

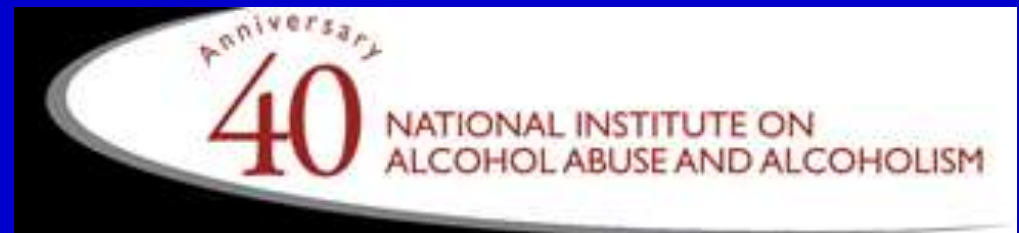
# HIV Progression, Alcohol, and Aging *Towards a combined prognostic index for survival in HIV infection – the role of Non-HIV Markers*

3<sup>rd</sup> NIAAA International Conference on  
Alcohol and HIV/AIDS in Latin America,  
Cali Colombia  
March 25-27, 2010



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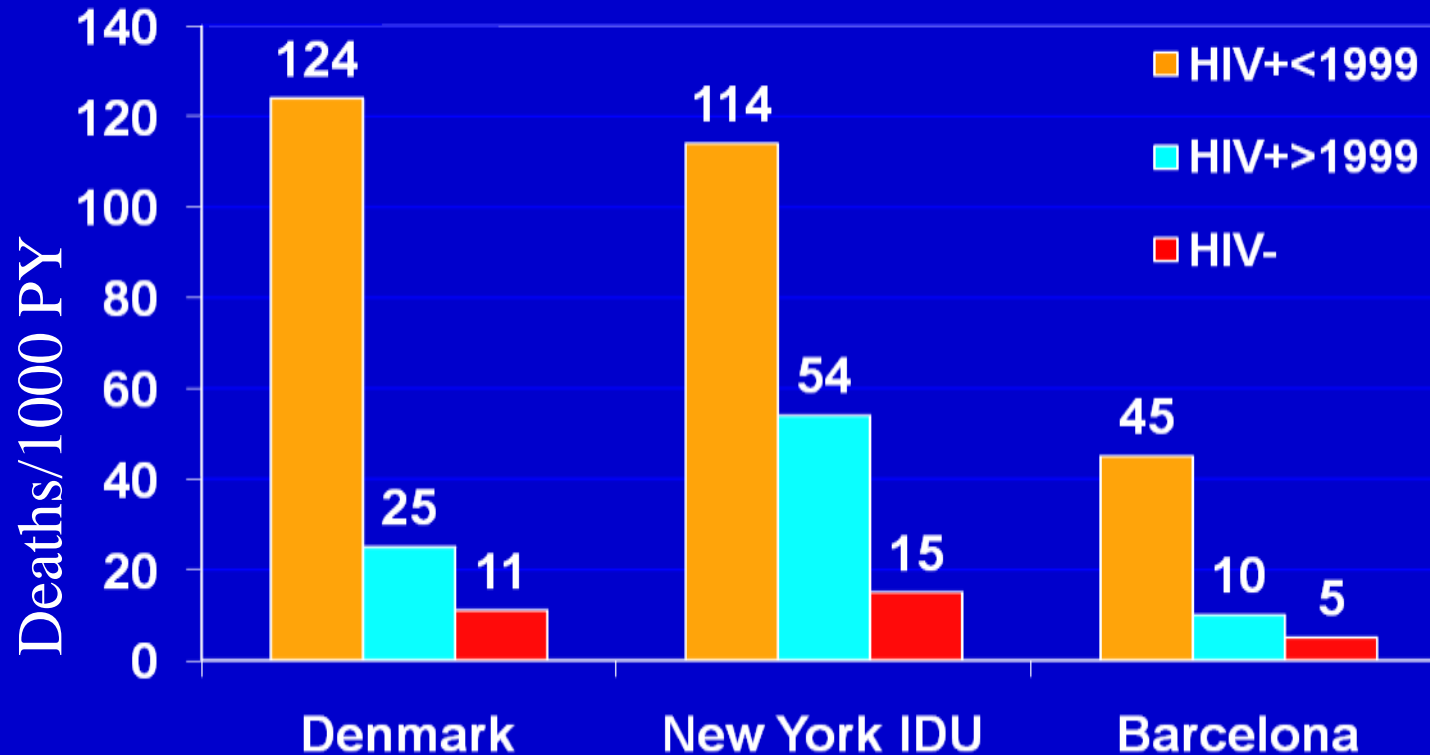
# The value of cohort studies for measuring progression and aging in HIV?

How can you assess the impact of different systems of care or specific interventions (for alcohol) within these systems?

## A few facts about alcohol and HIV

- In the U.S. 15-40% of HIV+ individuals have and a current alcohol use disorder
- International samples have exceeded 60%
- Physicians advise patients not to drink with cART treatment (per warning labels)
- 80% of patients continue drinking
- Heavy drinking will reduce expected life years by half (24 to 12)

# People with HIV are Living Longer



*Denmark: Ann Intern Med 2007;146:87-95*

*New York IDU: CID 2005;41:864-72*

*Barcelona: HIV Medicine 2007;8:251-8*

# Life Expectancy is Not “Normal”

At HAART Initiation	CD4 Cell Count (mm <sup>3</sup> )		
	<100	100-199	≥200
A 20 yr old will live to	52	62	70
A 35 yr old will live to	<u>62</u>	65	<u>72</u>
% Remaining Life Lost (all ages)	46%	27%	14%

Adapted from *ART-CC, Lancet 2008;372:293-99* by adding additional expected survival to age at treatment initiation.

“By 2015, an estimated 50% of people living with HIV/AIDS [in the US] will be over 50 years of age.”

Aging Hearing: HIV over fifty, exploring the new threat.  
Senate Committee on Aging. Washington, DC. 2005.

# “Non AIDS” Deaths HIV+ More Common

Source	Non AIDS	Leading Causes	Reference
NY Death Certificates	26%	Alcohol/drug abuse (31%), CVD (24%), Cancer (21%)	Ann Intern Med 2006;145:397-406
Barcelona Death Certificates	60%	Liver ( 23%), Infection (14%), Cancer (11%), CVD (6%)	HIV Med 2007;8;251-8
HOPS Chart Rev.	63%	Liver (18%), CVD (18%), Pulmonary (16%), Renal (12%), GI (11%), Infection (10%) Cancer (8%)	J Acquir Immune Defic Syndr 2006;43:27-34
Cascade Chart Rev.	63%	Liver (20%), Infections (24%), Unintentional (33%), Cancer (10%), CVD (9%)	AIDS 2006; 20;741-9

# Goals Cohort Studies

To understand the roles of aging, comorbidity, treatment toxicity and substance use (Alcohol and Drugs) in determining morbidity and mortality with HIV infection and

to use these insights to develop informatics based interventions to improve patient outcomes



# Three Assumptions

- Aging, comorbidity, treatment toxicity, and substance use interact with HIV infection
- Many of these interactions are modifiable – alcohol use is one of the most modifiable
- Strategies which individually tailor and prioritize care will be most effective

# VACS Virtual Cohort (VC)

## Sources of Data for Indicators

- **CURRENT DATA SOURCES:** National administrative, laboratory, pharmacy, cancer registry, MI quality of care, and all cause mortality (requesting Medicare)
- **SUBJECTS:** 41,753 HIV infected; 83,506 uninfected
  - All individuals with HIV diagnoses
  - Age, race/ethnicity, region 2:1 matched controls
  - Last updated: September, 2008
- **SITES:** All VA sites
- **BASELINE:** 1998 (11 years of follow up)
  - HIV infected veterans at initiation of HIV care
  - Controls selected and followed in same calendar year

# VACS 8

- CURRENT DATA SOURCES (VC sources plus)
  - Consented for all clinical data
  - Records for sentinel events requested outside VA
  - All VA Electronic medical records including text fields
  - DNA and tissue bank
  - Annual self completed surveys
- SUBJECTS:
  - 3,600 HIV infected (alcohol using); 3,600 uninfected
  - Group matched: age, race/ethnicity, and site
- SITES: Manhattan, Bronx, Washington DC, Baltimore, Pittsburgh, Atlanta, Houston, Los Angeles
- BASELINE: 2002 (8 years)

# DNA and Tissue Bank

(Collection Completed 8/31/07)

	HIV+	HIV-	Total
Unique Pts	1656	892	2548
DNA Samples	1656	892	2548
Tissue Samples	1542	867	2409

To collect serial samples on those newly initiating antiretroviral treatment in the future.

# Traditional Measures of Viral Replication and Immune Function

ARV Treatment Effectiveness

# AIDS Events Are Decreased on cART

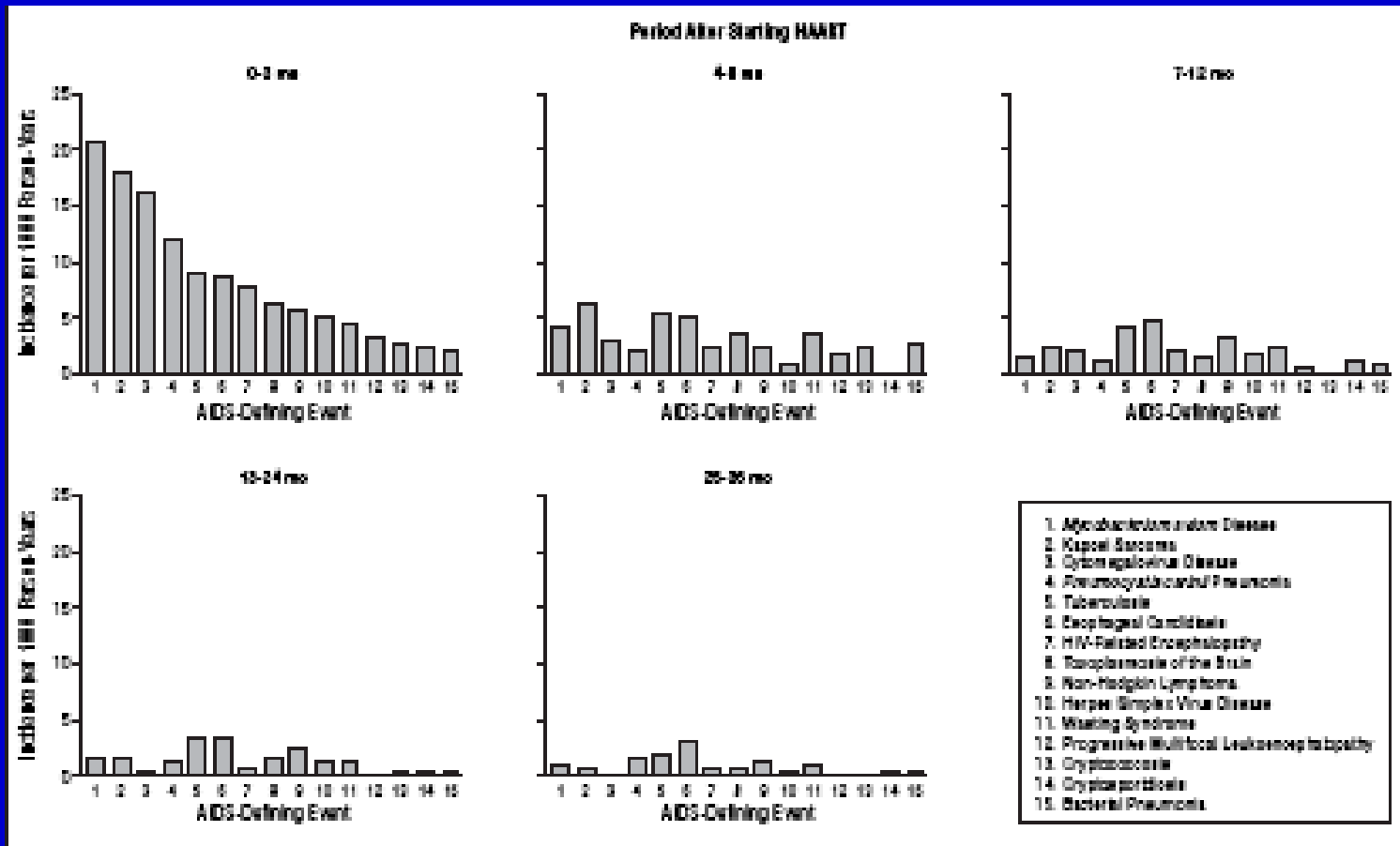
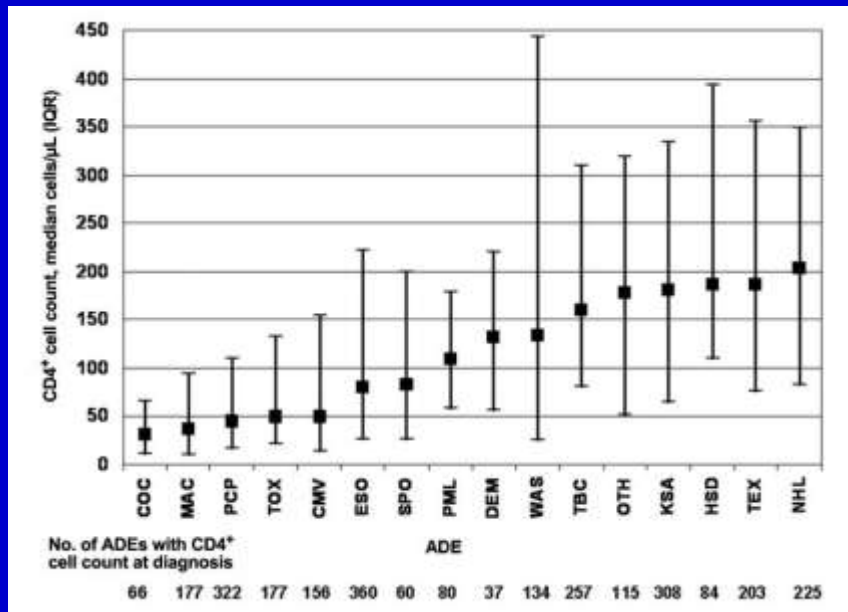


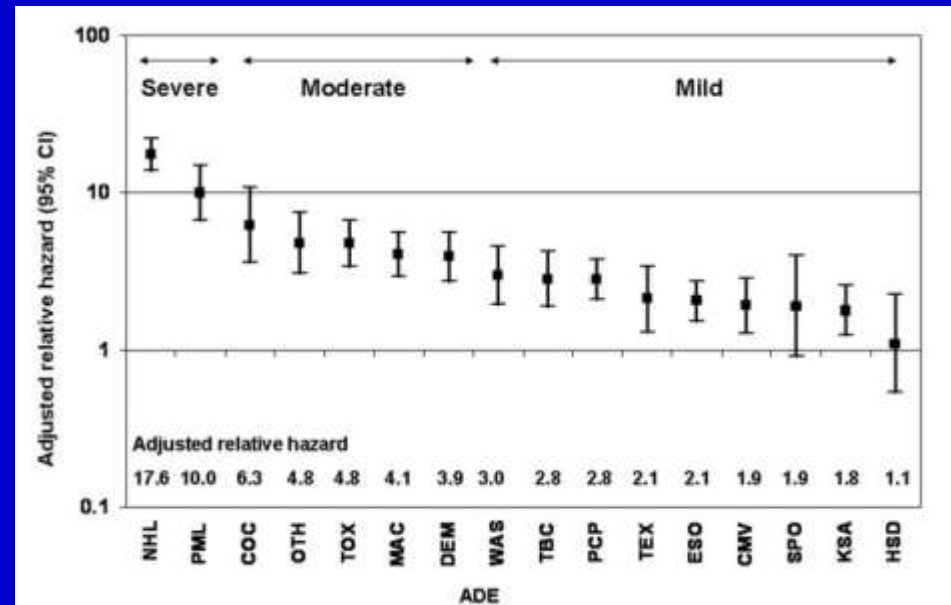
Figure 1. Incidences of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART).

# AIDS Events are Variably Associated with CD4 and Survival

By Median (IQR) CD4



By Relative Hazard of Death



# Is This the Price of Success?

- No surprise that older people have an increased risk of mortality
- Younger people may now be living long to die from other causes
- *Or, is something more subtle going on?*



# More AIDS and “Non-AIDS” Events Among Rx. Sparing Arm (HR 1.7 in SMART)

	Rx. Sparing	Rx. Intensive	Total
All Cause Death	55	30	85
Serious OI	13	2	15
Nonserious OI	63	18	81
Major CAD, Renal, or Liver Disease	65	39	104

# HIV Infection is a Complex Chronic Disease

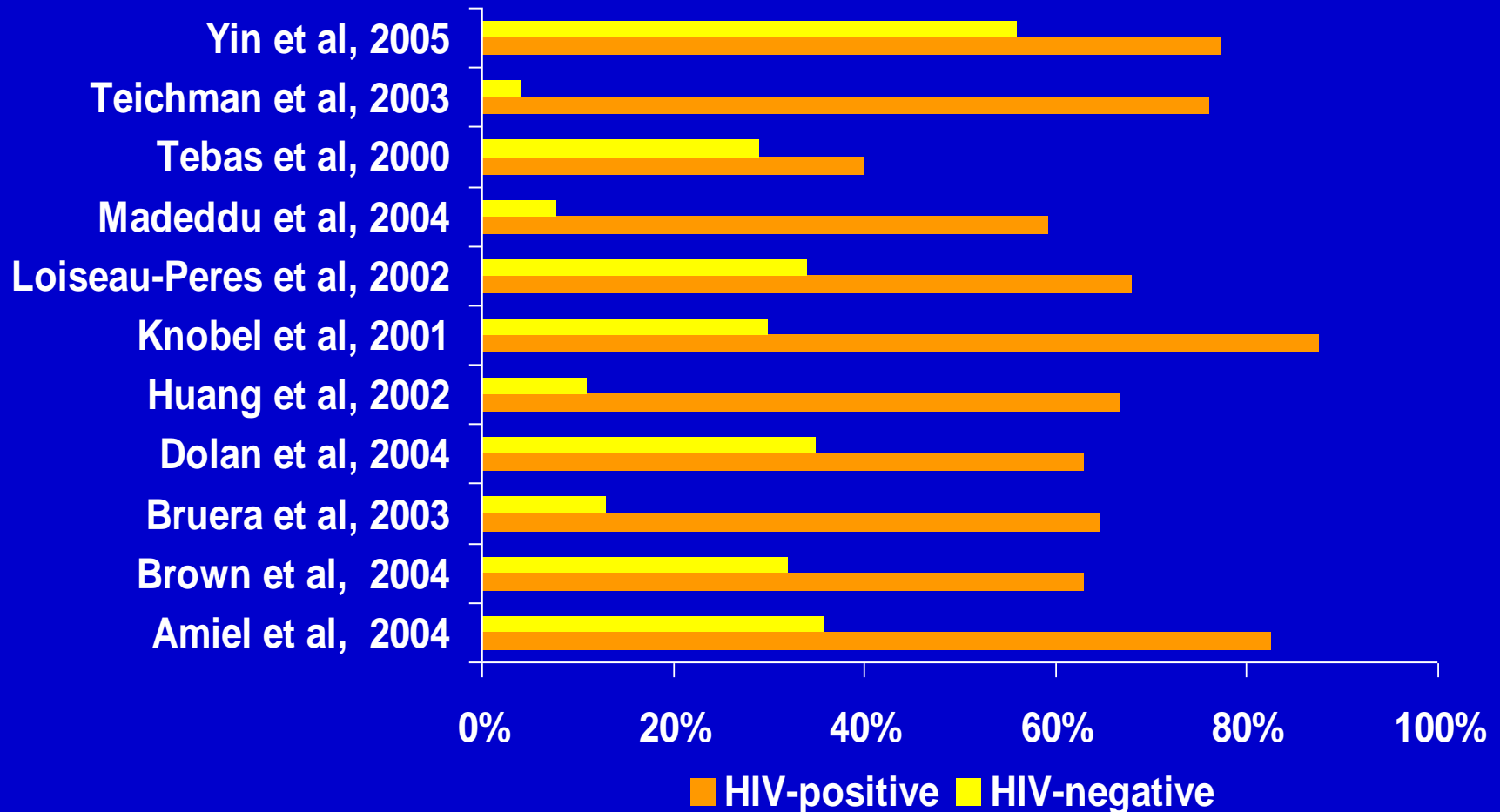
- Many common 'Non AIDS' conditions are associated with HIV infection and disease progression
- AIDS defining conditions are increasingly rare and variably associated with mortality

# Case History:

## Low Bone Mineral Density (BMD)

- 55 year old male with HIV
- DEXA scan shows BMD 1 SD below normal
- Body mass index of 30
- Long term alcohol abuse
- Long term smoker

# Decreased Bone Mineral Density

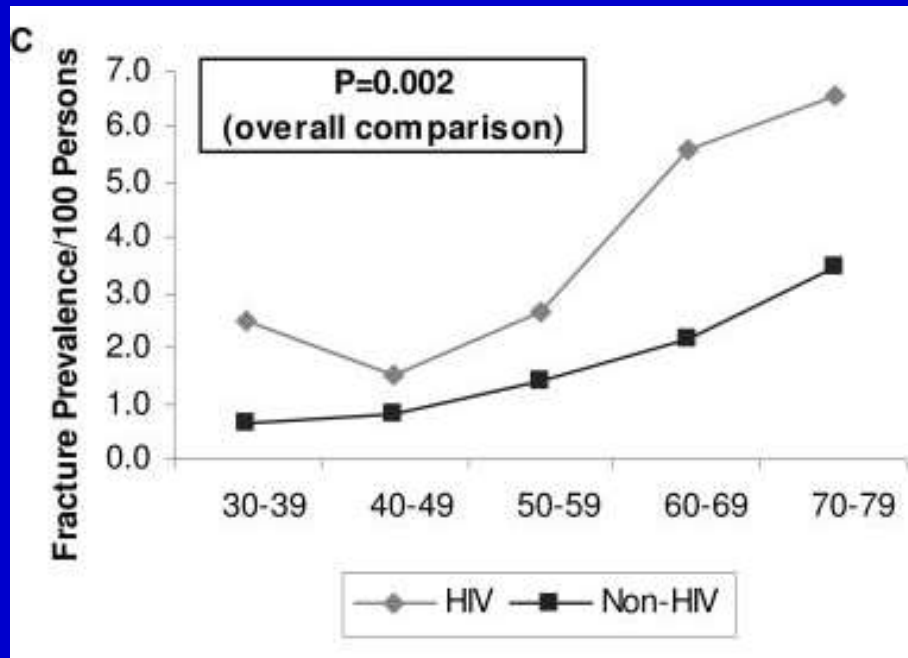


# BMD Vs. Fragility Fracture

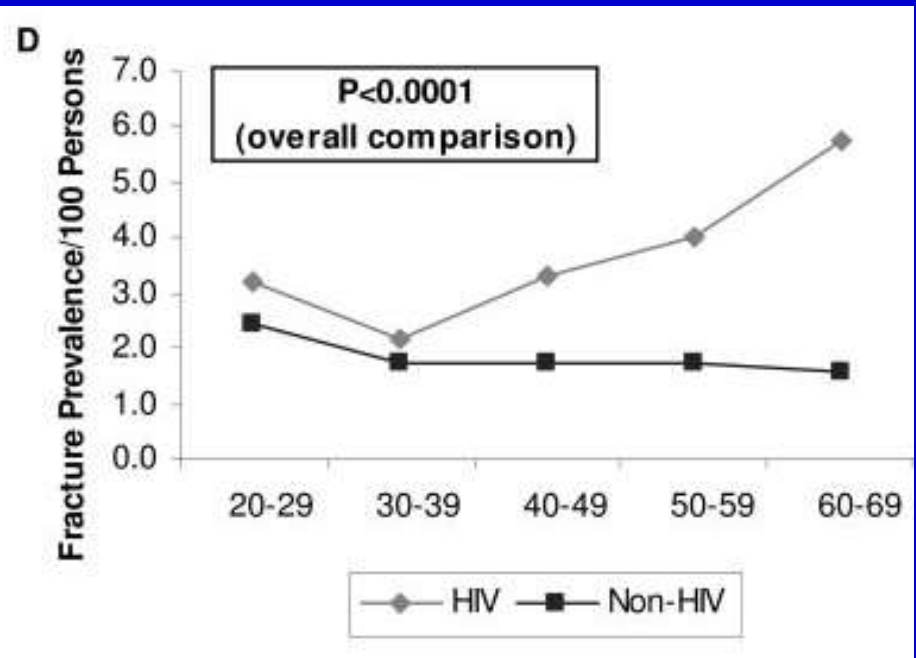
- Low BMD is a risk factor for vertebral, wrist, or hip fracture (fragility fracture)
- HIV and time on cART is associated with low BMD
- One age, race and gender, adjusted study has shown an increased risk of fragility fractures
  - 3.1 vs. 1.8 per 100 PY for HIV+/- men (72% increase)
  - 2.5 vs. 1.7 per 100 PY for HIV+/- women (47% increase)
  - But lets look at this more closely...

# 'Fragility Fracture' Prevalence

Women



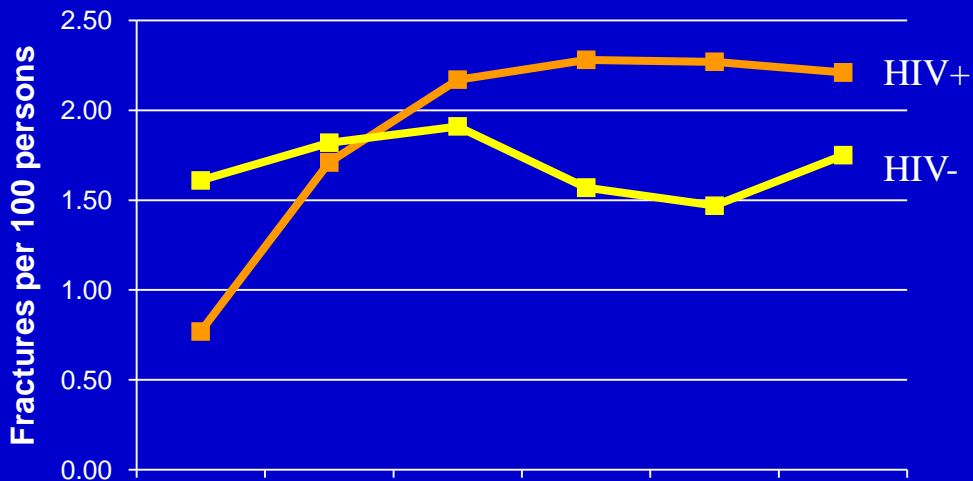
Men



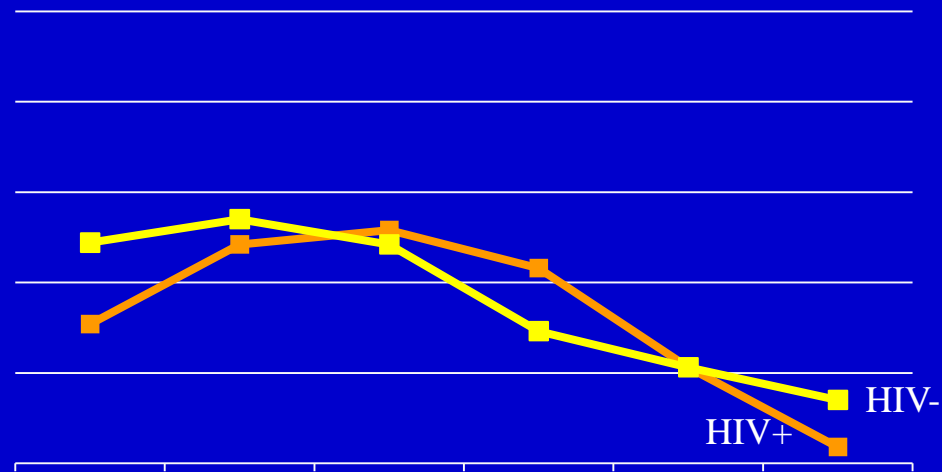
Includes fractures caused by violent injury. Not adjusted for Body Mass Index, smoking, alcohol, prior fracture, functional status or BMD.  
*Triant VA. J Clin Endocrinol Metab 93:3499-3504, 2008*

# VACS VC Prevalence in Men

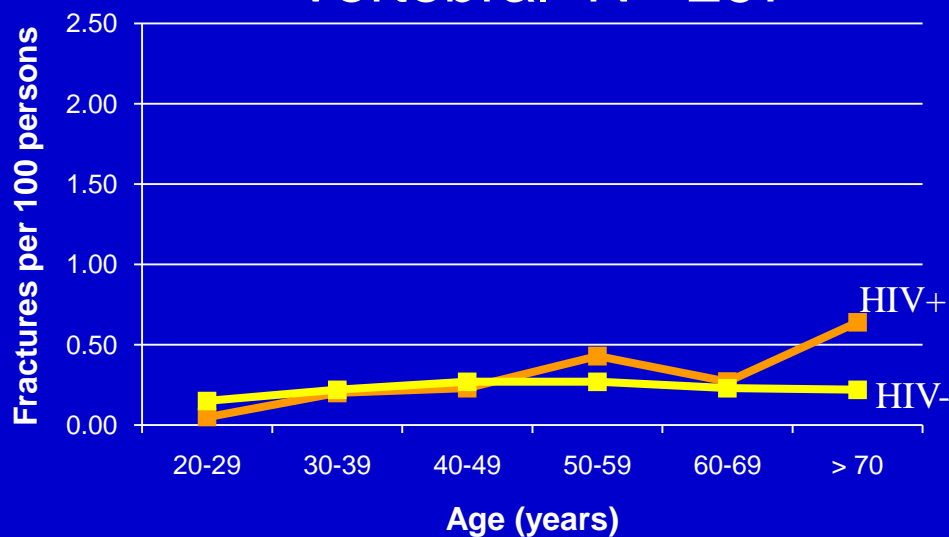
## Any N=2152



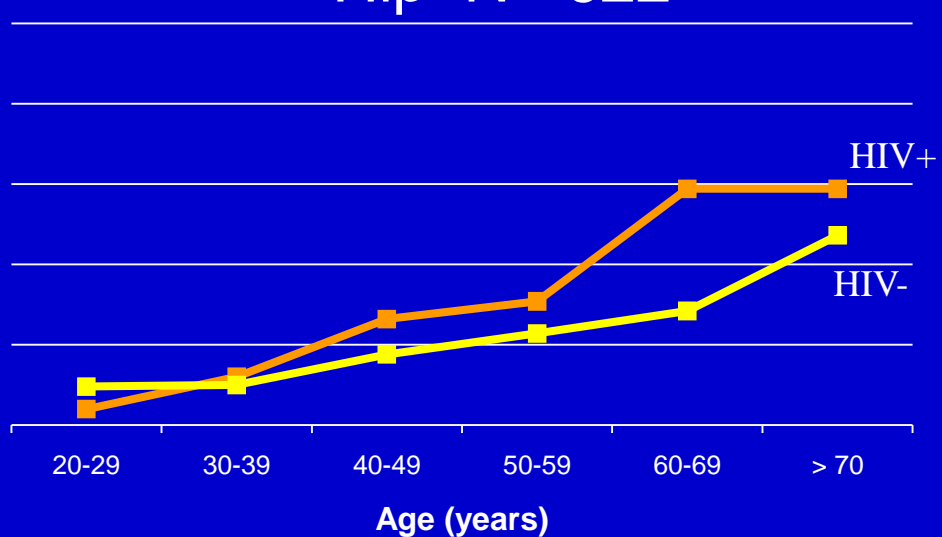
## Wrist N= 1233



## Vertebral N= 297



## Hip N= 622



# VC Incident Fragility Fractures in Men

	Unadjusted model	Full model	HIV-infected only
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
<b>HIV</b>	<b>1.53 (1.34, 1.75)</b>	<b>1.38 (1.18, 1.60)</b>	
Cachexia		2.83 (2.26, 3.54)	2.52 (1.82, 3.49)
Cerebrovascular disease		1.89 (1.34, 2.65)	1.70 (0.92, 3.14)
White		1.79 (1.57, 2.04)	1.81 (1.64, 1.99)
Alcohol dependence		1.73 (1.42, 2.10)	1.88 (1.37, 2.58)
Age (10 year increments)		1.53 (1.44, 1.63)	1.81 (1.47, 2.23)
Enrollment year before 1999		0.75 (0.64, 0.87)	0.89 (0.69, 1.14)
CD4 (per 100 cells/mm <sup>3</sup> )			0.96 (0.91, 0.99)
Tenofovir use at baseline			1.22 (0.72, 2.05)
NNRTI use at baseline			0.68 (0.45, 1.04)
PI use at baseline			1.22 (0.97, 1.53)

Also controlled for: congestive heart failure, pulmonary disease, peripheral vascular disease, drug abuse, major depressive disorder, CAD, diabetes, liver disease, renal insufficiency, osteonecrosis, steroid use at baseline.

Adjustment for non-proportionality: HIV\*log(time) HR: 1.09 (95% CI: 1.01, 1.18)



# Prevention of Fragility Fractures

- Behavior
  - Smoking and alcohol cessation
  - Exercise and weight maintenance
- Nutrition
  - Calcium, Vitamin D
- **Bisphosphonates** (Alendronate, Risedronate, etc.)
  - Toxicities: GI reflux, ulcers, esophageal cancer and jaw osteonecrosis
  - Unknown efficacy in HIV

# Also Under Study in VACS

- Liver Cirrhosis
- Non AIDS Cancers
- Anemia of Chronic Inflammation
- COPD and Bacterial Pneumonia
- Stroke
- Cardiovascular Disease
- Renal Disease

# Implications For An Aging Epidemic

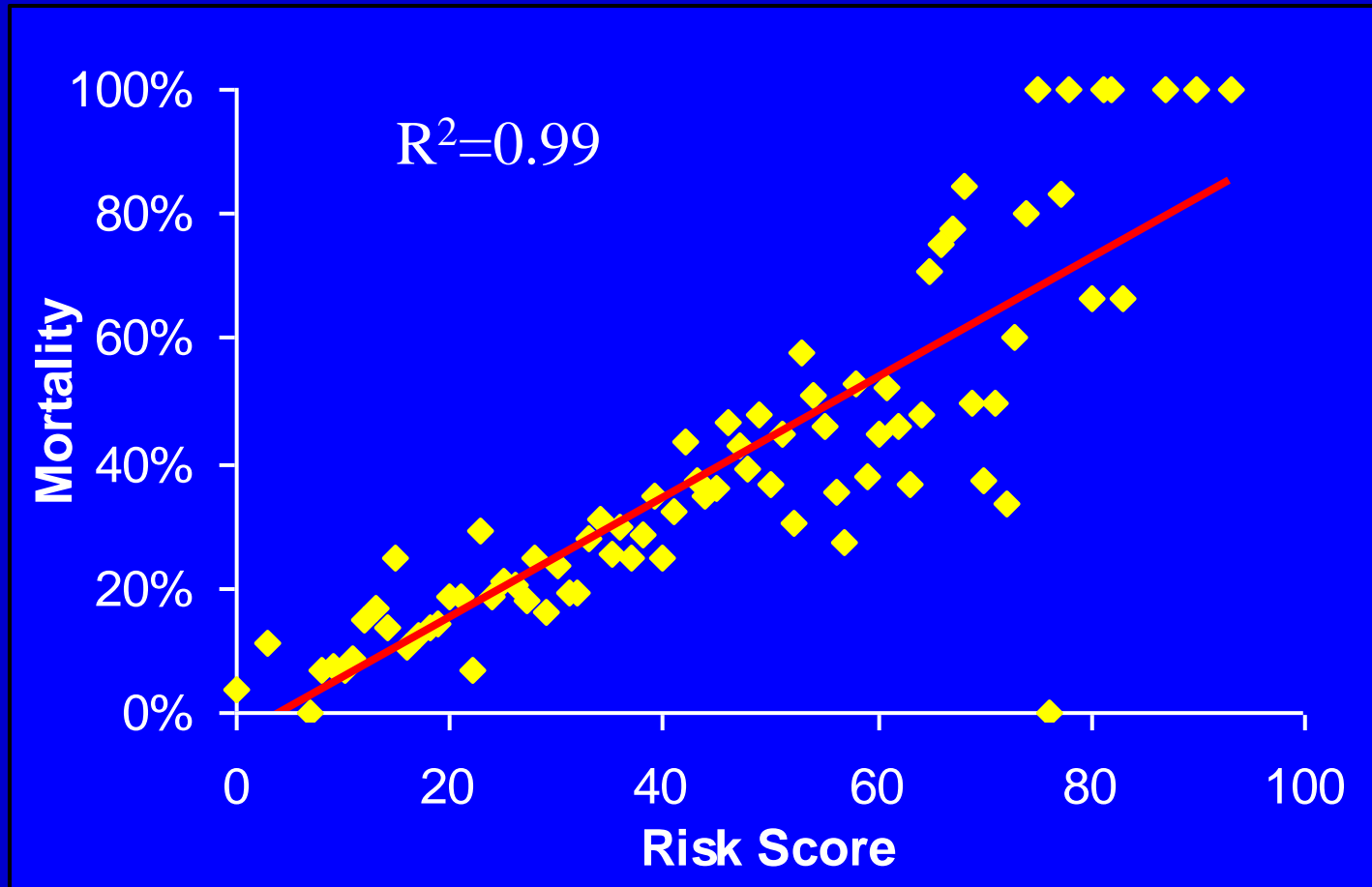
- HIV infection increases risk of common 'non AIDS' conditions but not as much as many established risk factors
- Primary care guidelines for non-AIDS condition must be adapted for those with HIV
  - Some non-AIDS conditions may justify earlier ARV treatment
  - Selected ARV treatments likely cause some non-AIDS conditions, but effects are often less than those of HIV itself
- We need a comprehensive index to chart changes in total risk of morbidity and mortality

		Points	HR
Age	<50	0	1
	50 to 64	9	1.45
	≥ 65	27	2.94
CD4	<50	17	1.98
	50 to 99	14	1.72
	100 to 199	11	1.54
	200 to 349	8	1.38
	≥350	0	1.00
AIDS defining condition		7	1.31
Log Viral load > 5		3	1.14
Hemoglobin	> 12	0	1.00
	10-12	9	1.43
	< 10	13	1.67
FIB4	<1.45	0	1.00
	1.45 to 3.24	10	1.50
	> 3.25	18	2.09
Estimated GFR < 30		12	1.61
Alcohol or Drug Abuse		8	1.35
Hepatitis B or C		9	1.45

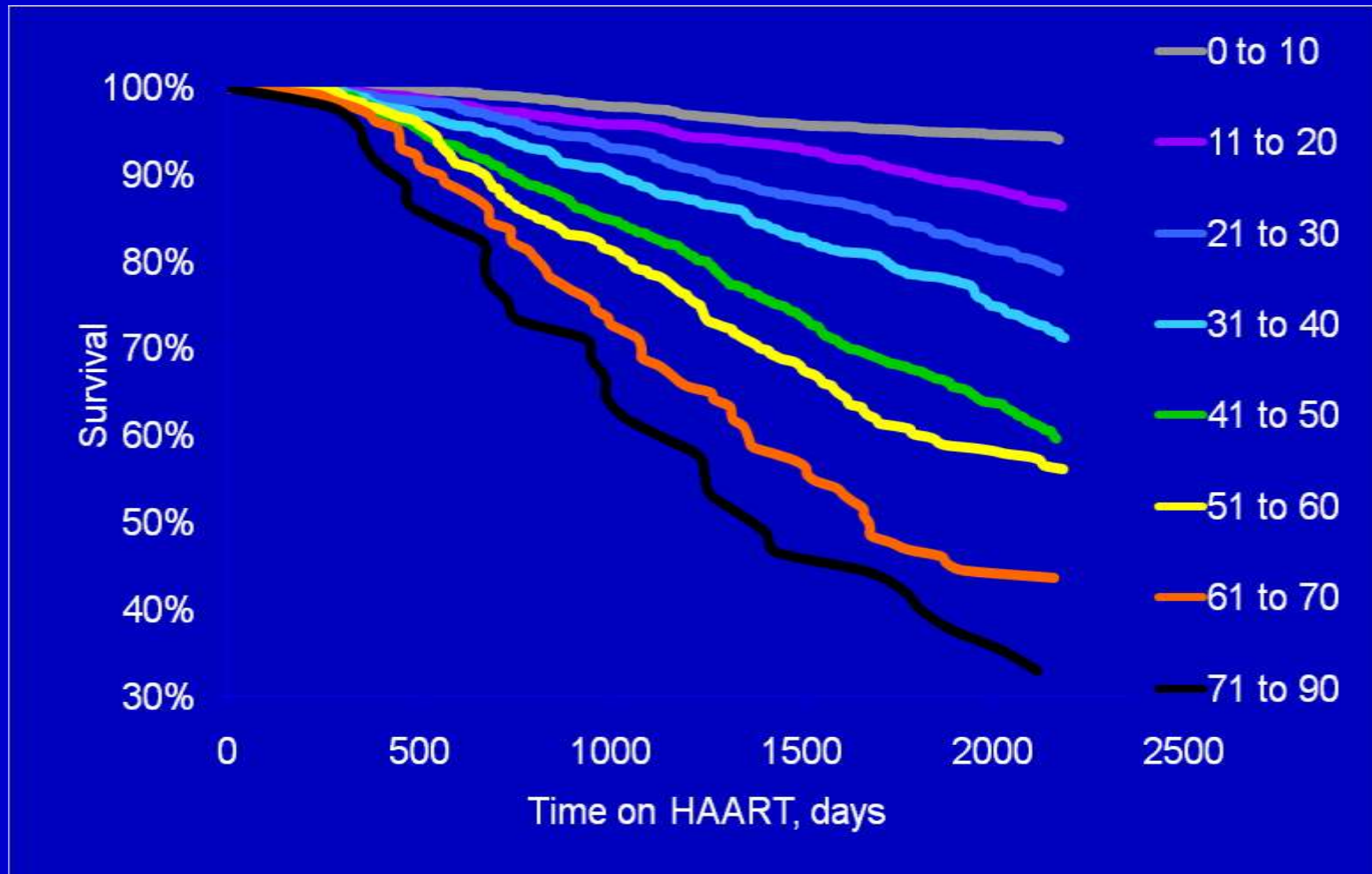
# Veterans Aging Cohort (VACS) Risk Index

*Justice 2009 HIV Medicine  
published electronically*

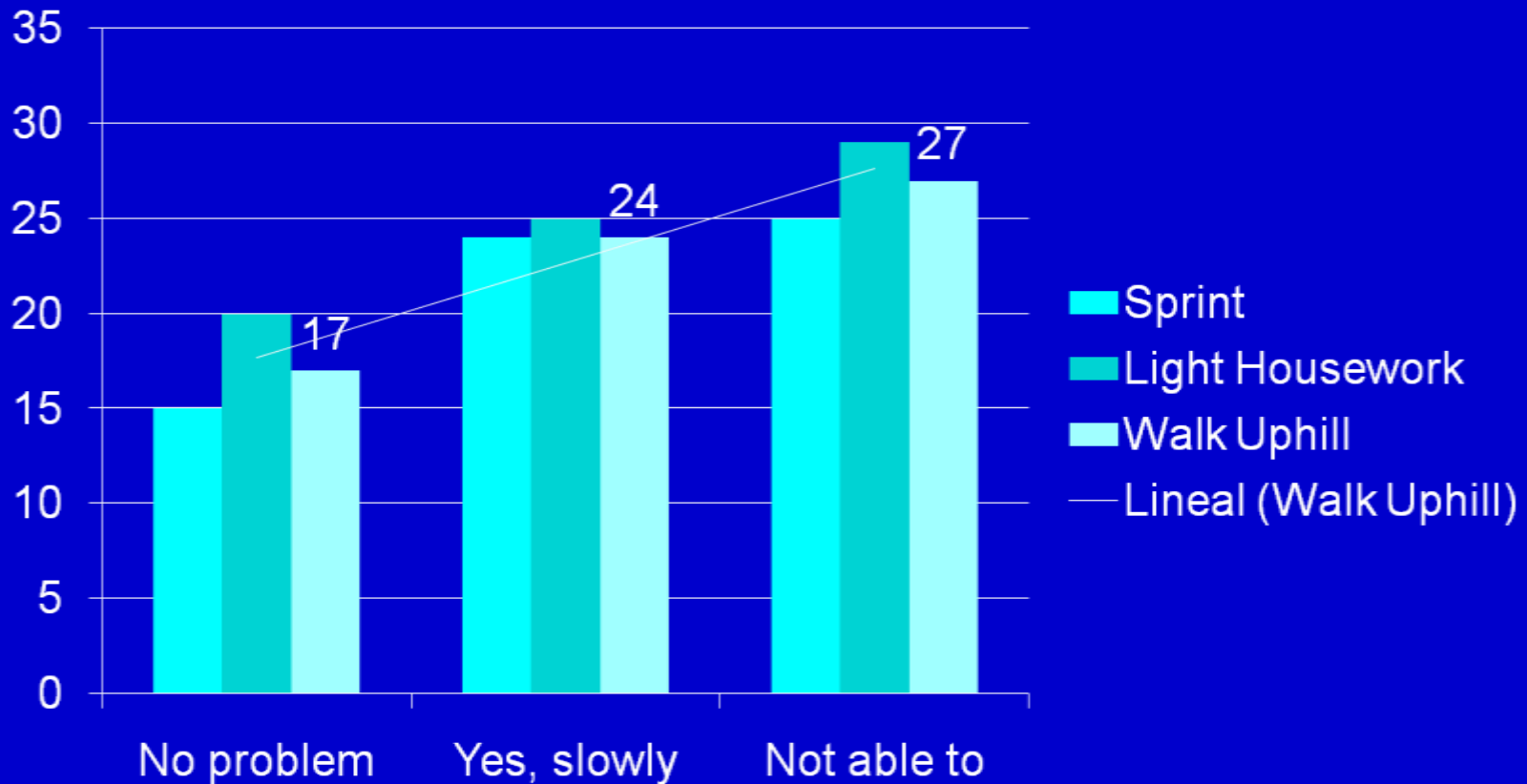
# Individual Score Pre cART

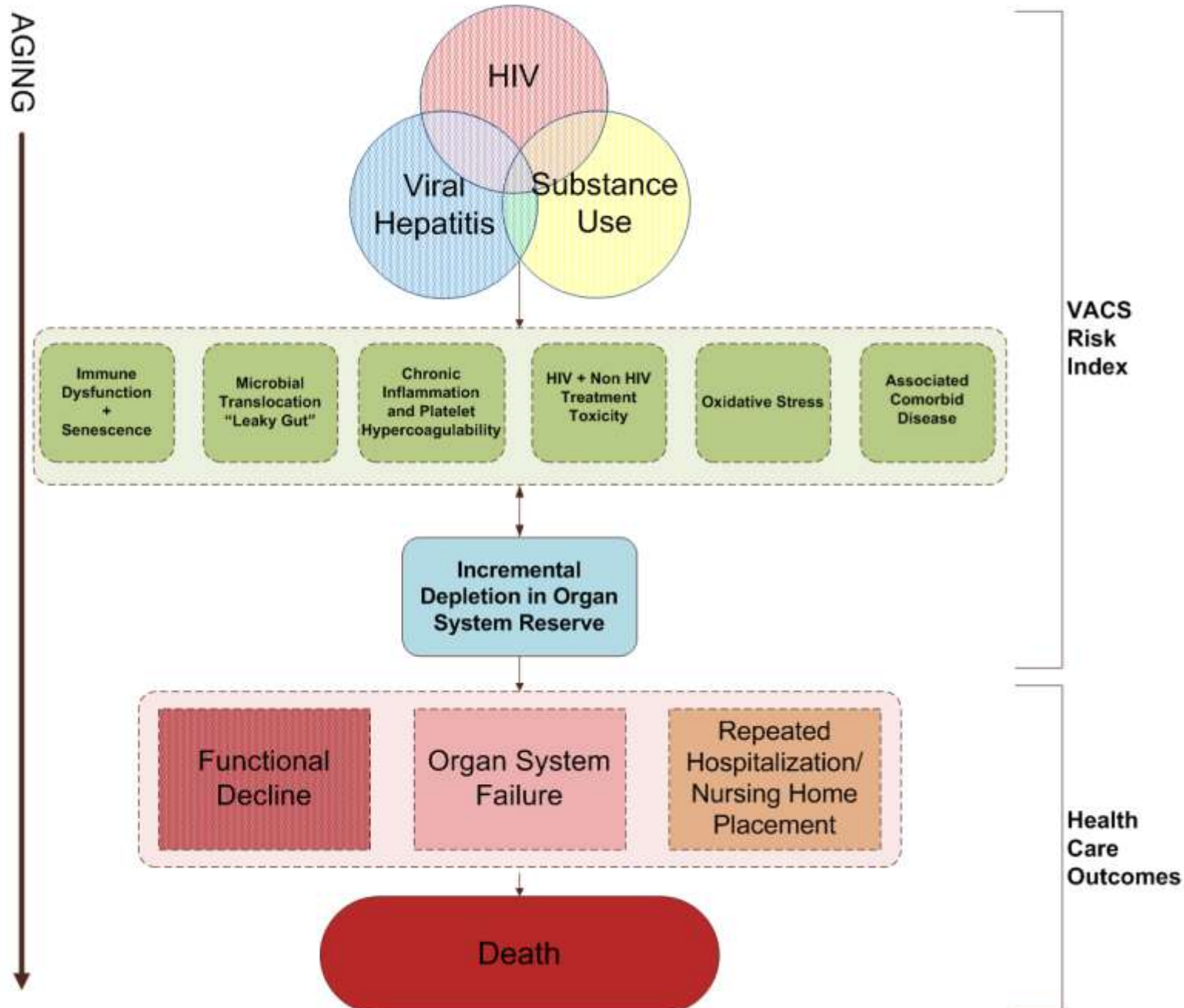


# Survival by VACS Index Score (6 years)



# Median VACS Index Score and Self Reported Function







# Patient Normative Feedback

## Imagine!

- Welcome to *the Latin American Cohort Study (LACS) Risk Index Calculator*. If you have HIV infection, this calculator will determine your risk score. It does this using your age, whether or not you have started antiretroviral therapy, how long you have taken antiretroviral therapy, and your most recent routine laboratory values score and a few lifestyle questions.



# What is needed

- CD4 cell count, HIV viral load, creatinine, hemoglobin, Aspartate Transaminase (AST), Alanine Transaminase (ALT), platelet count, and hepatitis C test, and use of alcohol.
- In most healthcare settings, you can request these laboratory values from your provider or ask for a copy to be sent to you when your blood is drawn.
- After you enter this information at the prompts, the calculator will give you or your care provider a risk score

# The Best Index

- Demonstrate
  - Generalizability and Cultural Specificity
  - Responsiveness to interventions (adherence, cART, alcohol cessation, HCV treatment)
- Determine whether additional biomarkers improve Index and lifestyle questions to target brief interventions
- Create medical decision support tools to optimize care and motivate behavior change
- Use as surrogate outcome in health services strategy trials

# Thank You



# Website

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## Veterans Aging Cohort Study

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### Veterans Aging Cohort Study

The Veterans Aging Cohort Study (VACS) is a prospective, observational cohort study of HIV- positive and an age/race/site matched control group of HIV- negative veterans in care in the United States. The study's aim is to understand the role of comorbid medical and psychiatric disease in determining clinical outcomes in HIV infection. It is funded primarily by the National Institute on Alcoholism and Alcohol Abuse, National Institutes of Health. The study has a special focus on the role of alcohol use and abuse in determining clinical outcomes.

The VACS study is built around the Veterans Health Administration (VA), the largest integrated health-care system in the United States, providing care to 3.6 million patients annually. The VA is also the largest single provider of HIV care in the nation, serving 19,000 HIV-positive veterans in 2003. The VA provides inpatient and outpatient medical care, pharmacy, mental-health services, substance-abuse treatment, long-term care, homeless care, and hospice services. The VA also has a national, fully electronic medical-record system that includes all routine clinical data, administrative data, and comprehensive follow-up data for mortality, as the VA pays some burial expenses for veterans.

### 2008 VACS Scientific Conference

October 13-15, 2008  
New Haven, CT

Participants are asked to arrive on Monday, October 13, in time for a welcome reception. A full-day of meetings and presentations will be take place Tuesday, October 14, followed by a half-day session Wednesday, October 15. Further information will follow.



# Veterans Aging Cohort Study

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- **PI and Co-PI:** AC Justice, DA Fiellin
- **Scientific Officer (NIAAA):** K Bryant
- **Participating VA Medical Centers:** Atlanta (D. Rimland), Baltimore (KA Oursler, R Titanji), Bronx (S Brown, S Garrison), Houston (M Rodriguez-Barradas, N Masozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, J Leung), Pittsburgh (A Butt, E Hoffman), and Washington DC (C Gibert, R Peck)
- **Core Faculty:** K Mattocks (Deputy Director), S Braithwaite, C Brandt, K Bryant, R Cook, K Crothers, J Chang, S Crystal, N Day, J Erdos, M Freiberg, M Kozal, M Gaziano, M Gerschenson, A Gordon, J Goulet, K Kraemer, J Lim, S Maisto, P Miller, P O'Connor, R Papas, C Rinaldo, J Samet
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- **Major Collaborators:** VA Public Health Strategic Healthcare Group, VA Pharmacy Benefits Management, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Yale Center for Interdisciplinary Research on AIDS (CIRA), Center for Health Equity Research and Promotion (CHERP), ART-CC, NA-ACCORD, HIV-Causal
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