Forum for Collaborative HIV Research

Review of Cardiovascular Disease risk in HIV Treatment

Veronica Miller PhD

Forum for Collaborative HIV Research

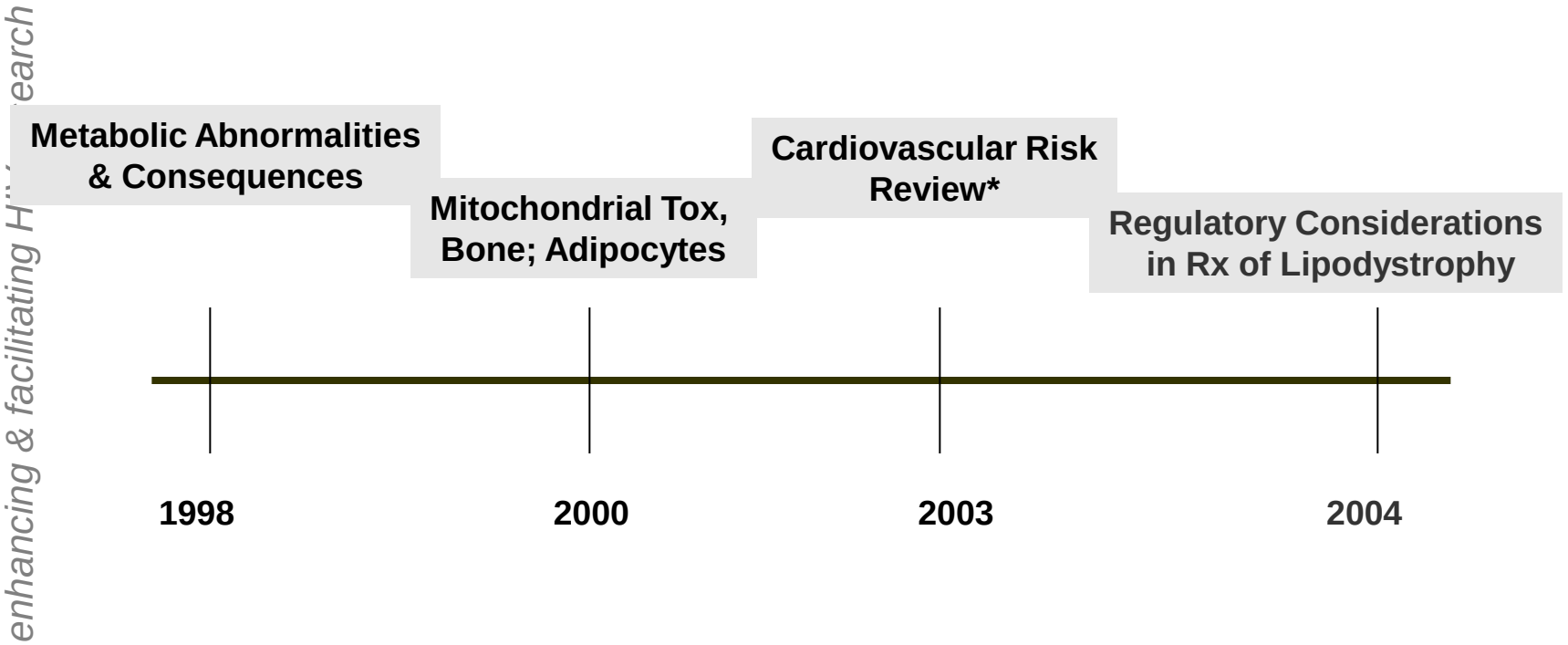
Forum Mission

- The Forum for Collaborative HIV Research is a public/private partnership including government agencies, industry, HIV researchers and clinicians, payors, foundations and the HIV patient advocacy community.

  Our mission is to facilitate and enhance HIV research.

enhancing & facilitating HIV research

History of FCHR Work on Metabolic Abnormalities and Cardiovascular Risk



http://www.hivforum.org/index.php?option=com_content&task=blogcategory&id=108&Itemid=102

*with support from HAART Oversight Committee

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- Pfizer
- Tibotec
- ViiV

Today's Agenda

- Session I: Observational Cohort Studies
- Session II: Pathophysiology
- Session III: Clinical, Policy and Research Implications

Session I

- Bob Munk PhD
  - AIDS InfoNET/ UNM
- Wendy Post MD
  - Assoc Prof Medicine JHU/ Ciccarone Center of Prev of Heart Disease
- Jur Strobos MD
  - Forum for Collaborative HIV Research; UCB School of Public Health
- Linda Lewis MD
  - FDA
- Filip Josephson MD PhD
  - Swedish Med. Products Agency/EMA

CARDIOVASCULAR DISEASE RISK IN PEOPLE WITH HIV: A PATIENT PERSPECTIVE

Robert Munk

DRAMATIC HIV ADVANCES

1987	2010
Do you have a will?	“Normal” life span (-10 yrs?)
Surviving opportunistic infections	Dealing with aging
1 approved antiretroviral drug	24 approved drugs
30 – 50 daily pills to deal with OIs	20 – 25 daily pills to deal with side effects, BP, cholesterol, bone

WHAT RISK INFORMATION GETS THROUGH?

- Headlines stick!
  - "Ritonavir increases CVD risk"
  - "Abacavir doesn't increase inflammation"
- Statistical significance is not always clinically significant
- Difficult to get balanced view

HIV SPECIALISTS

- Infectious disease! Identify the bug and kill it.
- Drug interactions & resistance
- Focus on CD4 count and viral load
- Changing meds: easy way out?

NEW APPROACH NEEDED

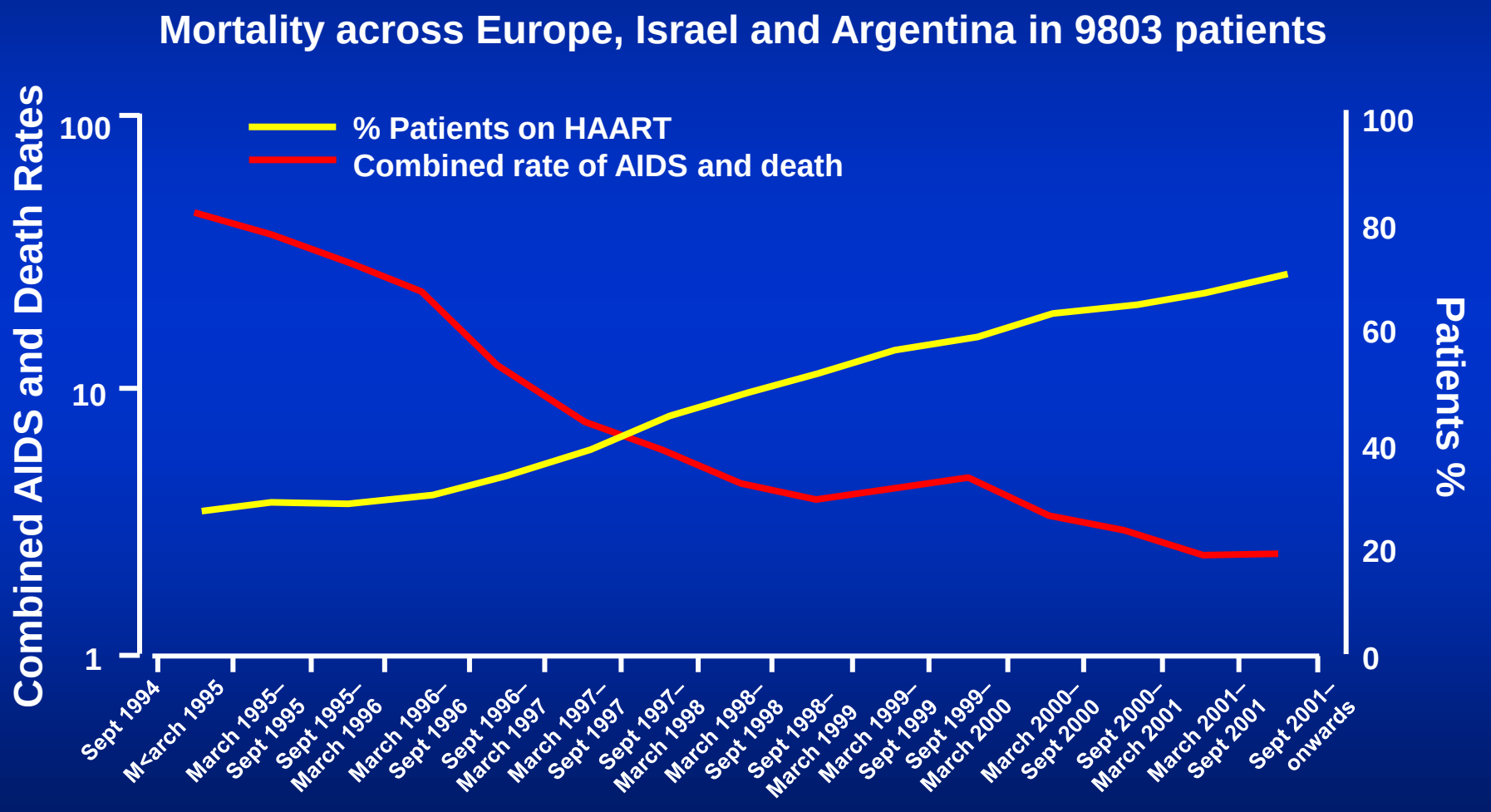
- Deal with multiple chronic conditions
- Routine monitoring: bone density, depression, cardiac risk
- Focus on quality of life
- Lifestyle changes: challenging!

Is There Increased Cardiovascular Risk in Patients with HIV?

Wendy Post, MD, MS

Associate Professor of Medicine
and Epidemiology
Cardiology Division
Johns Hopkins University
Baltimore, Maryland, USA

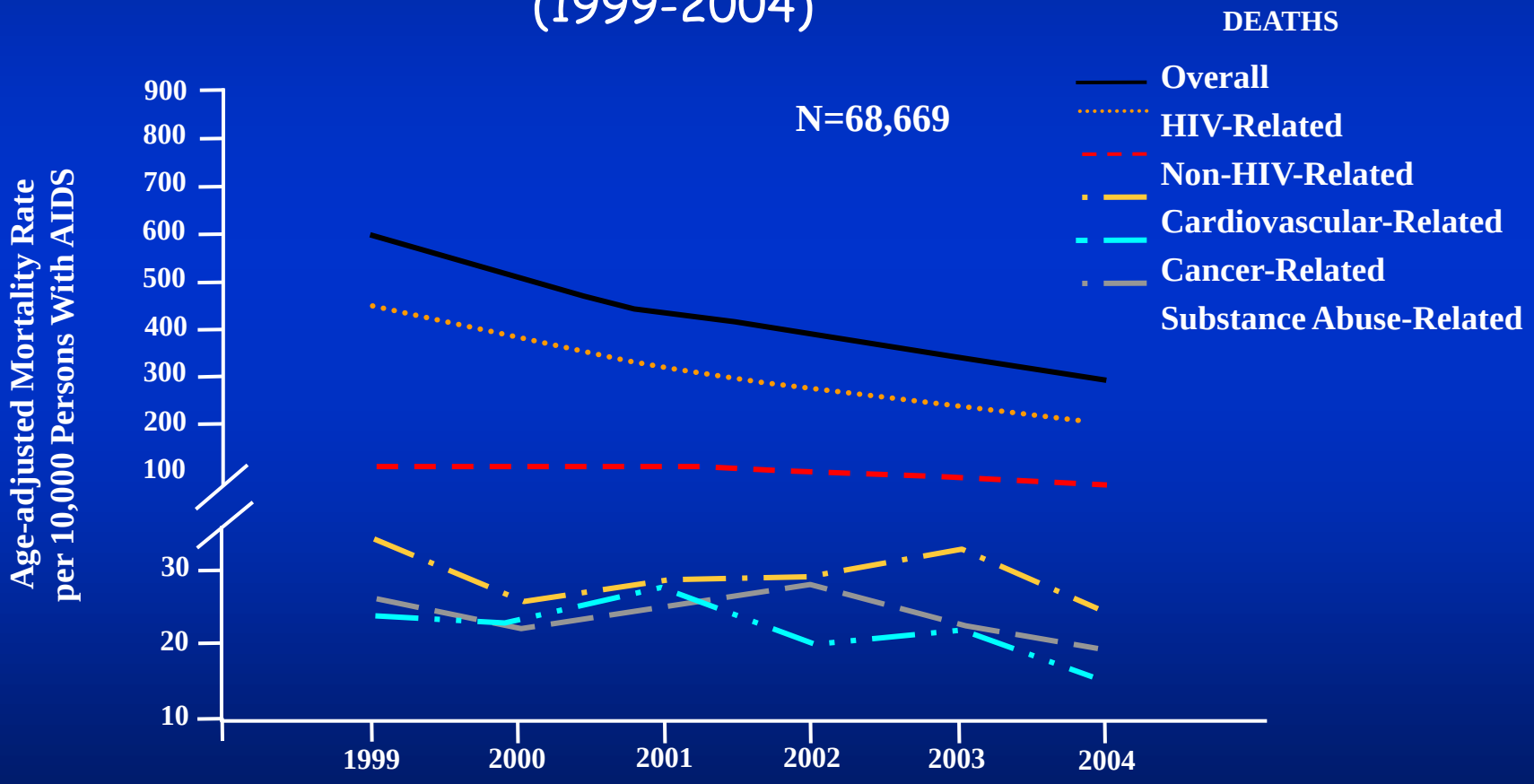
EuroSIDA: Decreases in AIDS and Death Since the Introduction of Active ART



Mocroft A, et al. Lancet 2003;362:22

Cardiovascular-related Disease is a Leading Cause of Non-HIV-related Death

Age-adjusted Mortality Rate in HIV+ by Underlying Cause of Death, New York City (1999-2004)



Sackoff, et al. Ann Int Med. 2006;145:397-406.

HIV and/or ART may increase risk for CHD

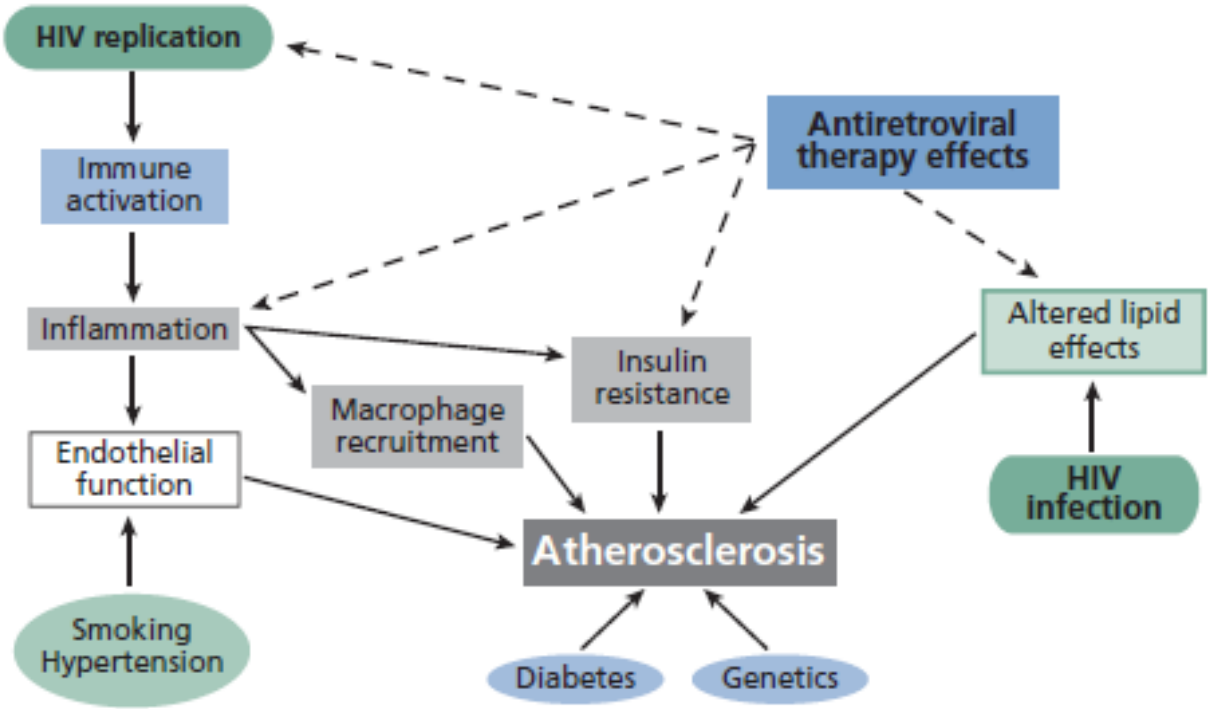
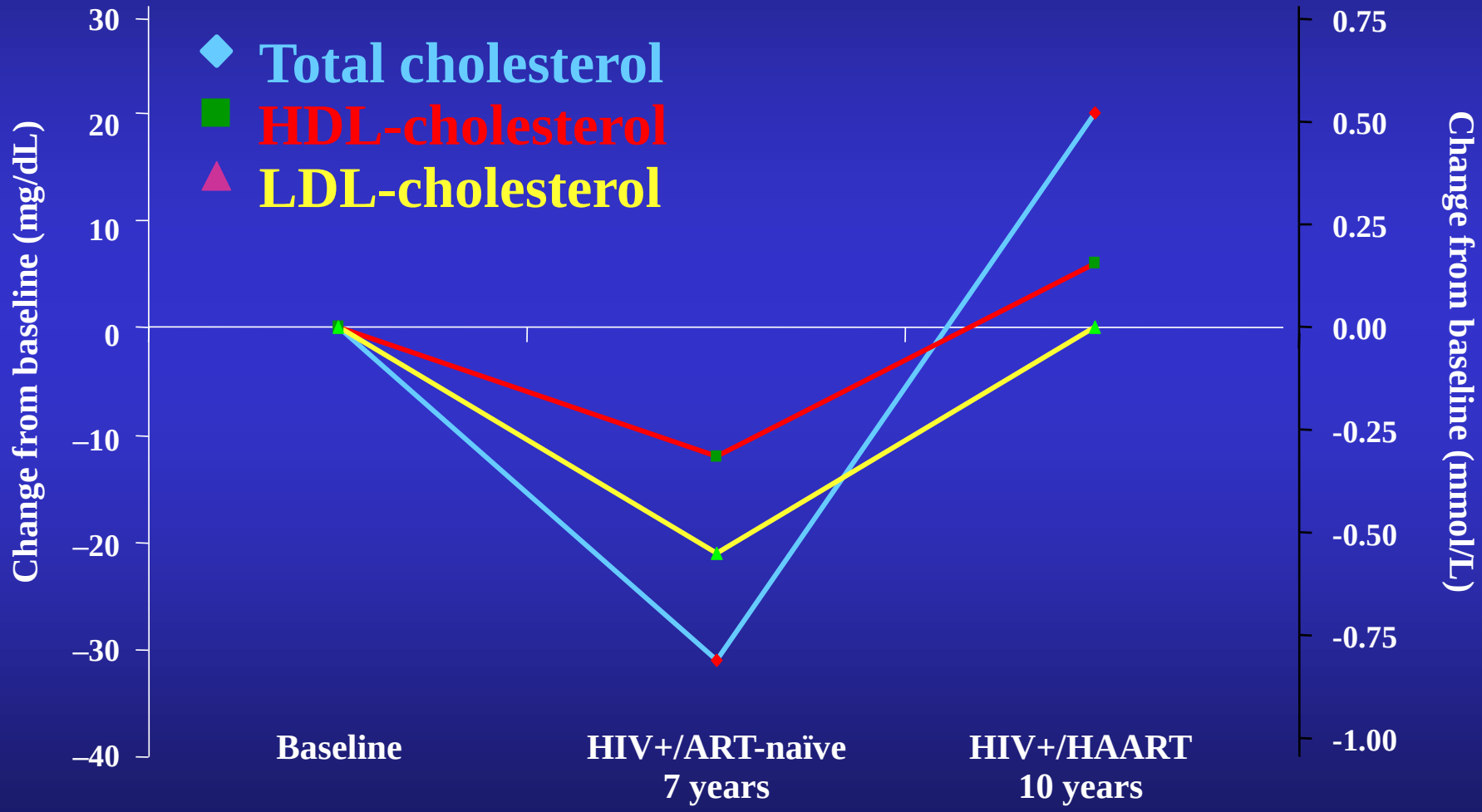


Figure **2.** Interaction of host, virus, and antiretroviral therapy effects in cardiovascular disease risk.

Currier J. Topics HIV Med 2009;17(3): 98-103.

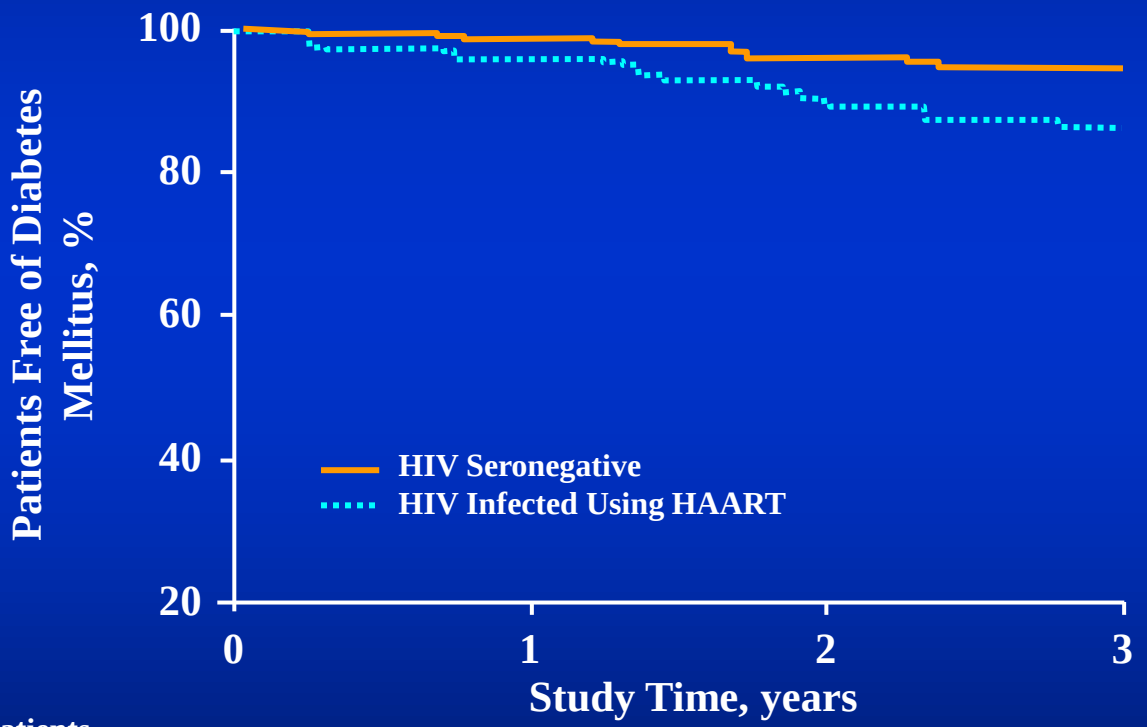
HIV Infection and HAART Can Contribute to CV Risk



Riddler SA, et al. JAMA 2003; 289: 2978-82.

HAART Can Contribute to CV Risk

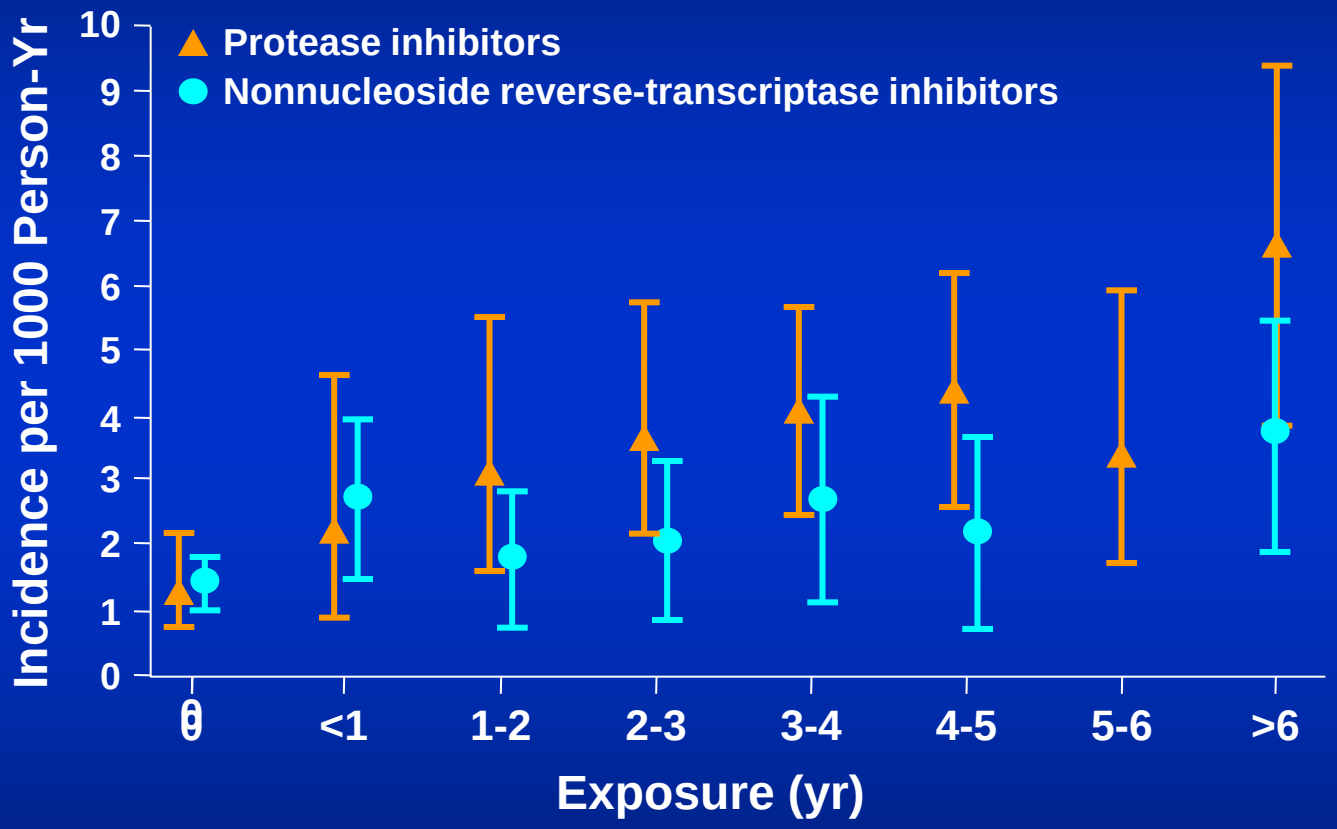
MACS: Diabetes Mellitus is more than 4 times higher in HIV-infected patients on HAART as compared to the general population



No. of Patients				
HIV Seronegative	361	265	177	89
HIV Infected Using HAART	229	204	145	62

Brown TT, et al. Arch Int Med. 2005;165:1179-1184.

Use of Protease Inhibitors Increased MI Risk in the D:A:D Study



PIs: adjusted RR = 1.16 (1.10-1.23, p<0.001)

NNRTIs: adjusted RR = 1.05 (0.98-1.13, p=0.17)

DAD Study Group. N Engl J Med 2007; 356:1723

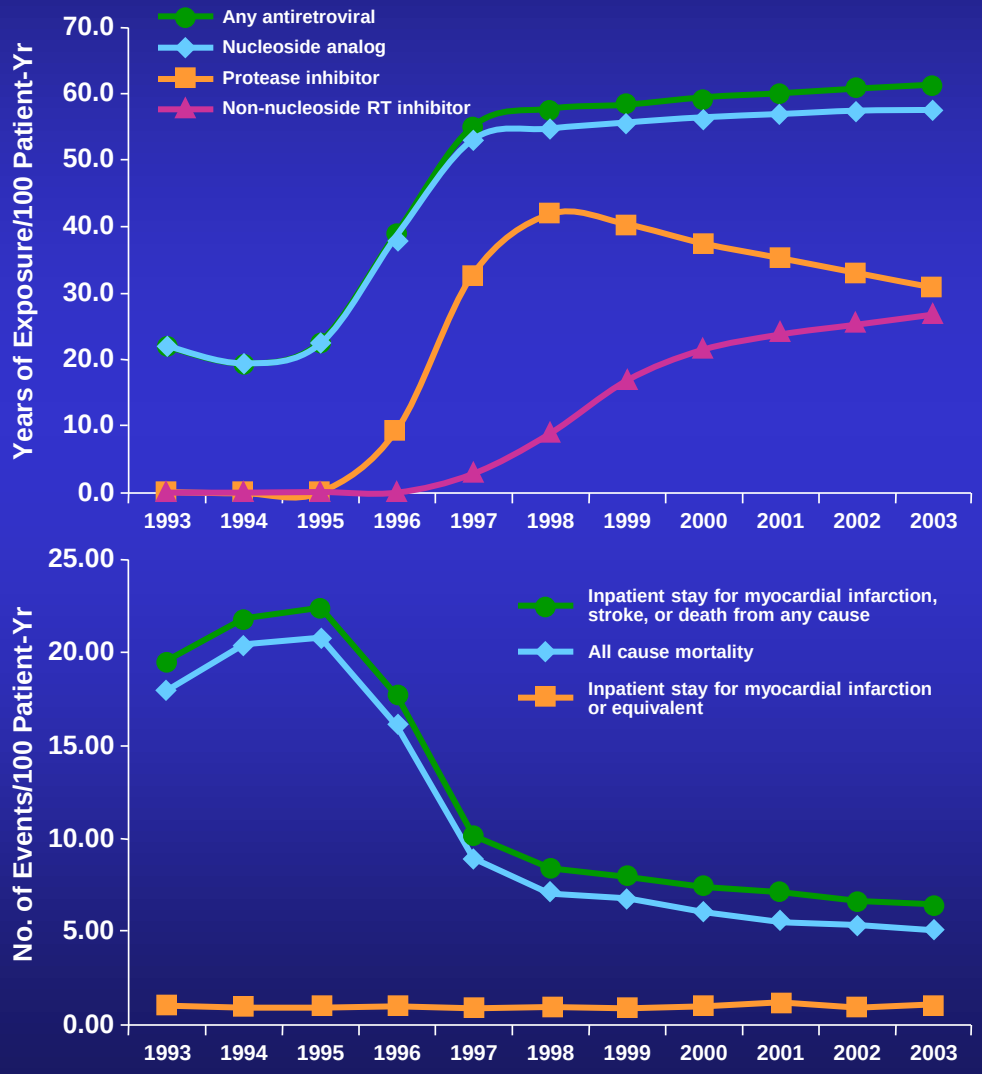
Risk Factors for MI in D:A:D

	Adjusted Model 1		Adjusted Model 2	
	Relative Rate (95% CI)	P Value	Relative Rate (95% CI)	P Value
Exposure to PIs (per year)	1.16 (1.10-1.23)	<0.001	1.10 (1.04-1.18)	0.002
Age (per 5 yr)	1.39 (1.31-1.46)	<0.001	1.32 (1.23-1.41)	<0.001
Male sex	1.91 (1.28-2.86)	0.002	2.13 (1.29-3.52)	0.003
BMI >30 kg/m^2	1.70 (1.08-2.69)	0.02	1.34 (0.77-2.34)	0.31
Family history of CHD	1.56 (1.10-2.23)	0.01	1.40 (0.96-2.05)	0.08
Smoking status				
Current	2.83 (2.04-3.93)	<0.001	2.92 (2.04-4.18)	<0.001
Former	1.65 (1.12-2.42)	0.01	1.63 (1.07-2.48)	0.02
Previous cardiovascular event	4.30 (3.06-6.03)	<0.001	4.64 (3.22-6.69)	<0.001
Diabetes mellitus	-	-	1.86 (1.31-2.65)	<0.001
Hypertension	-	-	1.30 (0.99-1.72)	0.06
Total cholesterol (per mmol/liter increase)	-	-	1.26 (1.19-1.35)	<0.001
HDL cholesterol (per mmol/liter increase)	-	-	0.72 (0.52-0.99)	0.05

DAD Study Group. N Engl J Med 2007; 356:1723

VA Study
No increased CHD risk

- *Retrospective study of electronic data from VA (1993-2003)*
- *168,213 person-yrs of follow-up*
  - Average f/up = 4 years
  - 19,898 deaths, CVD admissions, strokes
- *CHD rate not increased by any ART class*



Bozette S, et al. JAIDS 2008; 47:338

Table 5. Studies of cardiovascular disease in antiretroviral-treated HIV patients

	Type of study (*N*)	Endpoints	Association with CVD
Klein[143]	Retrospective analysis of KPNC database (*N* = 573)	Hospital admission & discharge diagnosis of CHD	No[a]
Bozzette[144]	Retrospective analysis of patients receiving HIV care at VA (*N* = 36,766)	Admission for and/or death from CVD, cerebrovascular disease, death from any cause	No
Mary-Krause[145]	Retrospective analysis of data from FHD (*N* = 34,916)	Incidence of MI	Yes (higher MI incidence rate among men exposed to PI for ≥18 months)
Currier[146]	Retrospective analysis of California Medicaid claims of HIV+ patients (*N* = 28,513)	Incidence of CHD	Yes (ART associated with CHD in individuals aged 18-33)
Holmberg (HOPS)[147]	Prospective, observational cohort (*N* = 5,672)	Verified MI, angina, CVA events	Yes (PI associated with MI)
Friis-Moller (DAD)[140]	Observational, international study (*N* = 17,852)	Acute MI	Yes[b]
Law (DAD)[141]	Observational, international study (*N* = 17,600)	Acute MI	Yes
DAD[142]	Observational, international study (*N* = 23,468)	Cardiovascular and cerebrovascular events and MI prediction	Yes[c]

Note: CVD = coronary vascular disease; KPNC = Kaiser Permanente Northern California; CHD = coronary heart disease; VA = Veterans Administration; FND = French Hospital Database, MI = myocardial infarction; PI = protease inhibitor; ART = antiretroviral therapy; CVA = cerebrovascular accident.

[a]There was a significantly higher rate of CHD and MI hospitalizations among HIV+ patients compared with HIV- controls.

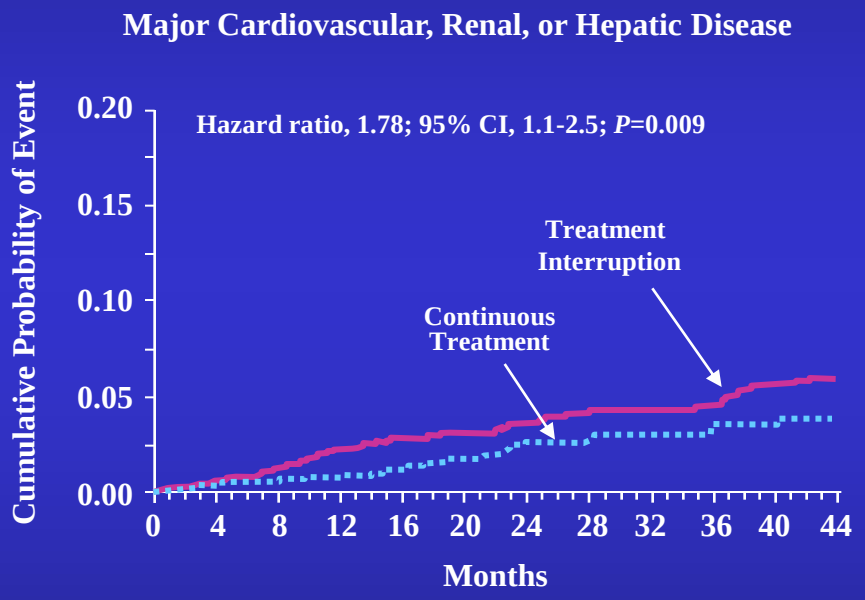
[b]The incidence of MI increased with longer exposure to combination antiretroviral therapy (CART) (adjusted relative rate of 1.26; 95% CI 1.21–1.41; $p < .001$).[140]

[c]The increase in MI risk could be mostly explained by CART-associated changes in conventional CVD risk factors.

Mehta N. HIV Clin Trials 2005;6(1):5-24.

SMART Study: HIV Viremia Can Contribute to CV Risk

N=5472 HIV-infected patients with a CD4+ cell count >350mm^3



No. at Risk												
Treatment Interruption	2720	2070	1663	1292	1041	867	693	543	443	375	273	157
Continuous Treatment	2752	2077	1692	1307	1070	899	713	563	462	380	282	165

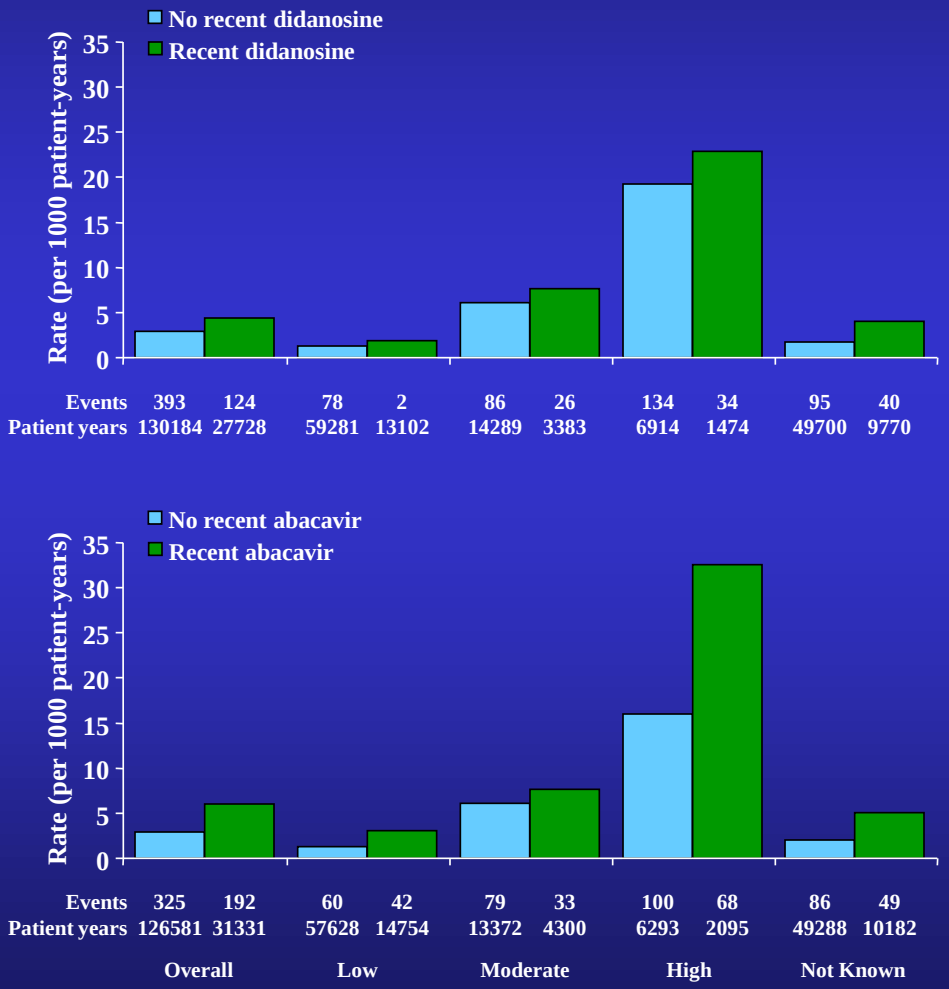
Endpoint	Hazard Ratio (95%CI)*	*P* Value
Death, any cause	1.8 (1.2-2.9)	0.007
Major cardiovascular, renal or hepatic disease	1.7 (1.1-2.5)	0.009
Fatal or non-fatal CVD	1.6 (1.0-2.5)	0.05

*Treatment Interruption vs. Continuous Treatment

SMART Study Group. N Eng J Med. 2006;355: 2283-2296.

NRTIs and MI Risk in D:A:D

- *Increased risk from ABC and ddI most marked in those at "high" risk (6% of D:A:D)*



DAD Study Group. Lancet 2008;371:1417
Stein JH, Currier JS. Lancet 2008;371:1391

MACS: Subclinical atherosclerosis

Cross sectional analysis results

- Similar prevalence of CAC among HIV+ and HIV- men, after adjusting for CVD risk factors
- Among men with CAC, the extent of CAC is lower in HAART treated men than HIV- men
- Carotid IMT and plaque do not differ between HIV+ and HIV- men
- Carotid artery plaque is more prevalent in HIV+ men with a CD4 count < 200 cells/mm^3

Kingsley LA et al. AIDS 2008;22(13):1589-99.
Kaplan RC et al. AIDS. 2008 Aug 20;***22(13)***:***1615-24***.

Important study design and interpretation issues of observational datasets

- Power
  - Sample size
  - Numbers of events (young age)
  - Limited follow-up time
  - Don't just look at point estimates, but also look at confidence intervals
- Appropriate control groups
  - Differences in environmental factors and lifestyle risk factors
    - Not easy to measure
  - Residual confounding
  - Biases related to non-randomized prescribing of ART
- Accuracy of data
  - Self report, chart review, retrospective versus prospective acquisition of data
- Relative risk versus absolute risks
- Need to evaluate consistency or lack of consistency of study results
- Multiple testing

Summary

- Observational studies suggest an increased risk for CHD associated with HIV infection and HAART
- Not all studies find consistent results

Statistical Standards: Review of A Roundtable on Statistical Issues in Assessing Cardiovascular Risk in Persons with HIV

Jur Strobos, MD, FACEP
Forum for Collaborative HIV Research
University of California Berkeley

Observational Studies: The Issue

- Randomization generally ensures homogeneity between groups
  - Can also test for empiric bias
- In observational studies, homogeneity between compared groups cannot be achieved
- Eg, differences in MI among those in the group who took a drug and those in a group that did not may be related to other non-homogeneous factors

Observational Studies: Principles for Critical Reading

- Consider study design and methods of data collection
- Evaluate adjustments for bias
  - THERE IS NO CLEAR-CUT MEANS TO REMOVE ALL BIAS
- Data access for internal validation
- Confirmation from other data sources

Types of Observational Studies

- Design
  - Retrospective
  - Cross-Sectional
  - Cohort Based (with or w/o matched controls)
- Prespecification of hypothesis and analytical plan
- Standardized protocol and data gathering instruments

Multiple testing

- Was there multiple testing?
  - Prespecified design
  - Single hypothesis
- Unless adjusted for multiplicity, repeat testing *must eventually* generate a "positive" finding
- Evaluation of 5 drugs, recent + cumulative = 10 tests

PreSpecified Design

- Design
  - Retrospective/Cross-Sectional/Cohort Based
- Standardized protocol/data instrument
- Prespecified hypothesis and analytical plan
  - Eg., 1° endpoint is assessment of PI risk
  - Other endpoints are exploratory and require confirmatory study
  - A form of multiple testing

Missing Data

- All studies have missing data but how much?
  - Contemporaneous parallel data collection, as in modern randomized studies, minimizes impact
  - Retrospective studies and post hoc chart reviews limit data to what was relevant for patient care
  - Information on known covariates can be missing
- Publications should disclose the data collection methodology, instrument and the quantitative impact of missing data

Missing Data Imputations

- All analyses impute missing data
  - Missing ≠ absent
  - Imputations for unbalanced missing data should ensure underestimation of the hazard ratio for the variable of interest
- Publications should disclose missing data imputations and the impact of different choices of imputations

Definitions of Variables

- All clinical variables are subjectively defined
  - Laboratory values ∝ quality and lab normals
  - EKGs are read differently; MI definitions evolve
  - Hospitalization criteria vary
  - Discharge diagnoses may not be reliable
- Variance in definitions among sites and over time introduces bias
- Publications should disclose methods of variable adjudication and homogeneity across groups

Use of Matched Controls

- Matched controls improve homogeneity of variables that are unrelated to the disease entity or its treatment
- Matched controls may be a better model to adjust for unbalanced variables unrelated to disease v. standardized adjustments (eg, Framingham)
- Publications should disclose the methodology for control selection and demographic and other differences with the test group

Bias Adjustment

- Types of bias: channeling or confounding by indication; time-dependent; empiric bias
- Historic adjustment methods
  - Matching, stratification, covariance adjustment wtih or w/o instrumental variables, propensity scores.
  - Can only address channeling bias
- New methods are useful for internal validation
  - Hold-back datasets, recursive partitioning, high computing non-linear modeling
- The lower bound of the hazard ratio should be emphasized, esp. when adjustment lowers the HR

Residual Bias

- Linear adjustments for bias employ clinically-identified models
  - Eg., if baseline cardiovascular is unbalanced, a known time-dependent equation of risk from those factors is used to adjust for differences
- The newer methods may provide information on whether the chosen model is 'good enough'

Open Access

- Federal law requires access to pharmaceutical study designs, public access to data and publication of results
- Publications increasingly require access to raw data to ensure integrity
- New technology simplifies open access to observational databases
- Publications should require open deposit of de-identified raw data to ensure public health decisions are the best possible

External Validation

- Any one data source must be assumed to contain unadjusted bias
- Sensitivity analyses may *help*
  - But, there may be intrinsic, systematic or unknown unbalanced and unadjusted bias
- Confirmation by analysis of an alternative data source is essential to validation
  - However, two data sources may have still have the same embedded bias if subject characteristics, study methodology, demographics and design were similar

An Example

- Testing the impact of multiple specific drugs on cardiovascular risk cannot correct for multiplicity
- Adjustment for time dependency is not possible when definitions of MI events vary over time, drug regimens change frequently based on clinical failure or new product introduction, and uncontrolled disease or co-morbid uncontrolled inflammation are known risk factors
- Newer methods for bias adjustment should be used to confirm validity of the linear model chosen
- Absence of open access precludes appraisal of reliability
- Findings should not be accepted until confirmed from data sources collected with a different design

HIV, ART and cardiovascular risk in practice guidelines

Filip Josephson M.D., Ph.D.

Swedish Medical Products Agency/ European Medicines Agency (EMA)

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

The adoption of evidence in clinical guidelines

- **Guidelines define standard-of-care**
- **By necessity often based on evidence from observational trials rather than RCTs**
- **Indicates the level of evidence considered sufficiently compelling to act upon**
- **Shape the considerations determining drug use and clinical trial design, thereby strongly influencing the possibility of confirming evidence from observational trials**

Recommendation and evidence rating

Table 2. Rating Scheme for Recommendations (Updated November 3, 2008)

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

Many guidelines use bi-dimensional rating scales indicating the urgency of the recommendation as distinct from the strength of the evidence supporting it

Also: ”should”, ”is recommended”, ”consider”

DHHS does not include high CVD risk as a listed consideration for earlier treatment initiation

Conditions Favoring More Rapid Initiation of Therapy

Deferring antiretroviral therapy may be appropriate in some cases. However, several conditions increase the urgency for therapy, including:

- Pregnancy **(AI)**
- AIDS-defining conditions **(AI)**
- Acute opportunistic infections (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm^3) **(AI)**
- Rapidly declining CD4 counts (e.g., >100 cells/ mm^3 decrease per year) **(AIII)**
- Higher viral loads (e.g., >100,000 copies/ml) **(BII)**
- HIV-associated nephropathy **(AII)**
- HBV coinfection when treatment for HBV is indicated **(AIII)**

However, the DHHS panel was divided as regards the strength of evidence

In the accompanying text it is also stated:

”Panel members favouring earlier initiation of therapy base their recommendation on several recent developments (…) Collectively data (…) suggest that early control of HIV replication with antiretroviral therapy can be used as a strategy to reduce CVD risk (recommendation / evidence level BIII)”

DHHS: Abacavir relegated from first line recommendations due to concerns about lower efficacy of ABC/3TC vs TDF/FTC, as well as due to CVD risk association

Panel's Recommendations:

- *The Panel recommends initiating antiretroviral therapy in treatment naïve patients with 1 of the following 3 types of regimen:*
  - *NNRTI + 2 NRTI*
  - *PI (preferably boosted with ritonavir) + 2 NRTI*
  - *INSTI + 2 NRTI*
- *The Panel recommends the following as preferred regimens for treatment naïve patients:*
  - *Efavirenz + tenofovir + emtricitabine (AI)*
  - *Ritonavir-boosted atazanavir + tenofovir + emtricitabine (AI)*
  - *Ritonavir-boosted darunavir + tenofovir + emtricitabine (AI)*
  - *Raltegravir + tenofovir + emtricitabine (AI)*
- *A list of Panel recommended alternative and acceptable regimens can be found in Table 5a.*
- *Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.*
- *Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.*

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor

Also:Lopinavir/r no longer preferred drug in treatment naives due to "higher ritonavir dose, higher rate of GI side effects and hyperlipidemia

EACS guidelines: Consider earlier treatment initiation in patients with high CVD risk

Recommendations for Initiation of Therapy in Naive HIV-Infected Patients

SYMPTOMATIC	• CDC stage B and C: treatment recommended • If OI, initiate as soon as possible*
ASYMPTOMATIC	• CD4 < 200: Treatment recommended, without delay. • CD4 201-350: treatment recommended. • CD4 350-500: - Treatment recommended if hepatitis C co-infection, hepatitis B co-infection requiring therapy, HIV-associated nephropathy or other specific organ deficiency; - Treatment should be considered if VL>10^5 c/ml and/or CD4 decline >50-100/mm^3/year or age >50 or, pregnancy, high cardiovascular risk, malignancy. • CD4 > 500: - Treatment should generally be deferred, independently of plasma HIV RNA; closer follow-up of CD4 if VL > 10^5 c/ml. - Treatment can be offered if presence of ≥ 1 of the above co-morbid conditions (CD4 350-500). • Whatever CD4 and Plasma HIV RNA, treatment can be offered on an individual basis, especially if patient is seeking and ready for ARV therapy

EACS: abacavir first line option, but use with caution in case of high CVD risk

Initial Combination Regimen for Antiretroviral-Naïve patient

SELECT 1 DRUG IN COLUMN A AND 1 NRTI COMBINATION IN COLUMN B	A	B	REMARKS
Recommended	NNRTI • EFV[1] • NVP[5] or ritonavir-boosted PI • ATV/r[6] • DRV/r[6] • LPV/r[7] • SQV/r	TDF/FTC ABC/3TC[2-3-4]	- TDF/FTC co-formulated - ABC/3TC co-formulated - EFV/TDF/FTC co-formulated - ATV/r: 300/100 mg qd - DRV/r: 800/100 mg qd - LPV/r:400/100 mg bid or 800/200 mg qd - SQV/r:1000/100 mg bid
Alternative	SQV/r FPV/r RAL[9]	• ZDV/3TC[8] • ddI/3TC or FTC[8]	- SQV/r: 2000/100 mg qd - FPV/r:700/100 mg bid or 1400/200 mg qd - RAL: 400 mg bid - ZDV/3TC co-formulated

1 EFV: not recommended in pregnant women or women with no reliable and consistent contraception; not active on HIV-2 and HIV-1 group O
2 Contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory
3 ABC + NVP contra-indicated, unless HLA B*5701 negative
4 Abacavir should be used with caution in patients with a high cardiovascular risk and/or patients with a viral load higher than 100,000 copies/ml.

Conclusions: ART to reduce CVD risk

A growing body of epidemiological and pathophysiological studies link HIV infection per se to an increased risk of CVD/MI

The unexpected outcomes of the SMART study remain the main source of ”clinical” evidence on which a qualified recommendation of earlier ART initiation to reduce CVD risk is based.

A general trend to recommend earlier ART initiation may preceed the confirmation that earlier initiation of ART decreases CVD risk

Conclusions drug toxicity

We presently lack positive evidence from RCT or metaanalyses of RCT as regards the CVD risk of specific antiretroviral drugs

Evidence from observational trials have informed recommendations in guidelines, which affect prescribing regardless of level of evidence, and in the absence of a clear mechanistic rationale

The adoption of findings from observational trials into clinical guidelines and practice may strongly affect the possibility of confirming outcomes from the same studies

Session II

- Nisha Chandra Strobos MD
  - Prof Medicine JHU School of Med
  - Chief, Div of Cardiology JHU Bayview MC
- Alan Landay PhD
  - Prof and Chair, Dept of Immunology and Microbiology
    Rush University
- Virginia Triant MD MS
  - Instructor in Medicine
    Mass General Hospital

CV RISK: UNDERSTANDING PATHOPHYSIOLOGY

NISHA CHANDRA – STROBOS MD

PROF OF MED

CHIEF OF CARDIOLOGY

JOHNS HOPKINS BAYVIEW MED CENTER

JOHNS HOPKINS UNIV SCHOOL OF MEDICINE

CARDIOVASCULAR RISK IN HIV PTS:WHY DOES CAD OCCUR?

- 3 LAYERS OF RISK
- THE PT AT BASE LINE
- THE INFLAMMATORY DISEASE
- THE TREATMENT

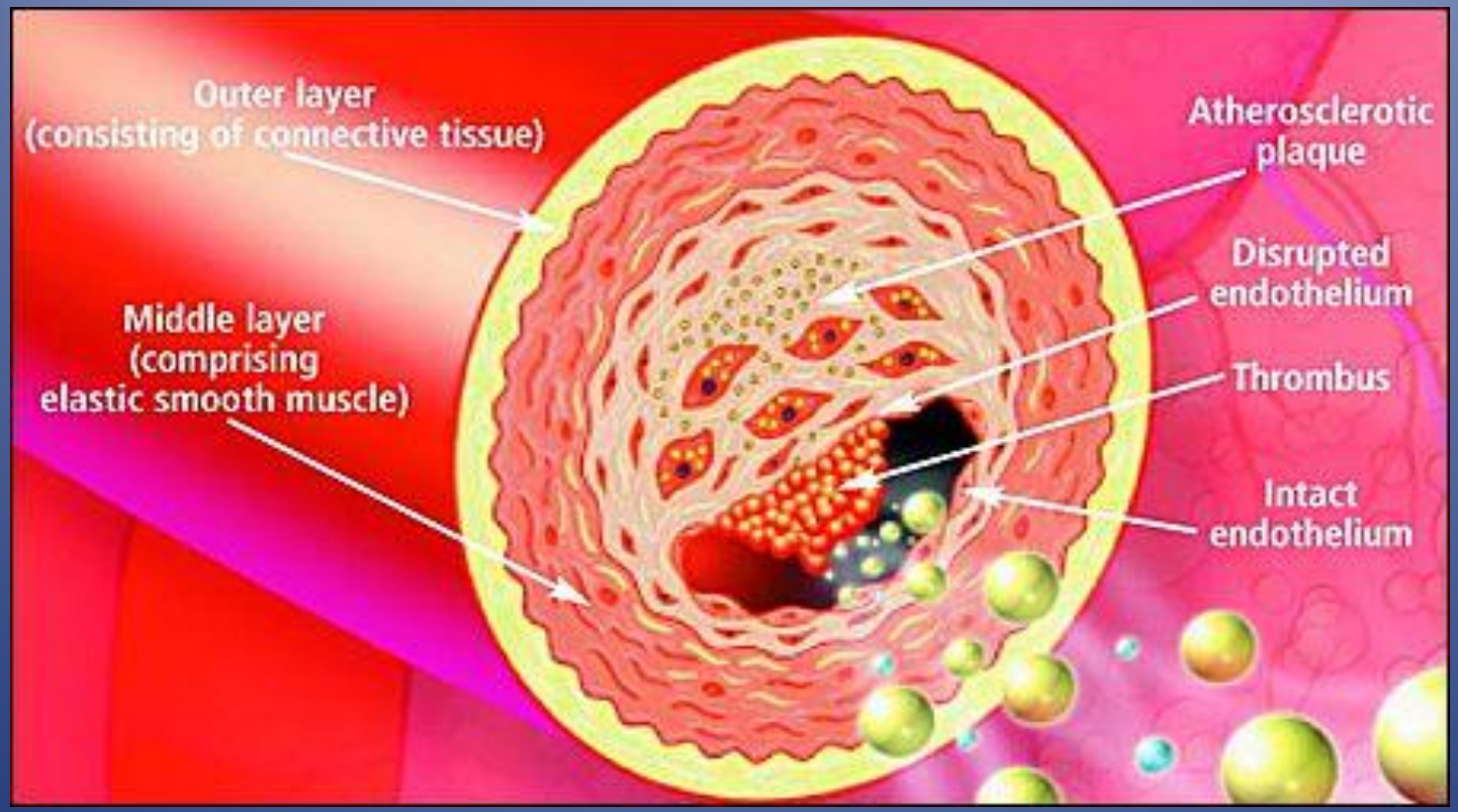
TRADITIONAL CAD RISK FACTORS

- OBESITY
- Hypertension
- TOBACCO
- Diabetes
- Age
- Family history

NON TRADITIONAL RISK FACTORS

- Serum Fibrinogen
- PA I 1
- CRP
- Coronary calcium
- Renal disease
- Rheumatologic diseases
- **OTHER CHRONIC INFLAM CONDITIONS?**

WHAT DOES CORONARY ARTERY DISEASE LOOK LIKE?



OTHER DELETERIOUS FEATURES OF CARDIOVASCULAR RISK IN HIV PTS

- IN PTS WITH HIV :
- I L-6 INCREASES, CRP INCREASES
- DYSLIPIDEMIA
- ENDOTHELIAL DYSFUNCTION
- CAROTID INTIMAL THICKNESS

ALL CONTRIBUTE TO PLATELET DYSFUNCTION AND PLAQUE PROGRESSION

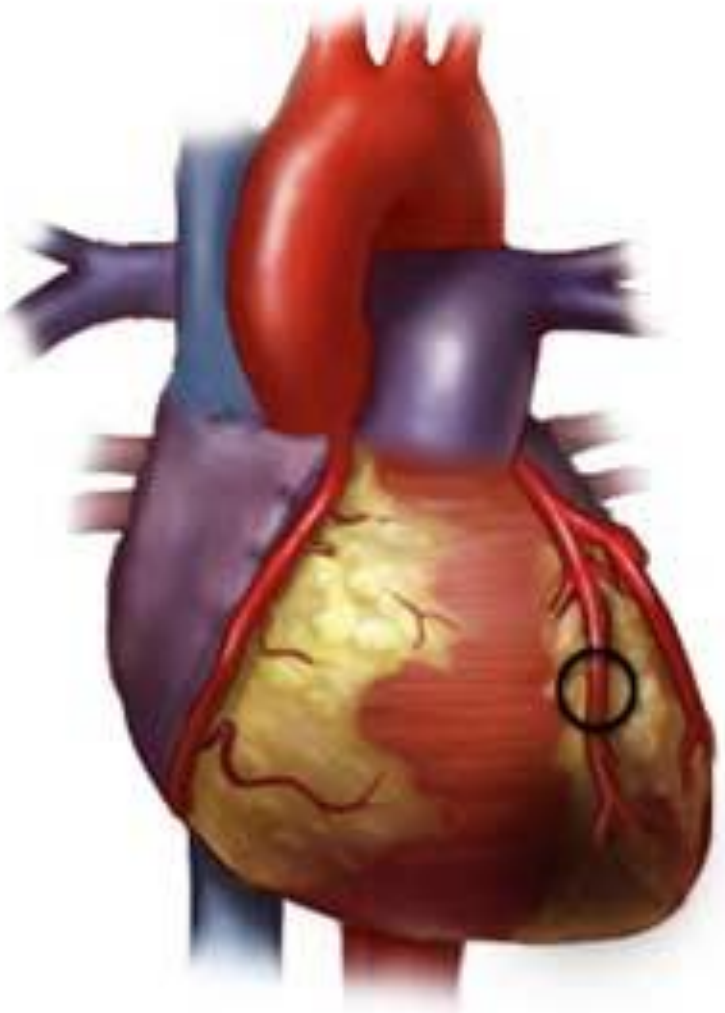
POINTERS OF SYSTEMIC INFLAMMATION

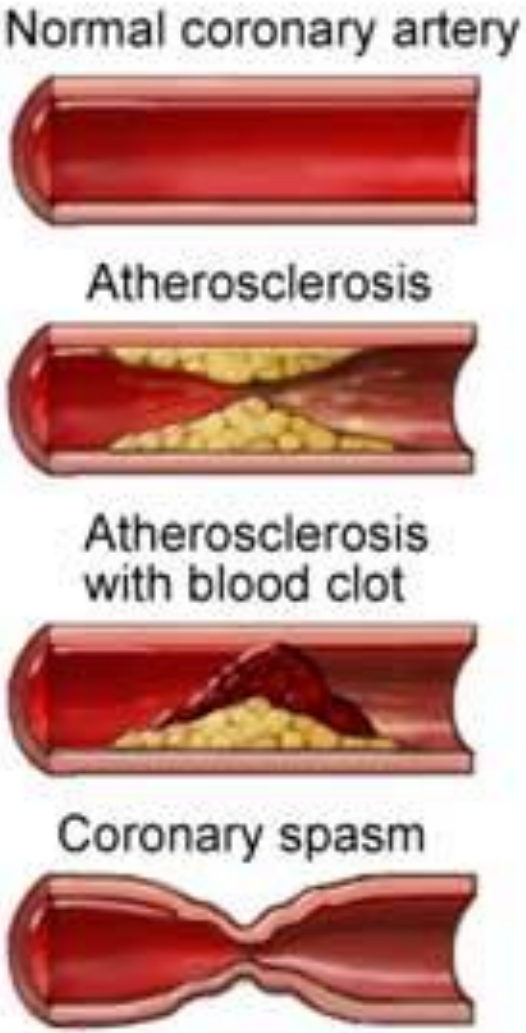
MECHANISMS FOR ACUTE MYOCARDIAL INJURY

- ACUTE PLAQUE RUPTURE PLATELET ACTIVATION
- SPASM
- FAILURE OF COLLATERALS
- "DEMAND ISCHEMIA"

THE MECHANISM OF INJURY GUIDES TREATMENT AND OUTCOMES

Coronary Artery Disease





CORONARY ARTERY DISEASE: ITS MANY MANIFESTATIONS

- ANGINA 30 - 40 %
- ACUTE MYOCARDIAL INFARCTION 30- 40 %

  ST ELEVATION MI, NON ST ELEVATION MI .
- HEART FAILURE 10 - 15%
- SUDDEN DEATH < 5%

CARDIOVASCULAR RISK IN HIV PTS: SISTER DISEASES?

- LUPUS: A SYSTEMIC INFLAMMATORY DISEASE MAY WELL BE A MODEL TO GUIDE RISK PREDICTION .
- PTS ARE AT INCREASE CARDIOVASC RISK
- INCREASE DISEASE ACTIVITY CORRERATES WITH SOFT CORONARY PLAQUE ON CT .

CRITICAL QUESTION ?

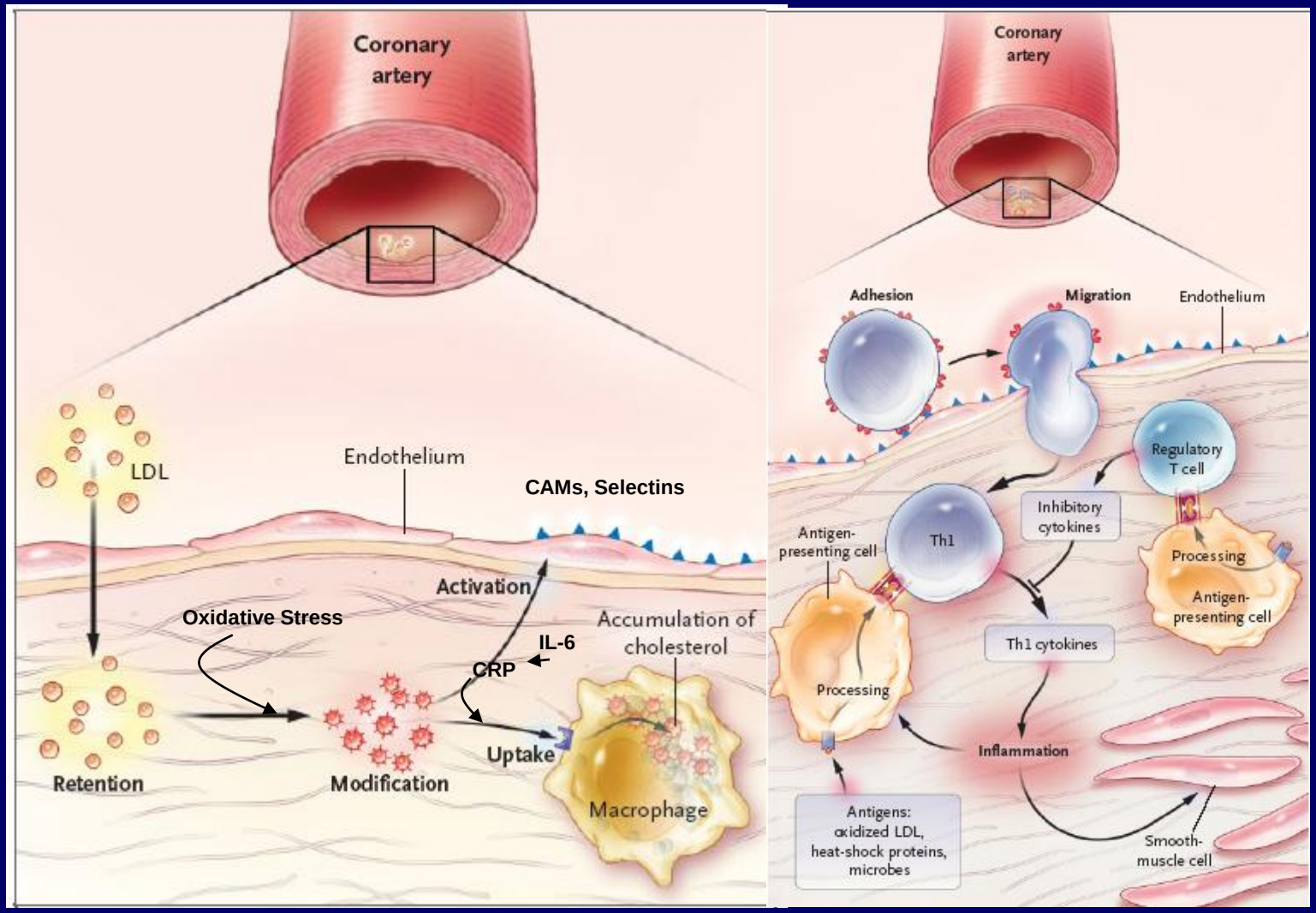
- MANIFESTATION OF CAD IN HIV PTS ?
- MECHANISM OF MYOCARDIAL INJURY :

  STEMI? NONSTEMI?

Role for Immune Activation/Inflammation in Cardiovascular Disease

Alan Landay, PhD
Professor and Chairman
Department of Immunology/Microbiology
Rush University Medical Center
Chicago, IL 60612

Innate and Adaptive Immunity in Human Atherosclerosis



Plus other components of the Innate Immune System such as:

- Complement
- Pentraxins
*** CRP**
*** SAP**
*** PTX-3**
-MØ TF→ IIa

Hansson G *N Engl J Med* 2005;352:1685-95

SMART: Inflammatory Markers Strongly Associated With Mortality and CVD Events

Biomarker	All-Cause Mortality (N=85)		Fatal or Non-fatal CVD (N=136)	
	OR	P-value	OR	P-value
hs-CRP	3.5	0.004	1.6	0.20
IL-6	12.6	<0.0001	2.8	0.003
Amyloid A	2.3	0.08	1.6	0.12
Amyloid P	1.1	0.90	2.8	0.002
D-dimer	13.3	<0.0001	2.0	0.06
F1.2	1.4	0.45	0.8	0.56

Kuller LH, et al. PLoS Med. 2008 ;5: e203. doi:10.1371/journal.pmed.0050203.

T-cell activation and carotid lesions

Multivariate analyses, HIV+ patients

	Prevalence Ratio$_{SD}$ Lesions	*95% Conf Interval*	*p*
CD4+ T-cell activation	**1.6**	**1.1, 2.2**	**0.02**
CD8+ T-cell activation	**2.0**	**1.2, 3.3**	**<0.01**
C-reactive protein	1.0	0.6, 1.4	0.84

Adjusted for HIV medication use, age, race, education, income level, family history of MI, smoking, alcohol consumption, opiate use, injection drug use, study site, lipids, glucose, BMI

Kaplan R, et al. CROI 2010. Abstract 709.

Senescent T cells Affect Organ Function

Cardiovascular Disease

Correlates with increased levels of TNF RII, IL-6, TNF-α, acute phase marker CRP and coagulation marker 2D-dimer

Neurocognitive (Alzheimer's disease)

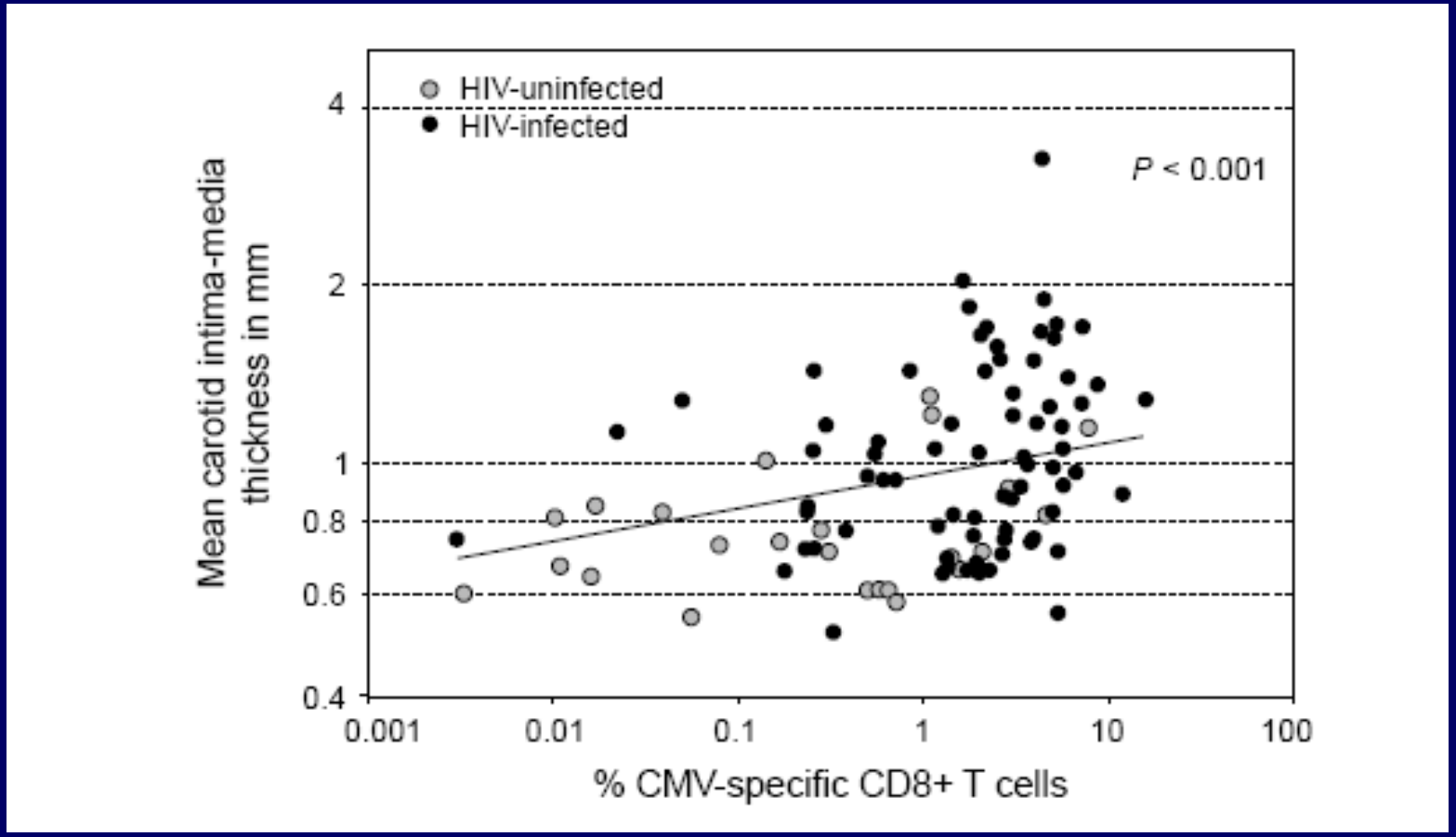
Telomere length correlates with disease status

Bone

Correlate with osteoporotic fractures

IL-6, TNF-α correlates with bone loss

Correlation of Carotid IMT in CMV Specific T-Cells Responses



AIDS 2006, 20:2275-2283, Priscilla Y. Hsue, et. all

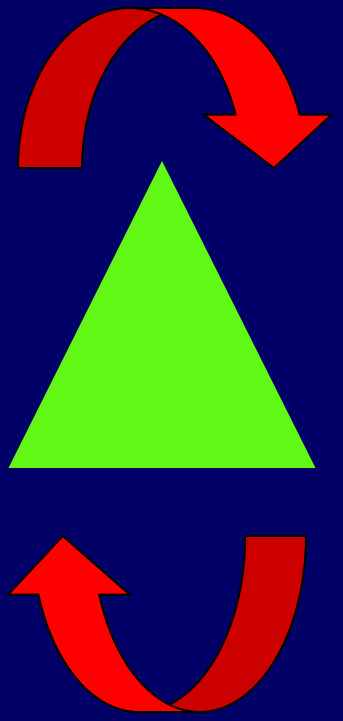
Potential clinical implications

Atherogenesis

Continuous ART Statins?

S-VCAM-1
MCP-1(CCL2)
IL-6
CRP
P-selectin
2D-Dimer

Pro-atherosclerotic



Adiponectin
IL-10

Anti-atherosclerotic

Viral Load ?

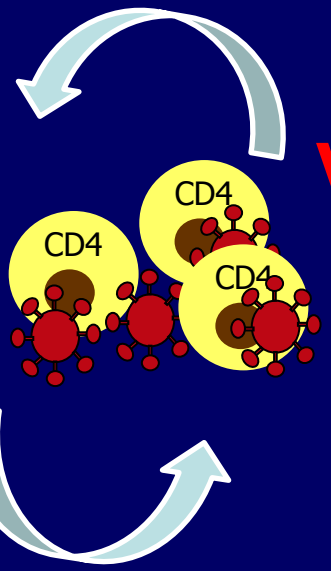
Inflammation

Activation

Coagulation

Microbial translocation

Latent virus



Viral Replication

Co-morbidities

CVD
Neurocog
Cancers
Liver Disease
Metabolic Disease

Premature Aging

Future Studies

- Determine how pro and anti inflammatory cytokines might modulate CVD
- Additional studies on coagulation markers in pro and anti coagulant and pro and anti fibrinolysis pathways
- Further evaluate the role of CMV in CVD and anti CMV therapy
- Determine effect of microbial translocation on inflammatory reponses and CVD

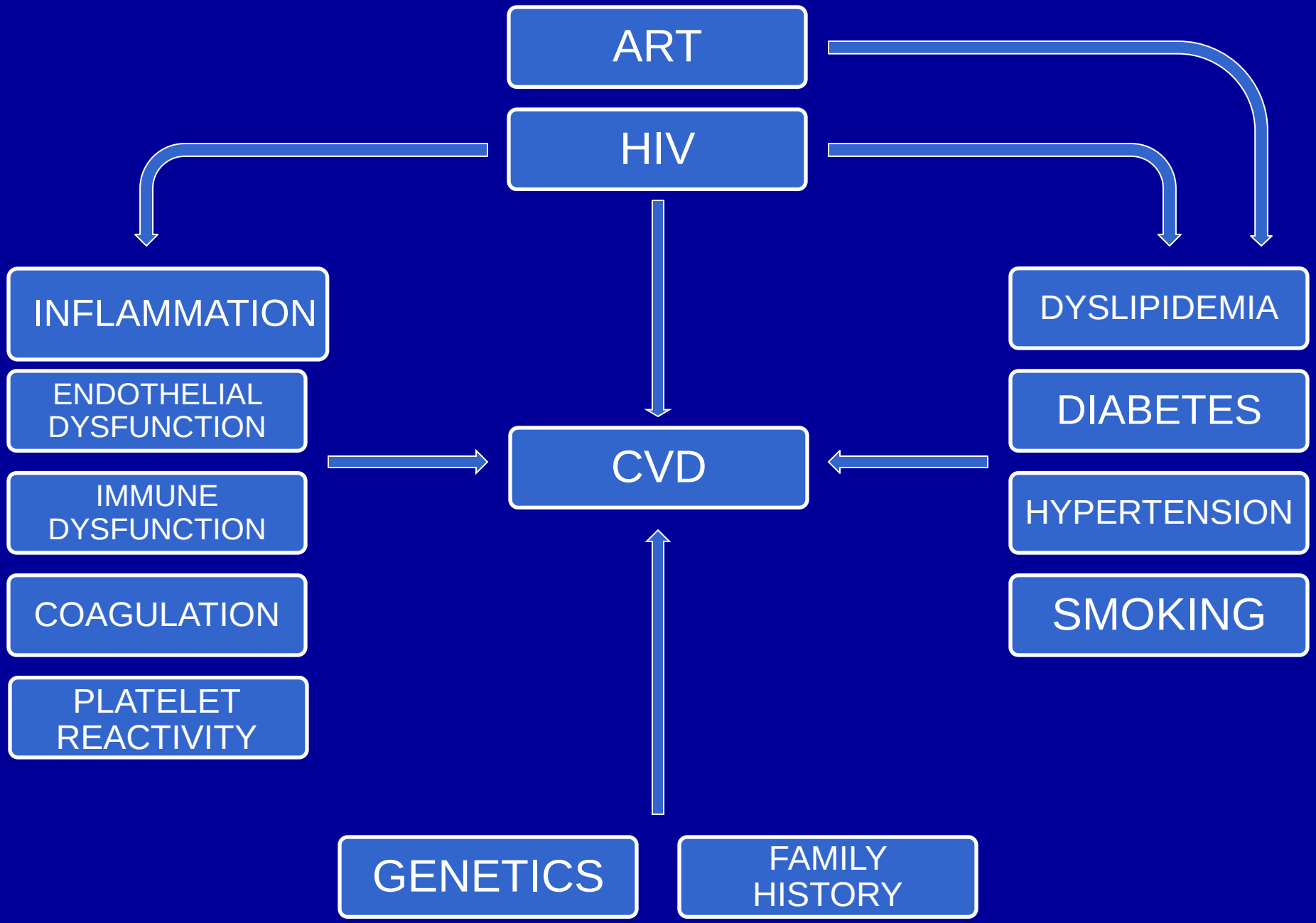
Potential Mechanisms of Cardiovascular Disease Among HIV Patients

Forum for Collaborative HIV Research

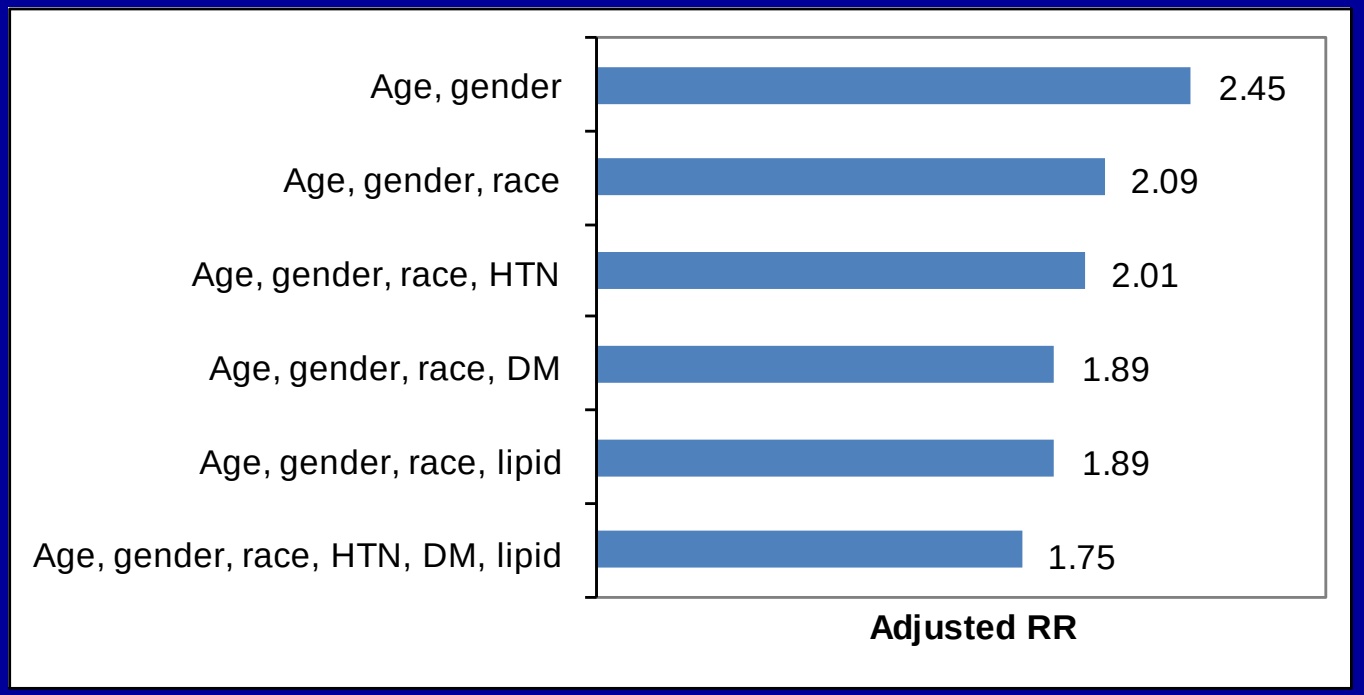
Virginia A. Triant, MD, MPH

Instructor in Medicine
Infectious Diseases Division
Massachusetts General Hospital

July 18, 2010


ART
HIV
INFLAMMATION
ENDOTHELIAL DYSFUNCTION
IMMUNE DYSFUNCTION
COAGULATION
PLATELET REACTIVITY
CVD
DYSLIPIDEMIA
DIABETES
HYPERTENSION
SMOKING
GENETICS
FAMILY HISTORY

Traditional CVD Risk Factors Do Not Explain the Whole Story



- Preclinical atherosclerosis: HIV infection associated with increased IMT independent of traditional CVD risk factors
- ART-related risk: Adjusting for lipids attenuated RR of AMI from 1.16 to 1.10 in D:A:D study

Triant et al. Clin Endocrinol Metab. 2007;92:2506-2512; Grunfeld et al. AIDS 2009;23:1841-49; Friis-Moller et al. NEJM. 2007;356:1723-1735.

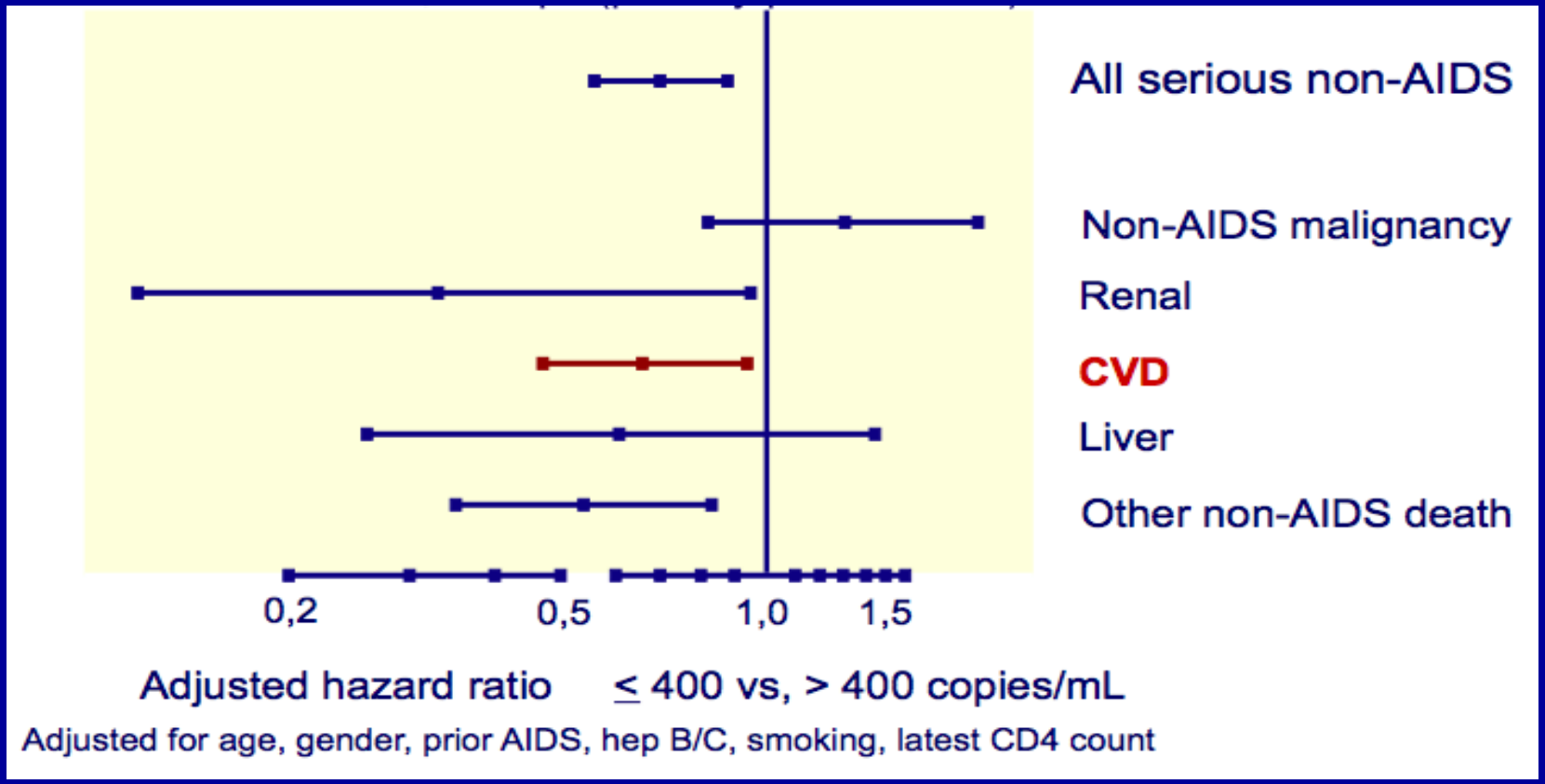
Evidence Supporting Inflammation

- SMART study showed unanticipated increase in CVD event rates in the drug conservation (episodic treatment) vs. the viral suppression (continuous treatment) group
- Inflammatory markers increased 1 month after treatment interruption in SMART study
  - IL-6 by 30% and d-dimer by 16%
  - Increase proportional to increase in HIV viral load
- Baseline levels of inflammatory markers strongly correlated to overall mortality in SMART study
  - Adjusted odds ratio for ≥ 75th percentile vs. ≤ 25th percentile

    3.1 for hsCRP; 12.4 for IL-6; 41.2 for d-dimer
- Higher HIV viral load associated with CVD mortality in CASCADE cohort
  - Hazard ratio 3.86

El-Sadr et al. N Engl J Med. 2006;355:2283-2296; Kuller et al. PLoS. 2008;5:1496-1508; Marin et al. AIDS. 2009;23:1743-1753.

Decreased Risk of CVD Events With Virologic Suppression



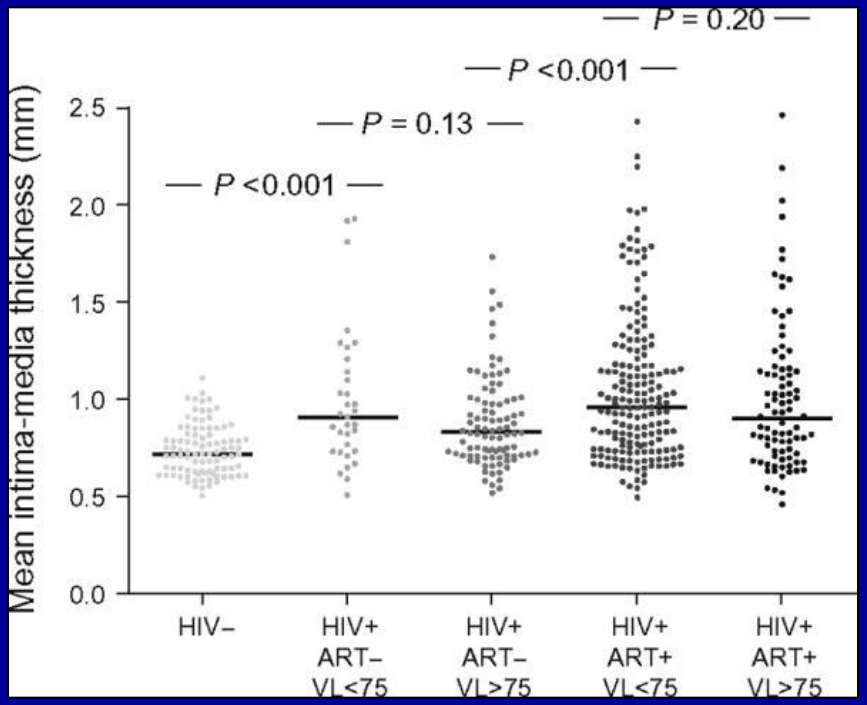
Phillips et al. AIDS. 2008;22:2409-2418.

Evidence Supporting Immune Dysfunction

- Assessment of the effect of initiating HIV treatment at higher CD4 counts on CVD risk
  - Measured arterial stiffness by pulse wave velocity
  - 80 virologically suppressed HIV patients starting ART in early or chronic phase
  - Nadir CD4 count < 350 independently associated with increased arterial stiffness
  - Traditional CVD risk factors also associated with arterial stiffness
- Study of the effects of HIV parameters, ART and traditional CVD risk factors on carotid plaque and carotid IMT
  - 1931 HIV and 859 non-HIV patients in WIHS and MACS cohorts
  - Recent CD4 count < 200 associated with 70-100% increased prevalence of carotid artery lesions
  - Adjusted for demographics and CVD risk factors
  - Traditional CVD risk factors associated with both IMT and carotid lesions

Ho et al. AIDS. 2010, epub; Kaplan et al. AIDS. 2008;22:1615-1624.

Evidence Supporting HIV-Specific Factors



- Compared marker of preclinical atherosclerosis in HIV controllers to treated and untreated HIV patients and HIV-negative control patients
- Carotid IMT increased among:
  - All HIV groups vs. controls, independent of ART exposure, viremia, or advanced immunodeficiency
  - HIV controllers vs. HIV negative controls independent of CVD risk factors

Hsue et al. AIDS. 2009;23:1059-1067.

Implications for Clinical Management and Policy

- Need for aggressive modification of traditional CVD risk factors
- Importance of ARV medication selection with respect to CVD risk and drug interactions
- Incorporation of “novel” CVD risk factors such as inflammatory or coagulation biomarkers into risk stratification
- Significance of groups who merit tailored research, such as women and patients in resource-poor settings
- Potential role for HIV treatment itself to decrease CVD risk, with beneficial effects on immune dysfunction and inflammation outweighing individual proatherogenic effects of ART

Session III

- Nisha Chandra Strobos MD
  - Prof Medicine JHU School of Med
  - Chief, Div of Cardiology JHU Bayview MC
- Wendy Post MD MS
  - Assoc Prof Medicine JHU/ Ciccarone Center of Prev of Heart Disease
- Judy Currier MD
  - Prof of Medicine
  - Chief, Div Inf Diseases UCLA

CV RISK IN HIV PATIENTS: CLINICAL IMPLICATIONS

NISHA CHANDRA – STROBOS MD

PROF OF MED

CHIEF OF CARDIOLOGY

JOHNS HOPKINS BAYVIEW MED CENTER

JOHNS HOPKINS UNIV SCHOOL OF MEDICINE

Prevention: Definition

Primordial Prevention: Prevent development of CVD risk factors

Primary Prevention: Modify CVD risk factors that are present in order to prevent or delay clinical CVD

Secondary Prevention: Treat patients with established CVD to reduce recurrent CVD events and cardiac mortality

CHD=Coronary heart disease

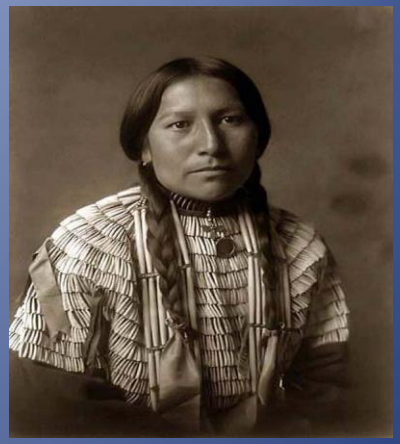
Making the Diagnosis

- History, risk factors
- EKG changes with pain
- Stress testing with echo / thallium
- Coronary calcium
- CT angiography
- Cardiac Cath

CAD PRESENTING SYMPTOMS IN MEN

“It feels like an Elephant on my chest”

CAD PRESENTING SYMPTOMS IN WOMEN



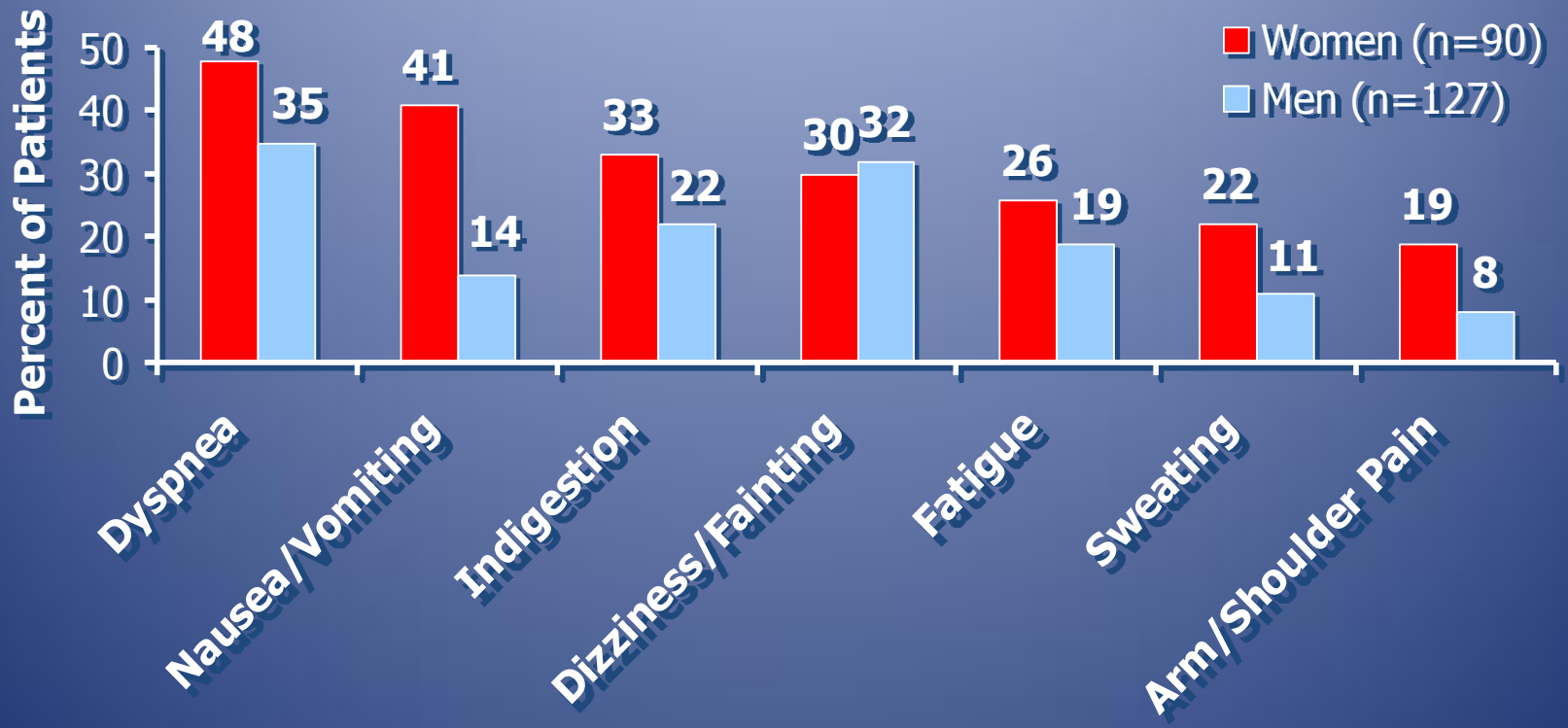
“I was very short of breath”

“I thought it was indigestion or my daughters lasagna”

“I felt bad all over”

“My tummy hurts”

Non-Chest Pain Presentations with Acute MI in Women vs Men



Milner et al. *Am J Cardiol*. 1999;84:396-399.

NON INVASIVE TESTING FOR CAD

- CORONARY CALCIUM SCORE
- STRESS TESTING { LIMITED VALUE ,MORESO IN WOMEN}
- STRESS IMAGING {NUCLEAR OR ECHO}

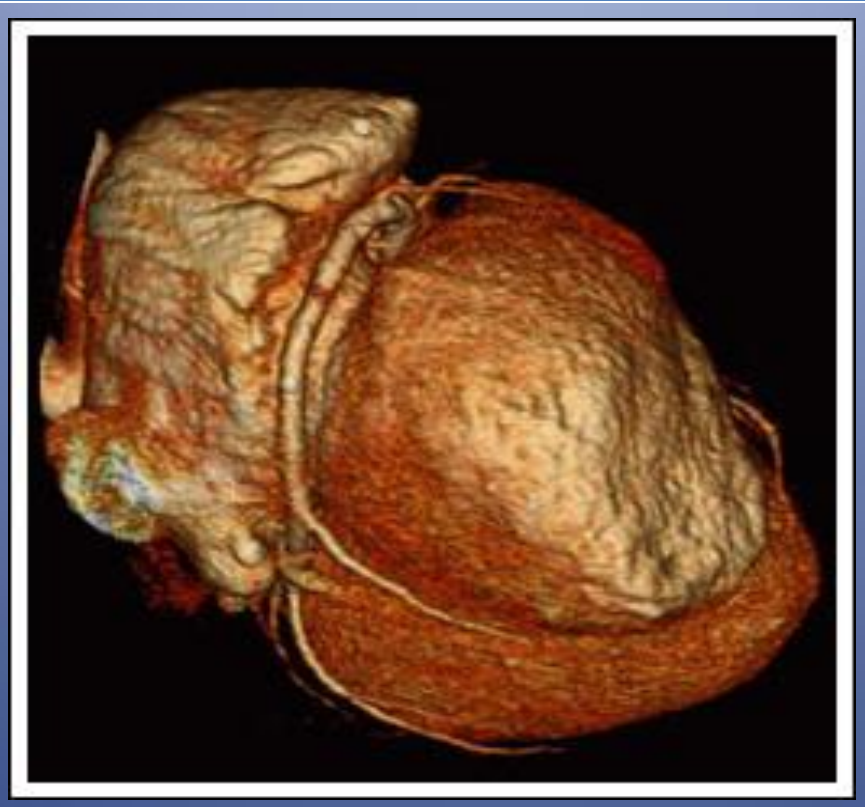
70 PLUS % PREDICTIVE ACCURACY

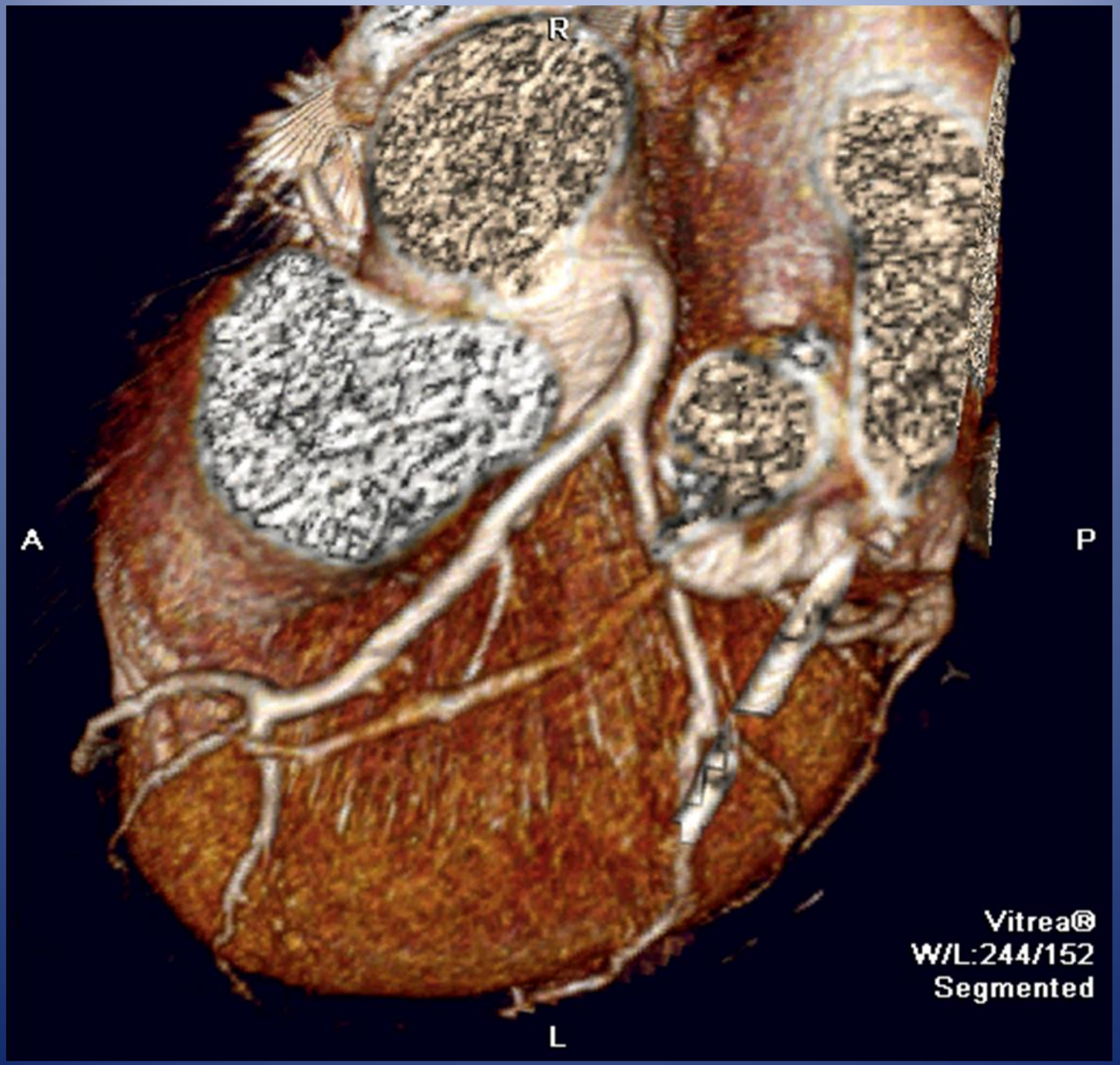
- CT ANGIOGRAPHY

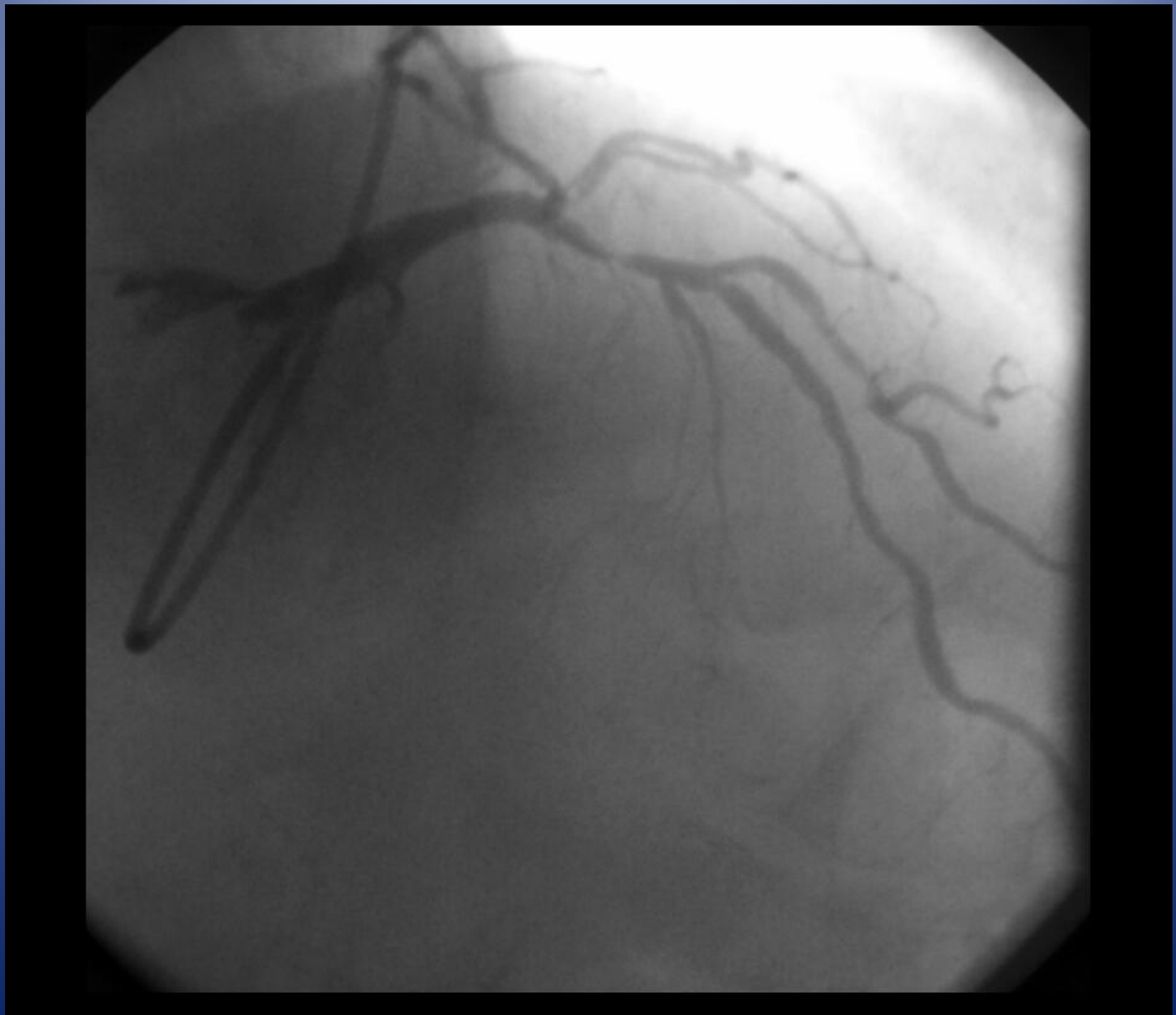
CT ANGIOGRAPHY

- **Non-invasive, but radiation dose similar to cardiac catheterization.**
- **Requires the use radiographic dye, hence dye risks.**
- **>90% sensitivity for identifying proximal and mid-coronary lesions**

CT ANGIOGRAPHY




R
A
P
L
Vitrea®
W/L:244/152
Segmented



CARDIOVASCULAR RISK IN HIV PTS

- CLASSIC RISK PREDICTION TOOLS ARE BASED ON AN UNDERSTANDING OF THE PATHOPHYSIOLOGY OF THE DISEASE ENTITY.
- IN TURN THERAPIES ARE DEVELOPED ON A SIMILAR UNDERSTANDING OF PATHOPHYSIOLOGY.
- OPPORTUNITY TO STUDY THE SYNDROME OF HIV DISEASE.

THE 3 A'S: A PARADIGM TO STUDY CARDIOVASC DISEASE IN HIV PTS

- ACCEPT the possibility it can happen
- ACQUIRE knowledge about why it happen
- ARREST the disease by modifying lifestyle

MULTIDISCIPLINARY RESEARCH EFFORTS ARE WARRANTED.

Assessment and Treatment of Traditional Risk Factors in the HIV Patient

Wendy Post, MD, MS

Associate Professor of Medicine
and Epidemiology
Cardiology Division
Johns Hopkins University
Baltimore, Maryland, USA

Coronary Heart Disease Risk Factors

The vast majority of CHD can be predicted by knowing a patient's traditional risk factors

Traditional CHD risk factors also are the major determinants of CHD risk in patients with HIV infection

Major Risk Factors for Coronary Heart Disease

- Aging
- Male sex
- Dyslipidemia
- Hypertension
- Cigarette smoking
- Diabetes mellitus
- Family history of premature CHD

Greenland P, et al. JAMA 2003;290:891

CHD Risk Assessment

A patient's absolute CHD risk determines the intensity of risk-reducing interventions

1. Evaluate for the presence of coronary heart disease or risk equivalent conditions
2. Count risk factors
3. Framingham risk assessment if ≥2 risk factors

Absolute risk is used to set goals for lipids and other preventive interventions – higher risk patients get more aggressive interventions

NCEP ATP III. JAMA 2001; 285:2486

Risk Stratification: Framingham Risk Score for Men

Step 1: Age Points

Years	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Step 2: Total Cholesterol Points

TC (mg/dl)	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Step 3: HDL-C Points

HDL-C (mg/dl)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Step 4: SBP Points

SBP (mmHg)	If untreated	If treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Step 5: Smoking Status Points

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Step 6: Sum of Points

Age
Total Cholesterol
HDL-C
Systolic Blood Pressure
Smoking Status
Point Total

Step 7: 10-year CHD Risk

Point Total	10-year Risk	Point Total	10-year Risk	Point Total	10-year Risk
<0	<1%	6	2%	13	12%
0	1%	7	3%	14	16%
1	1%	8	4%	15	20%
2	1%	9	5%	16	25%
3	1%	10	6%	≥17	>30%
4	1%	11	8%		
5	2%	12	10%		

Risk Stratification: Framingham Risk Score for Women

Step 1: Age Points

Years	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Step 2: Total Cholesterol Points

TC (mg/dl)	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

Step 3: HDL-C Points

HDL-C (mg/dl)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Step 4: SBP Points

SBP (mmHg)	If untreated	If treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Step 5: Smoking Status Points

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Step 6: Sum of Points

Age
Total Cholesterol
HDL-C
Systolic Blood Pressure
Smoking Status
Point Total

Step 7: 10-year CHD Risk

Point Total	10-year Risk	Point Total	10-year Risk	Point Total	10-year Risk
<9	<1%	15	3%	22	17%
9	1%	16	4%	23	22%
10	1%	17	5%	24	27%
11	1%	18	6%	≥25	>30%
12	1%	19	8%		
13	2%	20	11%		
14	2%	21	14%		

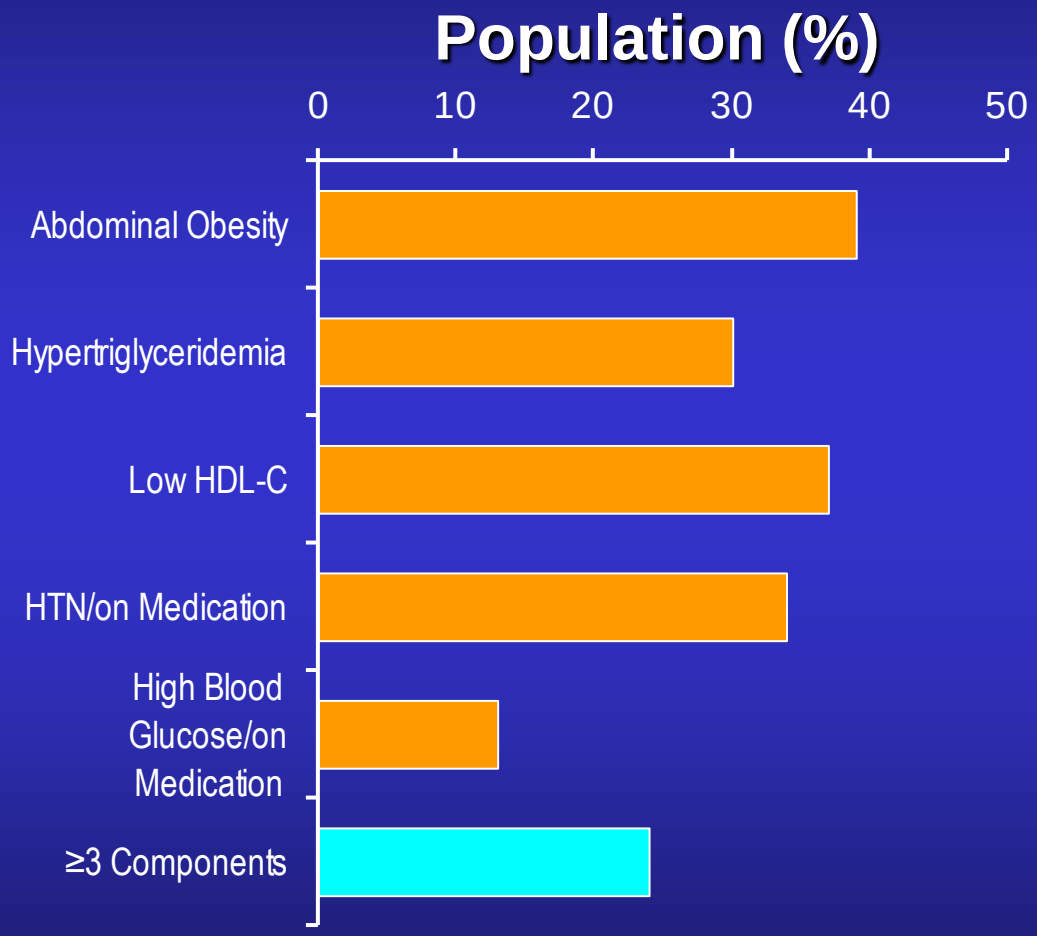
NHANES III

Nearly 25% of Americans Have Metabolic Syndrome

NCEP Criteria

At least 3 metabolic abnormalities:

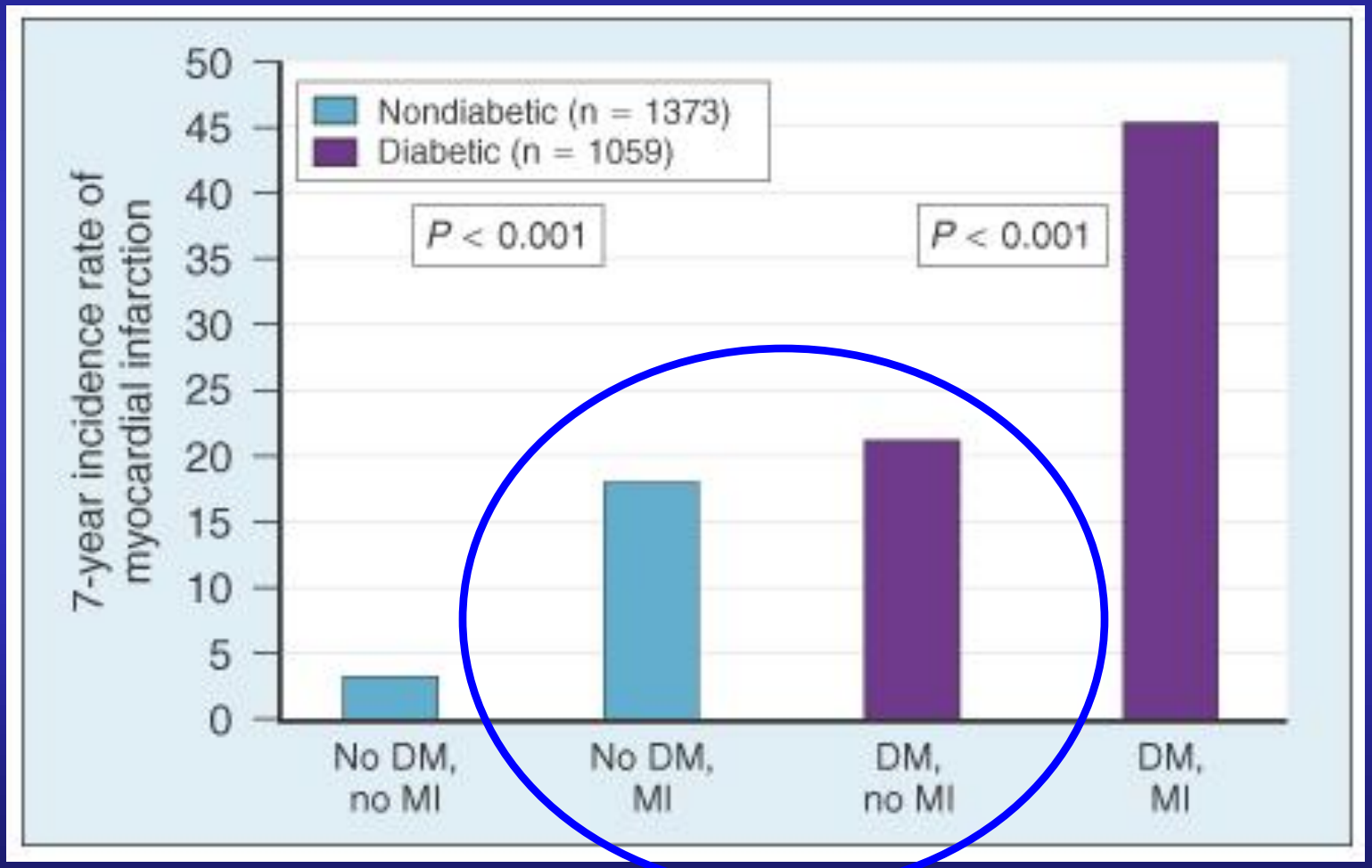
- Abdominal obesity (waist):
  - Men >102 cm (>40 in)
  - Women >88 cm (>35 in)
- FBG ≥110 mg/dL*
- Triglcerides ≥150 mg/dL
- HDL-C
  - Men <40 mg/dL
  - Women <50 mg/dL
- BP ≥130/85 mm Hg or on antihypertensive medication



*Fasting plasma glucose; NHLBI/AHA now recommends >100 mg/dL

Expert Panel. *JAMA*. 2001;285:2486-2497. Ford ES, et al. *JAMA*. 2002;287:356-359. Grundy SM, et al. *Circulation*. 2004;109:433-438.

Diabetes is a "cardiovascular disease risk equivalent"



Haffner SM, Lehto S, Ronnemaa T, et al: N Engl J Med 339:229-234, 1998

HMG-CoA Reductase Inhibitor: Chronological Order of Event Driven Trials

Study populations:

Primary prevention

Acute coronary syndromes (Secondary prevention)

Chronic Coronary heart disease (Secondary prevention)

1994	4S	2002	PROSPER
1995	WOSCOPS	2002	ALLHAT-LLA
1996	CARE	2002	ASCOT-LLA
1998	AFCAPS/TEXCAPS	2004	PROVE-IT
1998	LIPID	2004	A to Z
2001	MIRACL	2005	TNT
2002	HPS	2005	IDEAL
		2008	JUPITER

*Trials with clinical outcomes

LDL Cholesterol Goals are Based on Level of CHD Risk

CHD Risk Category	LDL-C Goal
High risk: CHD or CHD risk equivalents (10-y risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)
Moderately high risk: 2+ risk factors (10-y risk 10% to 20%)	<130 mg/dL (optional goal: <100 mg/dL)
Moderate risk: 2+ risk factors (10-y risk <10%)	<130 mg/dL
Lower risk: 0-1 risk factor	<160 mg/dL

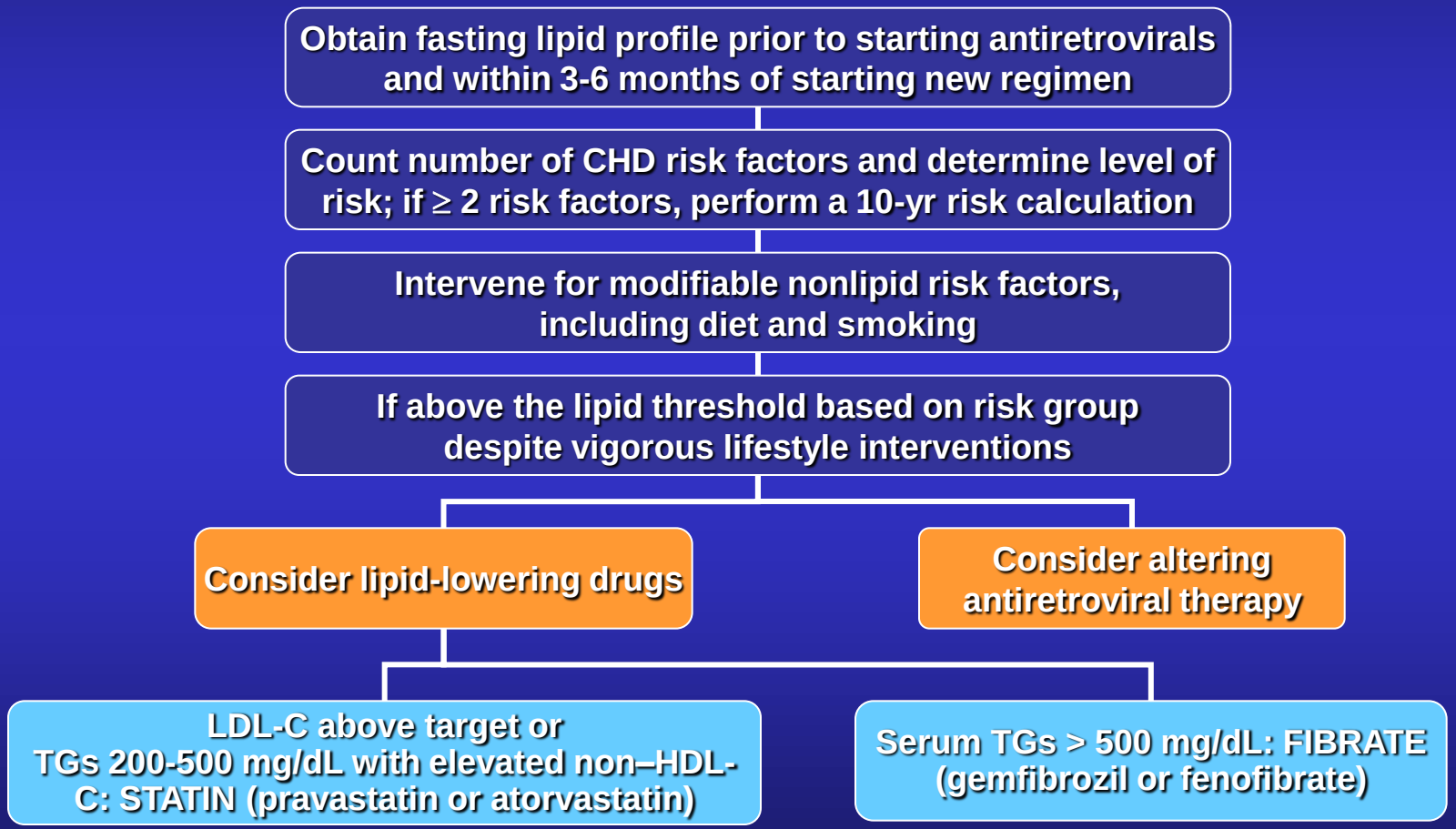
Grundy SM, et al. Circulation 2004;110:227

Elevated Triglycerides

Classification of Serum Triglycerides

• Normal	<150 mg/dL
• Borderline high	150–199 mg/dL
• High	200–499 mg/dL
• Very high	≥500 mg/dL

ACTG/IDSA HIVMA Guidelines: 2003



Dubé MP, et al. Clin Infect Dis. 2003;37:613

Blood Pressure Classification JNC-7

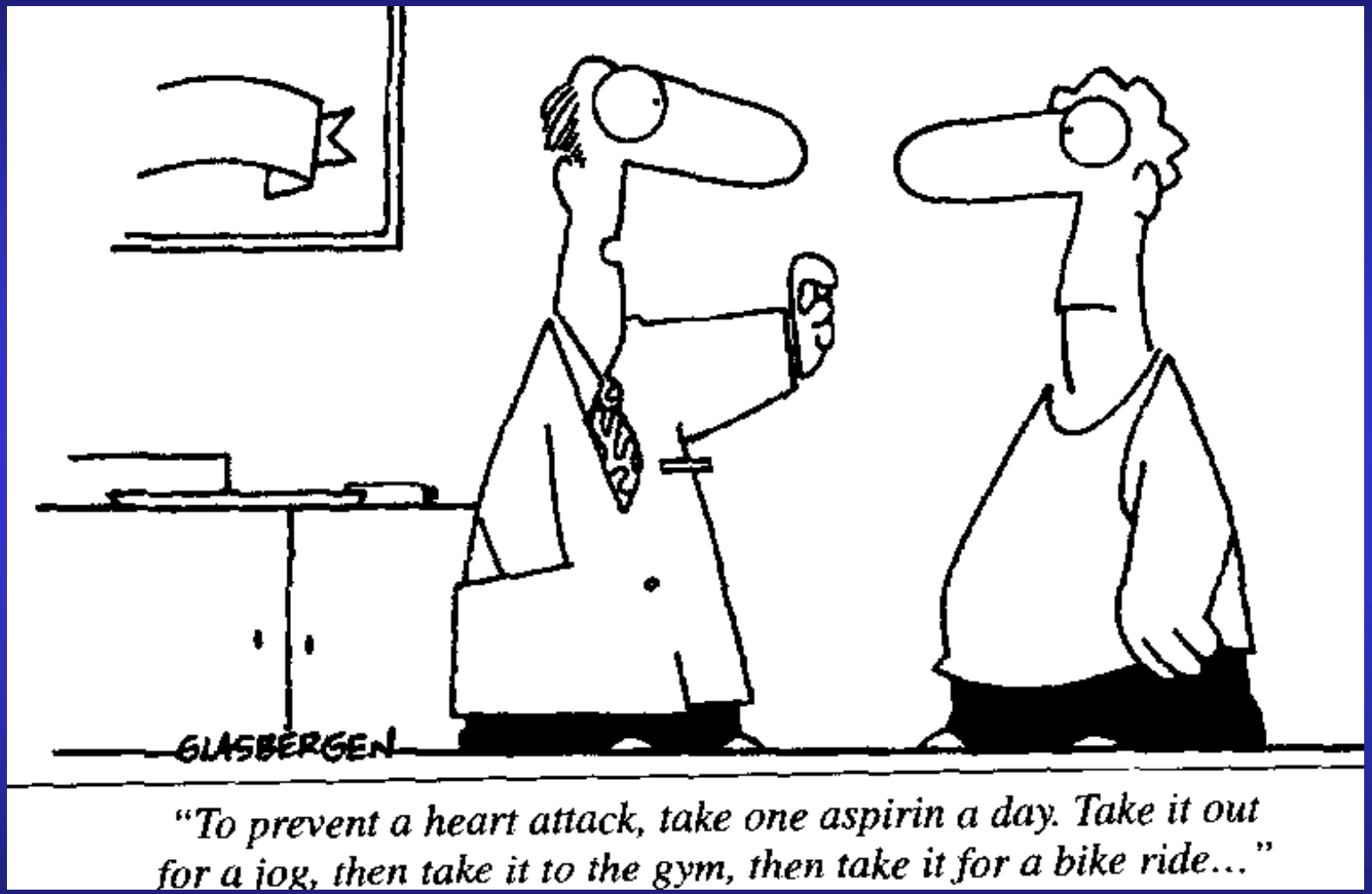
BP Classification	SBP mmHg		DBP mmHg
Normal	< 120	and	< 80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100

JNC VII Guidelines: Lifestyle Modifications for BP Control

Modification	Recommendation	Approximate SBP Reduction Range
Weight reduction	Maintain normal body weight (BMI=18.5-25)	5-20 mmHg/10 kg weight lost
DASH eating plan	Diet rich in fruits, vegetables, low fat dairy and reduced in fat	8-14 mmHg
Restrict sodium intake	<2.4 grams of sodium per day	2-8 mmHg
Physical activity	Regular aerobic exercise for at least 30 minutes most days of the week	4-10 mmHg
Moderate alcohol	≤2 drinks/day for men and ≤1 drink/day for women	2-4 mmHg

BMI=Body mass index, BP=Blood pressure, SBP=Systolic blood pressure

Chobanian AV et al. *JAMA* 2003;289:2560-2572



"To prevent a heart attack, take one aspirin a day. Take it out for a jog, then take it to the gym, then take it for a bike ride…"

Weight Management Recommendations

Goals

BMI 18.5 to 24.9 kg/m^2

Women: <35 inches
Men: <40 inches

10% weight reduction within the 1st yr of Rx

Recommendations

- Calculate BMI* and measure waist circumference
- Monitor response to treatment
- Start weight management and physical activity as appropriate
- If BMI and/or waist circumference is above goal, initiate caloric restriction and increase caloric expenditure

*BMI is calculated as the weight in kilograms divided by the body surface area in meters^2

BMI=Body mass index, Rx=Treatment

Smith SC Jr. et al. *JACC* 2006;47:2130-9

AHA Nutrition Committee Dietary Recommendations

Recommendations for Cardiovascular Disease Risk Reduction

- Balance calorie intake and physical activity to achieve or maintain a healthy body weight
- Consume a diet rich in fruits and vegetables
- Consume whole-grain, high-fiber foods
- Consume fish, especially oily fish, at least twice a week
- Limit intake of saturated fat to <7%, trans fat to <1% of energy, and cholesterol <300 mg/day by:
  - Choosing lean mean and vegetable alternatives
  - Choosing fat free (skim), 1% fat, and low-fat dairy products,
  - Minimizing intake of partially hydrogenated fats
- Minimize intake of beverages and foods with added sugar
- Choose and prepare foods with little or no salt
- If alcohol is consumed, do so in moderation

AHA=American Heart Association

AHA Nutrition Committee. *Circulation* 2006;114:82-96

Exercise and Physical Activity Guidelines

Goals	Recommendations
Minimum: 30-60 minutes, 5 days per week	Assess risk, preferably with an exercise test, to guide prescription
	Encourage aerobic activity (e.g., walking, jogging, cycling) supplemented by an increase in daily activities (e.g., walking breaks at work, gardening, household work)
Optimal: 30-60 minutes, 7 days per week	Encourage medically supervised programs (cardiac rehabilitation) for high risk patients (e.g. recent acute coronary syndrome or revascularization, heart failure)
	Encourage resistance training (e.g., weight machines, free weights) 2 days a week

Smith SC Jr. et al. *JACC* 2006;47:2130-9

Cigarette Smoking

- Cigarette smoking has a 2 to 4 -fold increase risk of heart disease.
- Stopping smoking is one of the most effective ways to reduce risk.
- A major reduction in risk occurs even within the first year after stopping smoking.
- Smoking cessation can prevent cancer and lung disease
- New medications

ABCs of CVD Risk Management

	•Intervention	•Goals
•A	• Antiplatelets	• Treat all high-risk patients with antiplatelet agents
	• ACE inhibitors/ARBs	• Optimize BP especially if CVD, type 2 diabetes, or low EF present
	• Antianginals	• Relieve anginal symptoms, allow patient to exercise
•B	• BP control	• Aim for BP <130/85 mm Hg, or <130/80 mm Hg for type 2 diabetes
	• •β-blockers	• Post MI, low EF, or angina

Braunstein JB et al. *Cardiol Rev*. 2001;9:96-105.

ABCs of CVD Risk Management (cont.)

	•Intervention	•Goals
•C	• Cholesterol management	• LDL-C targets, ATP III guidelines – CHD, CHD risk equivalents: – <100 mg/dL (< 70 mg/dl optional) • HDL-C: ≥40 mg/dL (men) – ≥2 RF: <130 mg/dL • Triglycerides: <150 mg/dL – 0–1 RF: <160 mg/dL
	• Cigarette-smoking cessation	• Long-term smoking cessation

Braunstein JB et al. *Cardiol Rev*. 2001;9:96-105.

ABCs of CVD Risk Management (cont.)

	•Intervention	•Goals
•D	• Dietary/weight counseling • • Diabetes management	• Achieve optimal BMI • ↓ saturated fats; ↑ fruits, vegetables, fiber • Achieve HbA_{1c} <7%
•E	• Exercise • Education of patients and families	• Improve physical fitness (aim for 30 min/d on most days per week) • Optimize awareness of CAD risk factors

Braunstein JB et al. *Cardiol Rev*. 2001;9:96-105.

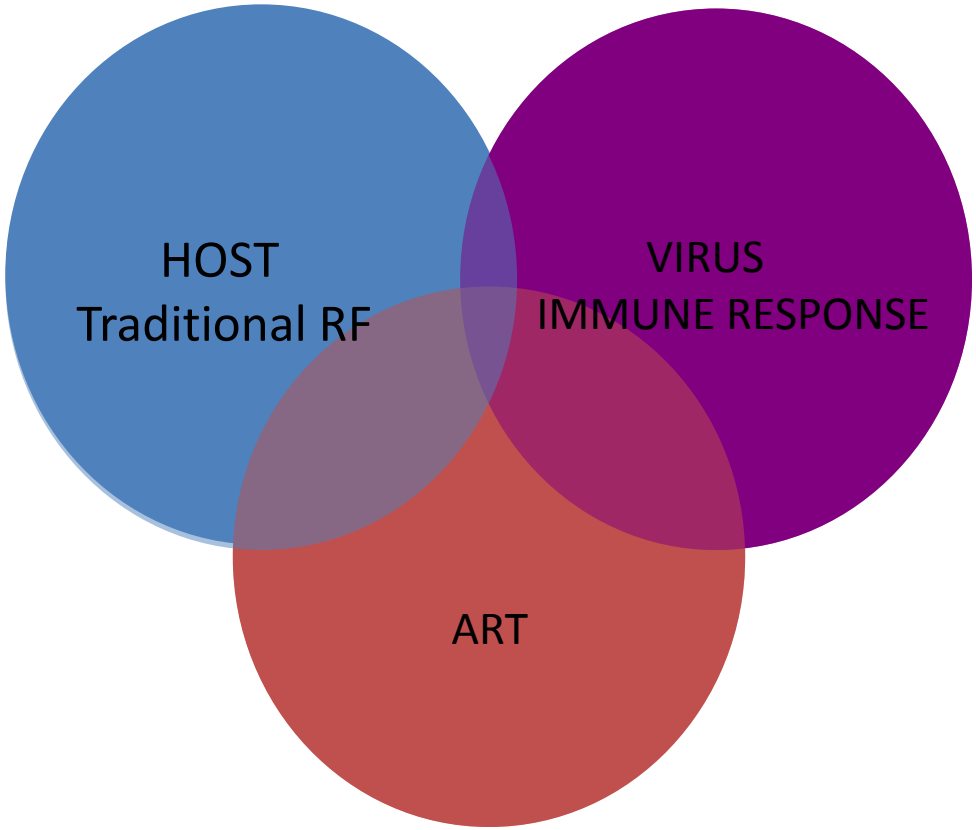
Session III:
The role of antiretroviral therapy

When to start ART

Which agents to use or avoid

Does changing ART reduce CVD risk?

What Explains the Higher Rates of CVD in HIV?



Understanding the relative contributions of each of these factors to the pathogenesis of CVD in HIV will help to inform the development of strategies for prevention and treatment.

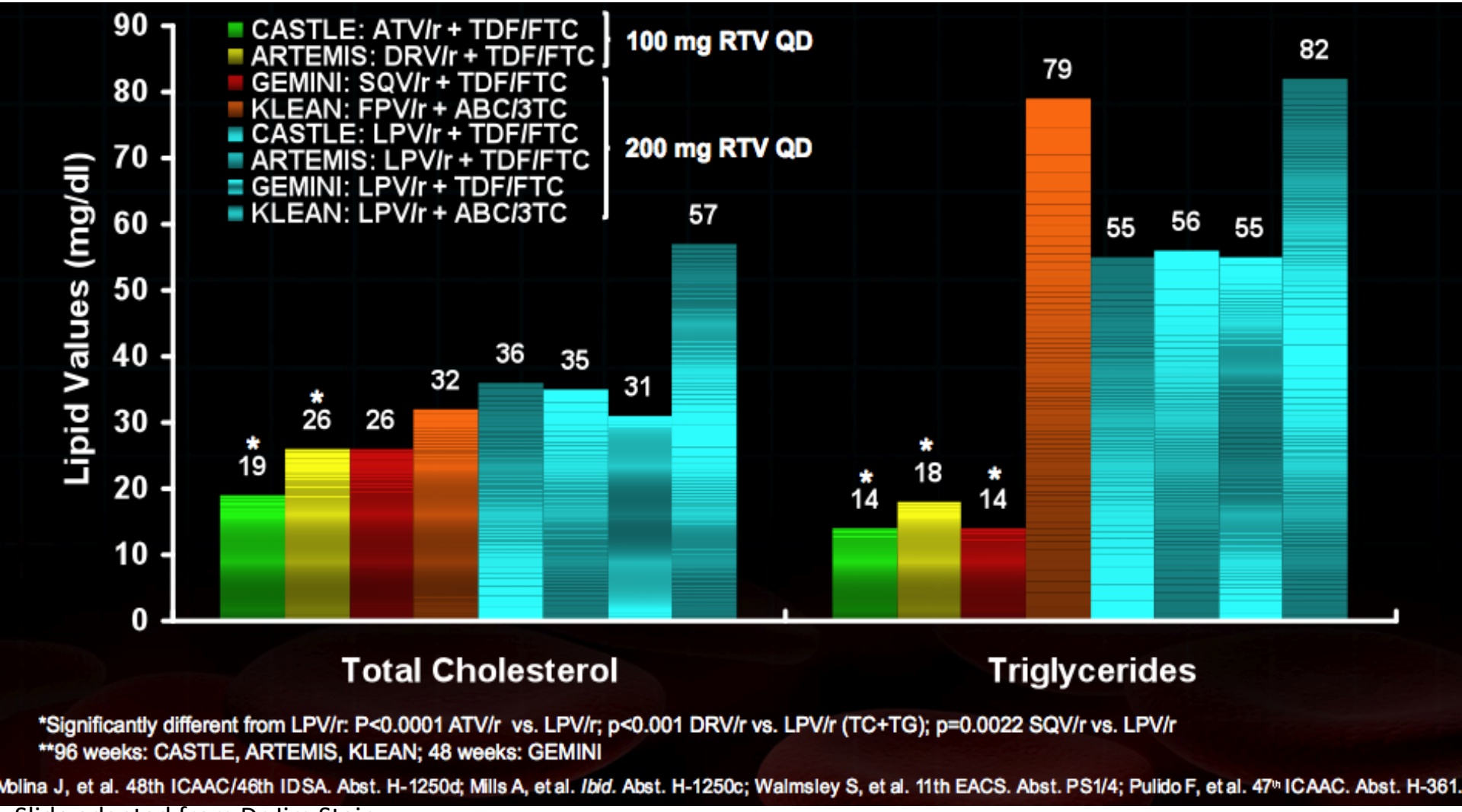
Point #1:
Benefits of ART outweigh Risk with respect to CVD and mortality

- ART may improve endothelial function in the short term and reduce short term risk of MI, compared to no ART
    - How ART lowers CVD risk not well defined
    - The association between stopping ART and increase MI risk partially mediated by changes in HDL cholesterol
    - Current ART guidelines advocate the use of ART among people with increased underlying CVD risk at higher CD4- await data from randomized trials of early ART

Point #2
ART agents have metabolic effects that may contribute to CVD risk once treatment is started

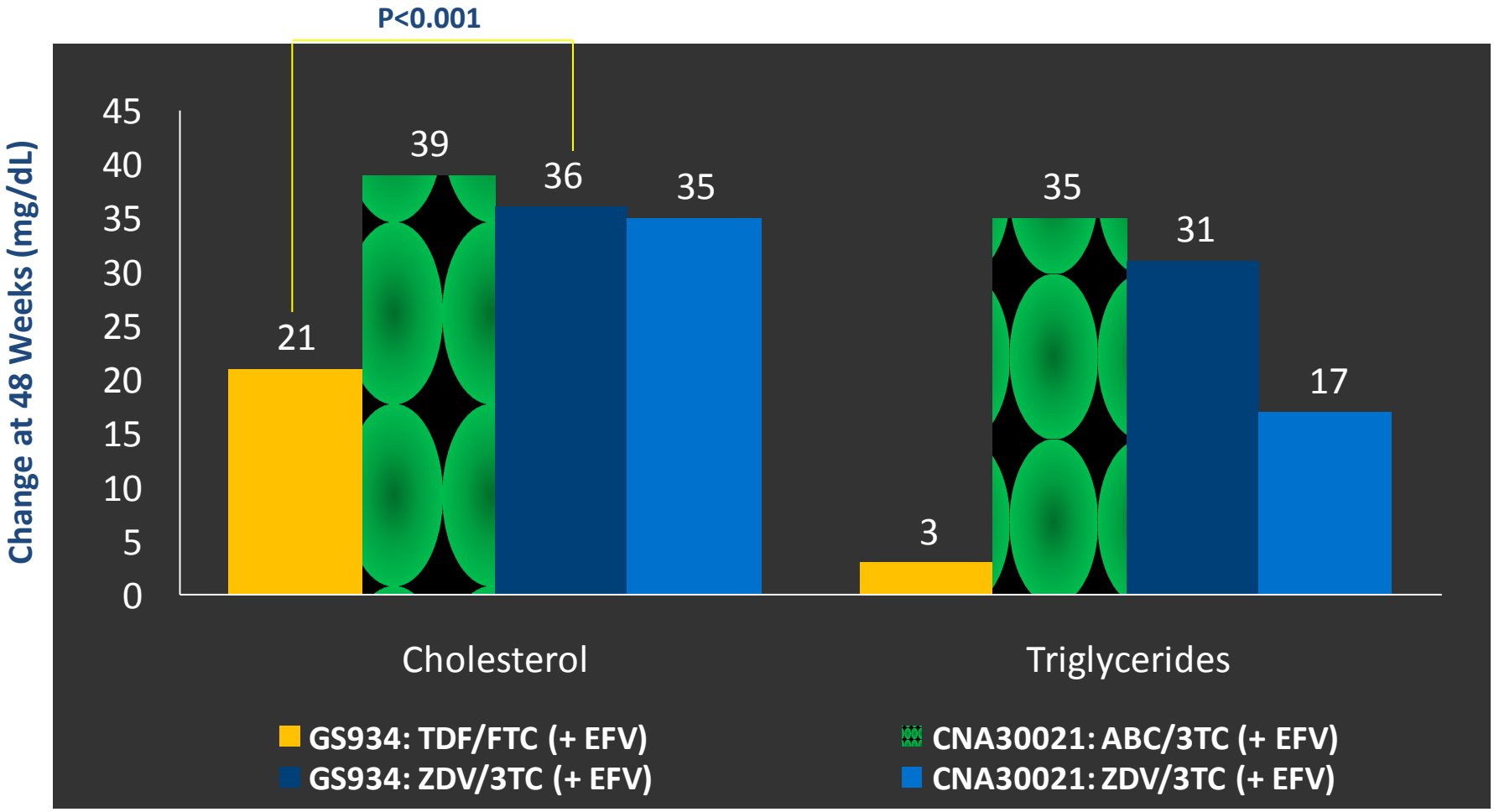
so choose wisely in high risk patients

Lipid Profiles With Boosted PI and NRTI Combinations



Slide adapted from Dr Jim Stein

GS934 and CNA30021: EFV Lipid Effects Depend on NRTIs



DeJesus E, et al. 43rd ICAAC (2003), #H-446; Moyle G, AIDS RDR; Gallant J, et al. 15th IAC (2004), #TuPeB4536.

Effects of Specific ART Classes and Agents on CHD Risk

Long-term use of PIs may increase CHD risk; an observation that is partially related to adverse metabolic effects

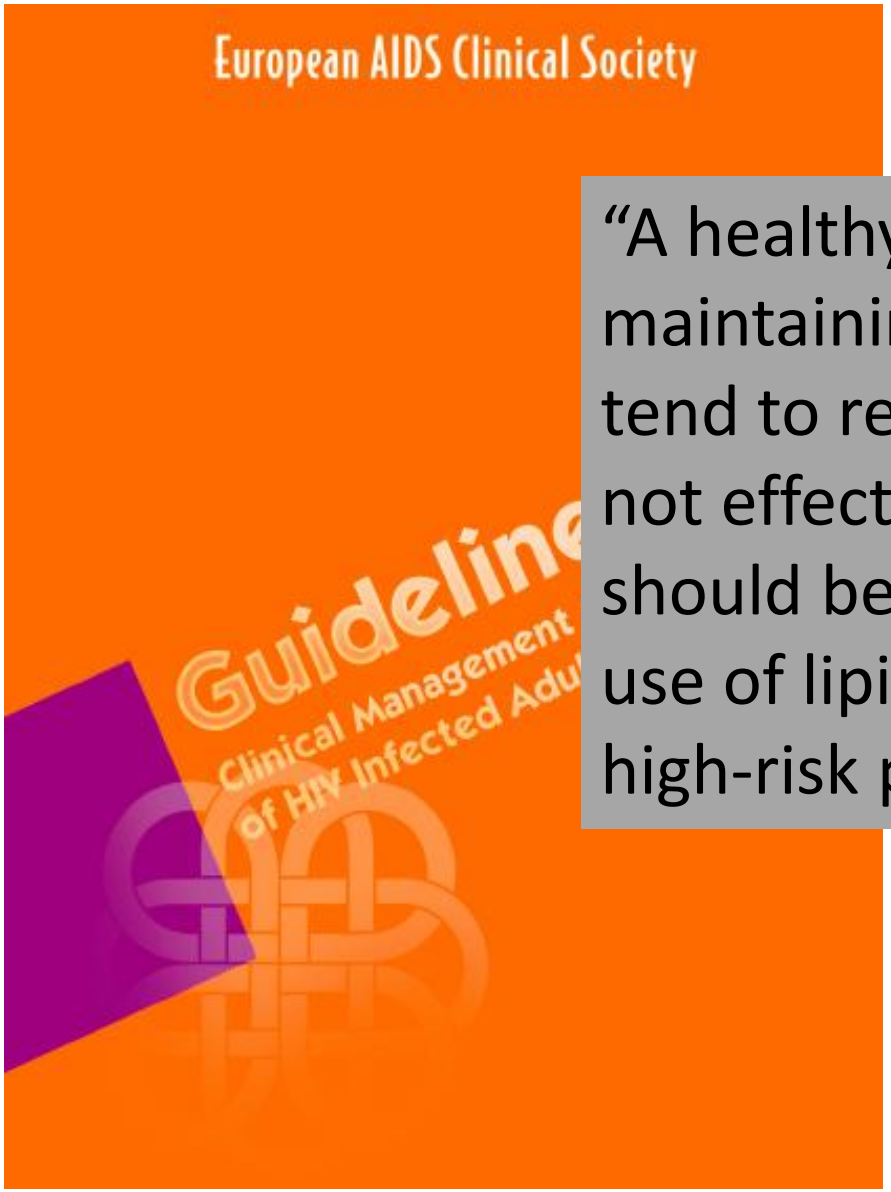
Use of abacavir may increase short-term CHD risk, this increase may be most important in patients with higher underlying CVD risk, the mechanism that underlies this association remains to be defined

Point # 3
The association between PI agents and MI risk is not all explained by lipid changes

We need to better understand role of other factors that change during treatment (body fat, inflammation)

Point # 4
Switching ART in virologically suppressed patients has a role in the management of CVD risk

Caution is advised in patients with a prior history of virologic failure



"A healthy diet, exercise and maintaining normal body weight tend to reduce dyslipidaemia; if not effective, a change of ART should be considered, followed by use of lipid-lowering medication in high-risk patients."

What we still need to learn

- How different initial ART regimens alter CVD risk
- The magnitude of benefit or early ART on CVD risk
- Optimal strategies for reducing long term CVD risk in HIV populations

Wrap-Up

- The Forum for Collaborative HIV Research thanks you for joining us today!
- Webcast will be available on www.hivforum.org