21623</b>

Friis-Møller N, et al. 13th CROI (2006) #144

## Prevalence of metabolic syndrome higher in HIV-infected subjects on HAART<sup>1</sup>

- N=574
- Groups matched for age and gender
  - Mean Age: 41.1 y
  - Male 71%



\*Metabolic syndrome defined according to the European Group for the Study of Insulin Resistance (EGIR)<sup>2</sup>

<sup>1</sup> Gazzaruso C, et al. *J Hypertens* 2003;21:1377-1382; <sup>2</sup> Balkau B, et al. *Diabetes Metab.* 2002;28:364-376.

## Features of the metabolic syndrome include:

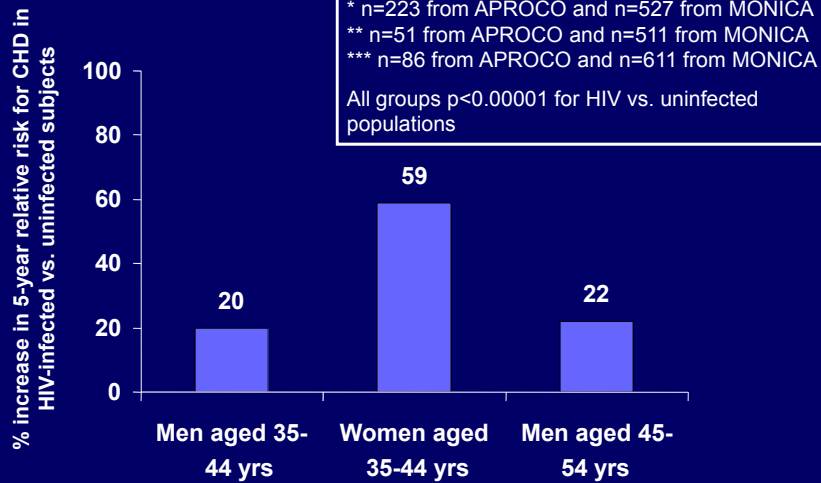
1. Central obesity
2. Hypertension
3. Insulin resistance
4. Dyslipidemia  
(hypertriglyceridemia  
and low  
high-density lipoprotein  
[HDL] cholesterol  
level)
5. All of the above



## Increased CV Risk in HIV

- HIV population older at diagnosis and surviving longer
- HIV populations have excess CVD risk factors
- ARV therapy and high prevalence of metabolic syndrome may exacerbate CVD risk
- HIV shown to have higher prevalence of CVD than general population

## Increased risk of CHD in HIV infected subjects vs. the general population



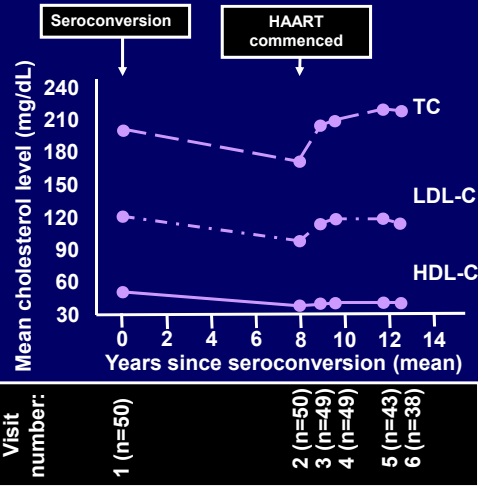
Saves M, et al. *Clin Infect Dis* 2003;37:292-8

## Lipids and CVD in HIV Infection

- Effects of HIV
- Effects of specific ART on lipids
  - NRTI backbone
  - NNRTI
  - PIs
- Effects of specific ART on glucose levels

## Impact of HIV infection and HAART on serum lipids

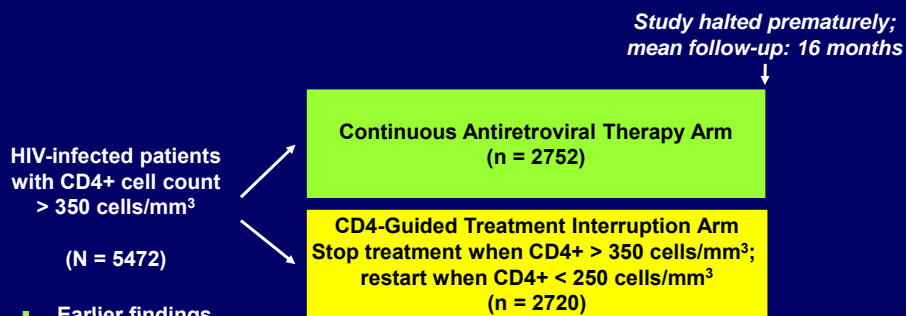
- Review of seroconversion and HAART in MACS subjects
- Seroconversion led to ↓ in TC, LDL-C, and HDL-C
- HAART therapy ↑ TC above normal
  - ↑ LDL-C to normal
  - HDL-C remained subnormal
- Early lipid changes may represent, in part, a return to health rather than toxicity



HAART=highly active antiretroviral therapy; MACS (Multicenter AIDS Cohort Study)

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

## SMART: CD4+-Guided Treatment Interruption and Risk of Events



▪ Earlier findings

- Risk of opportunistic disease or death higher in treatment interruption arm vs continuous therapy arm (hazard ratio: 2.61;  $P < .0001$ )
- Risk of nonopportunistic disease-related deaths also significantly higher in treatment interruption arm

El Sadr W, et al. CROI 2006. Abstract 106b. El Sadr W, et al. IAC 2006. Abstract WEAB0203.

## SMART: Exploratory Analysis of Risk of Major CVD Events as Function of TI

- Marginally statistically significant elevated risk of major CVD events in TI arm compared with viral suppression arm
- Elevated CVD risk greatest in small subgroup of TI patients not taking antiretroviral therapy at baseline
  - Being off antiretroviral therapy during follow-up in TI arm not associated with increased CVD risk
- Increased risk in TI arm not explained by acute changes in HIV-1 RNA level or CD4+ cell count
- Greater unfavorable lipid changes in TI arm (decrease in HDL) than in viral suppression arm
  - Especially in patients on NNRTI-based therapy at baseline

Phillips A, et al. CROI 2007. Abstract 41.

## SMART: Exploratory Analysis of Risk of Major CVD Events as Function of TI

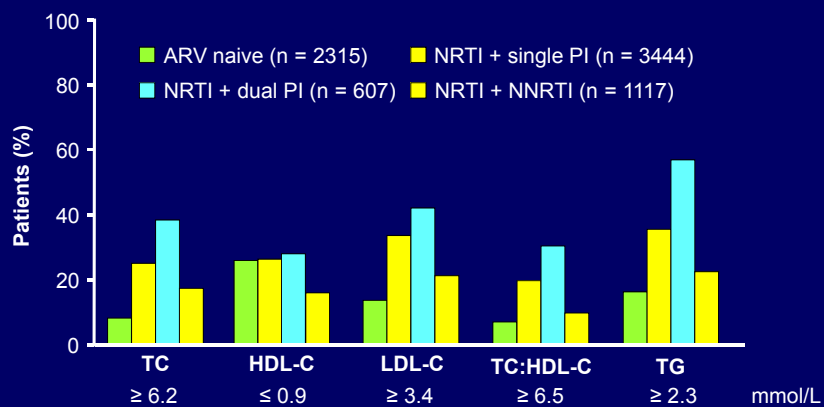
Risk of Major CVD Events, % <sup>[1]</sup>			Relative Hazard of Expanded CVD Events <sup>[2]</sup>		
Events	DC Arm	VS Arm	Event	RR (DC/VS) (95% CI)	P Value
Death from CVD	7	4	Clinical MI, silent MI, CAD requiring invasive procedure or surgery, death from CVD + PVD, CHF, CAD requiring drugs + unobserved death from unknown cause	1.57 (1.00-2.46)	.05
Nonfatal clinical MI	12	12			
Nonfatal stent MI	11	5			
Nonfatal stroke	8	3			
CAD requiring surgery of invasive procedure	22	14			
				1.49 (1.04-2.11)	.03
				1.58 (1.12-2.22)	.009

1. Phillips A, et al. CROI 2007. Abstract 41.
2. Visnegarwala F, et al. CROI 2007. Abstract 803.

## Morphology and Metabolism in HIV Infection

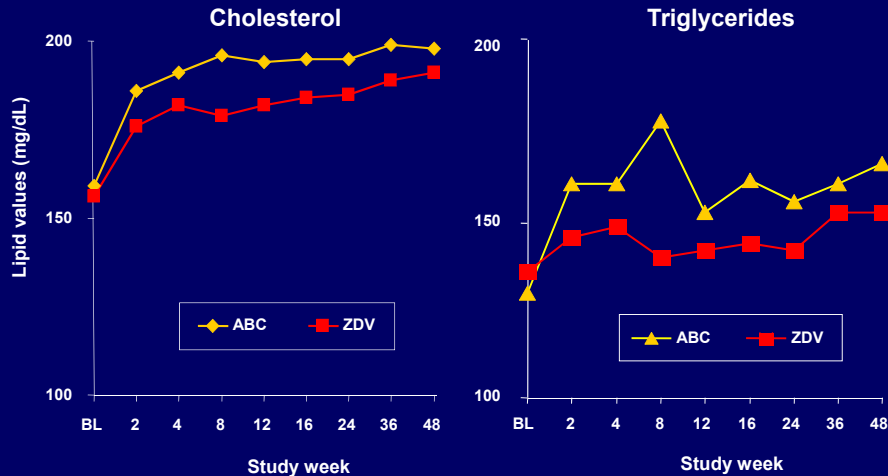
- Effects of HIV
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  - NRTI backbone
  - NNRTI
  - PIs
- Effects of specific ART on glucose levels

## D:A:D: Prevalence of Dyslipidemia at Study Entry



Fontas E, et al. J Infect Dis. 2004;189:1056-1074.

## CNA30024: ZDV/3TC vs ABC/3TC: Non-fasting Lipid Values



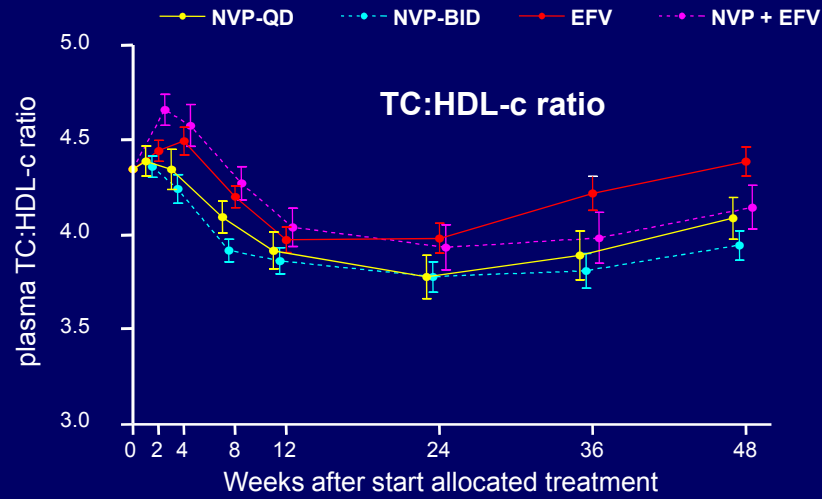
All medians below the NCEP cut-off, 5% each group grade 3/4

Moyle G AIDS Reader 2005; #15:62-66

## Morphology and Metabolism in HIV Infection

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  - NNRTI
  - PIs
- Effects of specific ART on glucose levels

## 2NN Changes in TC:HDL Cholesterol concentrations



van Leth F, et al. *Lancet* 2004;363:1253-63

## Metabolic Effects of Non-PIs

	Lipids	Glucose
<b>NRTIs</b>	↑ TC + TG with d4T ± ddl	↑ insulin resistance with lipomatrophy
<b>EFV</b>	↑ TC + HDL, ↑ TG	No Δ insulin sensitivity
<b>NVP*</b>	↑ TC + HDL, =/↑ TG	No Δ insulin sensitivity
<b>ENF</b>	No Δ	No Δ insulin sensitivity

van Leth F, et al. *PLoS Med.* 2004;1:e19.

## Morphology and Metabolism in HIV Infection

- Effects of HIV
- Effects of specific ART on lipids
  - NRTI backbone
  - NNRTI
  - PIs
- Effects of specific ART on glucose levels

## Lipid Effects of PIs

Drug	TG/MLDL-C	LDL-C	HDL-C
▪ RTV	↑↑↑	↑	↔
▪ LPV/RTV	↑↑	↑	↔/↑
▪ TPV/RTV	↑↑	↑	↔
▪ SQV/RTV	↑	↑	↑
▪ FPV/RTV	↑	↑	↑↑
▪ IDV/RTV	↑↑	↑	↔
▪ DRV/RTV	↑	↑/↔	↑?
▪ ATV/RTV	↑	↑/↔	↑
▪ NFV	↔?	↑	↑↑
▪ ATV	↔	↔	↔/↑?
▪ IDV	↔	↑	↔

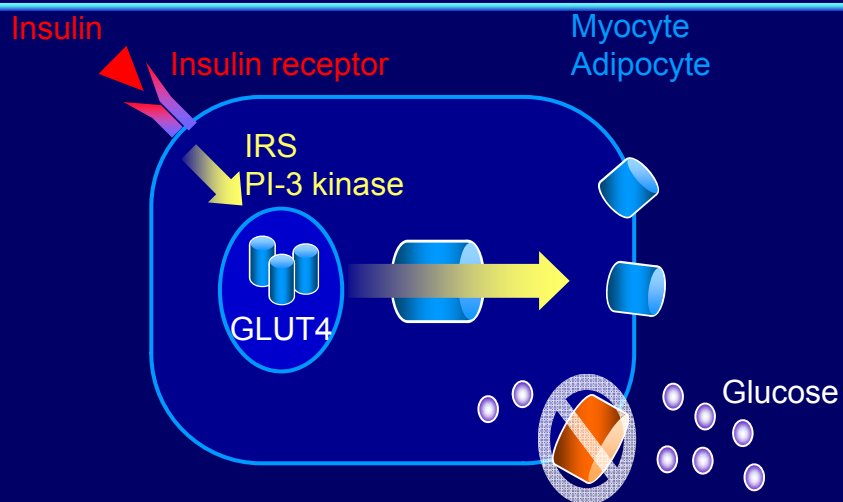
*This table represents the author's judgment about the relative lipid effects of the agents listed, based on accumulated data from studies to date. Different studies have reported varying lipid effects, probably influenced by stage of HIV infection, geographic representation, and other cross-study differences. As a result, some individual studies may seem inconsistent with the ratings in the table; nevertheless, this table represents the author's best attempt to reconcile all the available data.*

Slide courtesy of Stefan Mauss, MD

## Morphology and Metabolism in HIV Infection

- Effects of HIV
- Effects of specific ART on lipids
  - NRTI backbone
  - NNRTI
  - PIs
- Effects of specific ART on glucose levels

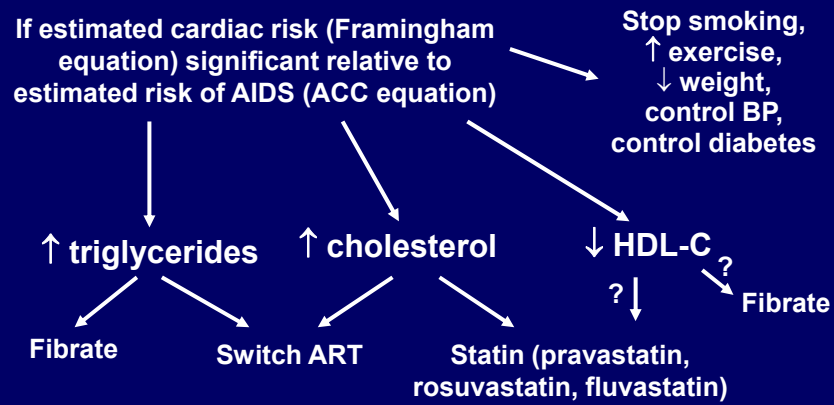
## Mechanism of glucose transport through GLUT4



Bryant M, et al. *Nat Rev Mol Cell Biol* 2002;3(4):267–277

## Management of CVD risk in HIV

### CV Risk Management Schema



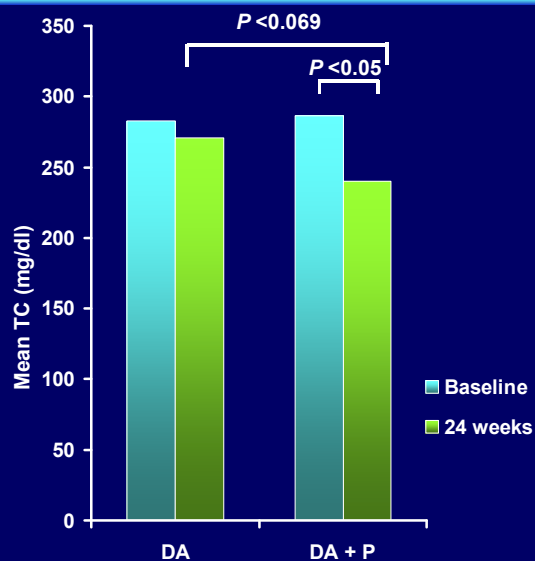
Adapted from: Grinspoon S and Carr A. *N Engl J Med.* 2005;352:48-62.

## Use of lipid lowering agents in HIV-related dyslipidemia

- Statins
- Fibrates
- Cholesterol absorption inhibitors
- Niacin
- Omega 3

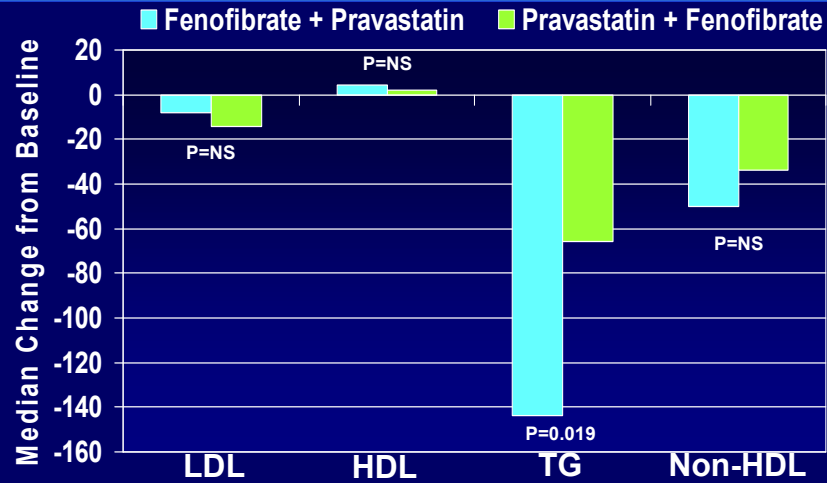
## Pravastatin + Diet Improve PI-associated Hypercholesterolemia

- Open-label, randomized pilot study of 31 men on PIs
  - Dietary advice (DA) vs. DA + pravastatin (P; 40 mg/d)
- TC fall significantly greater w/ D + PA
- No significant changes in TGs



<sup>1</sup>Moyle G *et al.* AIDS 2001;15:1503–1508.

## ACTG 5087: HAART-associated Hyperlipidemia Treatment

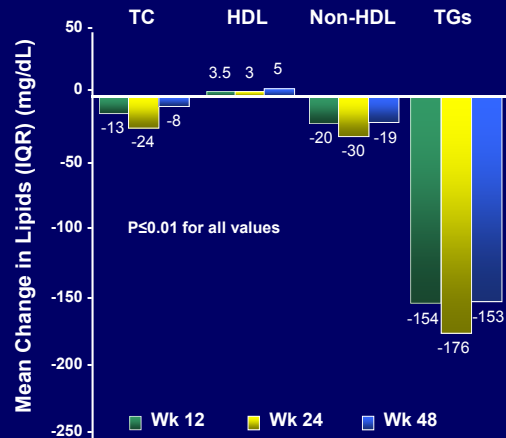


Only 3% of P + F and 7% of F + P met NCEP composite goals

Aberg JA et al. *AIDS Res Hum Retroviruses* 2005;21:757-67

## ACTG 5148: Niacin Supplementation

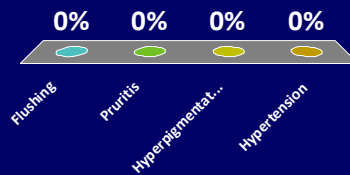
- N = 37 HIV-infected men
  - 4 wks dietary advice
  - 44 wks niacin (↑ dose)
- Significant improvements in lipids at Week 48
- Fasting insulin & HOMA-IR persistently elevated
  - However, insulin AUC during OGTT worsened only transiently



Dubé MP, et al. *7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV* (2005) #12

## Which of the following is NOT a potential side effect of Niacin?

1. Flushing
2. Pruritis
3. Hyperpigmentation
4. Hypertension



## Lipid Lowering Agents and ARVs: Drug Interactions

<p><b>Fibrates</b> Fluvastatin Pravastatin</p>	<p><b>Low interaction potential</b></p>	<ul style="list-style-type: none"> <li>• SQV/RTV<sup>1</sup> <ul style="list-style-type: none"> <li>– Atorvastatin ↑347% AUC</li> <li>– Simvastatin ↑3059% AUC</li> <li>– Pravastatin ↓50% AUC</li> </ul> </li> <li>• NFV<sup>2,3</sup> <ul style="list-style-type: none"> <li>– Atorvastatin ↑74% AUC</li> <li>– Simvastatin ↑505% AUC</li> <li>– Pravastatin ↓47% AUC</li> </ul> </li> <li>• LPV/r<sup>4</sup> <ul style="list-style-type: none"> <li>– Atorvastatin ↑588% AUC</li> <li>– Pravastatin ↑30% AUC</li> </ul> </li> <li>• fosAPV<sup>5</sup> <ul style="list-style-type: none"> <li>– Atorvastatin ↑130% AUC</li> </ul> </li> <li>• EFV<sup>6</sup> <ul style="list-style-type: none"> <li>– Atorvastatin ↓43% AUC</li> <li>– Simvastatin ↓58% AUC</li> </ul> </li> </ul>
<p><b>Statin-Fibrates</b> Atorvastatin</p>	<p><b>Use cautiously</b></p>	
<p><b>Lovastatin</b> Simvastatin</p>	<p><b>Contraindicated with PIs</b></p>	

<sup>1</sup>Fitchbaum CJ, et al. *AIDS*. 2002;16:569-577.  
<sup>2</sup>Hsueh PH, et al. *AAC*. 2001;45:3445-3450.  
<sup>3</sup>Gerber J, et al *2nd IAS* 2003, #870  
<sup>4</sup>Carr RA, et al. 40th ICAAC, Toronto, 2000. Abstract 1644.  
<sup>5</sup>Telzir Package Insert 2003.  
<sup>6</sup>Gerber JG, et al. *11<sup>th</sup> CROI*. 2004. Abstr# 603.

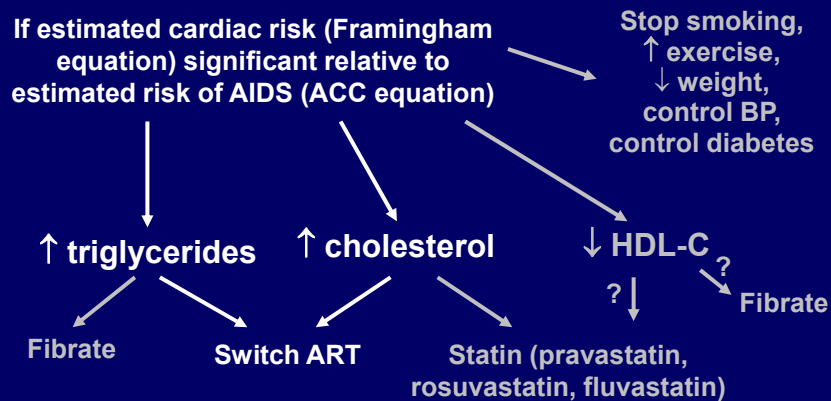
## Utility of Lipid-lowering Agents for Dyslipidemia in HIV Infection?

- There is a role for fibrates, statins and niacin

BUT

- Target lipid levels infrequently achieved in clinical trials
- Interactions between statins and PIs can complicate use
- Increased cost
- Increased pill burden
- Potential for glucose intolerance with niacin

## CV Risk Management Schema

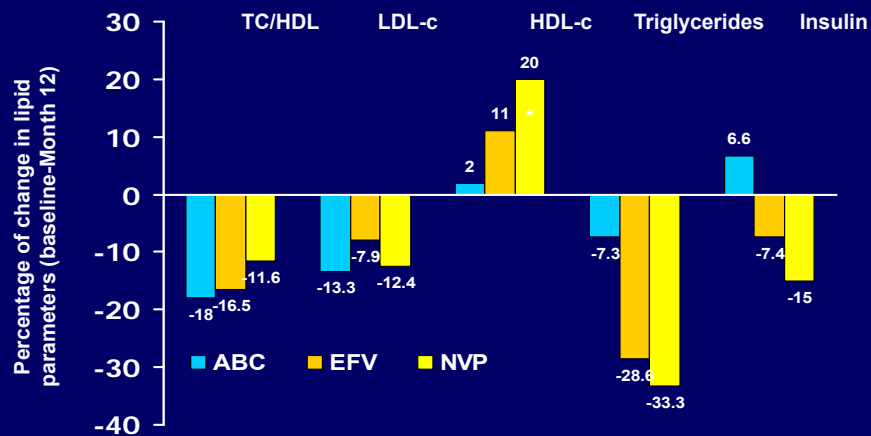


Adapted from: Grinspoon S and Carr A. *N Engl J Med.* 2005;352:48-62.

## Modifying Successful Therapy: Outcomes

- Maintain virological control
  - Maintain CD4 responses
- } Do no harm
- 
- Improve adherence and quality of life
  - Improve/resolve/prevent toxicities
- } Make things better

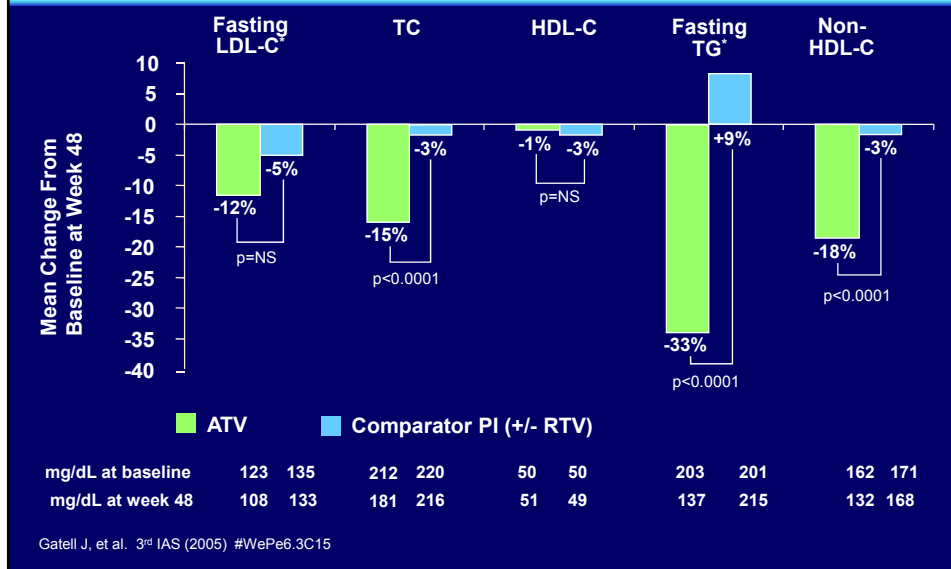
## NEFA study: PI to ABC, EFV or NVP Switch



Fisac C, et al. *AIDS* 2005;19:917-25.

\*p <0.005

## SWAN Study: PI or PI/r switch to ATV



## CVD: Summary

- CVD risk is increasing in the aging HIV population
- CVD risk is associated with HAART and lipid elevation
- Prevalence of dyslipidemia is substantial, especially with some PI-based regimens
- Emphasize smoking cessation, dietary modification, and aerobic exercise
- Assess for insulin resistance and the metabolic syndrome
- Use lipid lowering therapies based on NCEP guidelines
- Switching ART to less dyslipidemic agents may avoid need for additional interventions