

HIV and Aging: Time for a New Paradigm

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ACTHIV Meeting

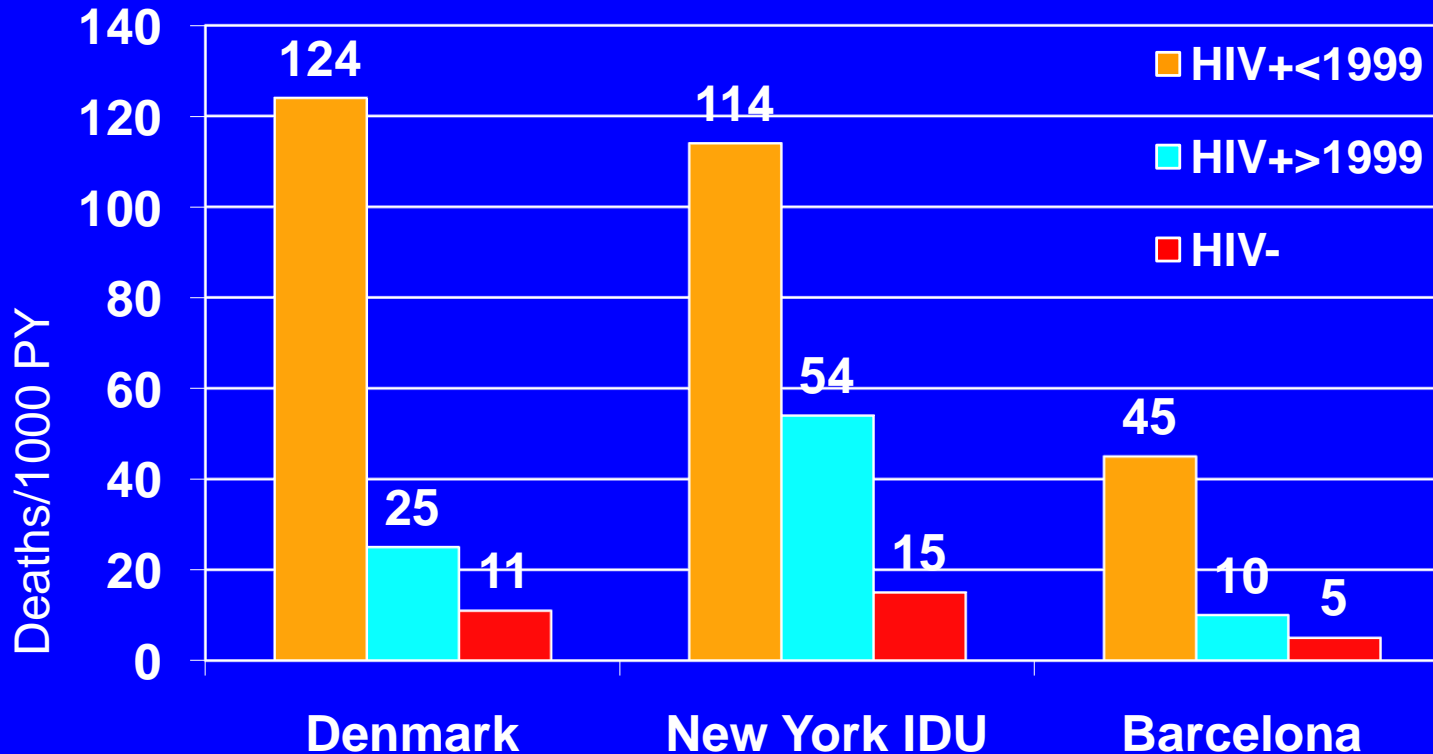
May 2010

ARS Question

Learning Objectives and Off Label Disclosure

- Discuss aging and life expectancy with persons on cART
- Use HIV and “non-HIV” biomarkers and conditions in estimating risk of patient outcomes
- Appraise the potential of a unifying risk index for clinical care, research, and health policy
- I will not discuss non-FDA-approved or investigational uses of any products/devices

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

“Non AIDS” Deaths 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

Life Expectancy is Not “Normal”

At HAART Initiation	CD4 Cell Count (mm ³)		
	<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.

AIDS Events Are Decreased on cART

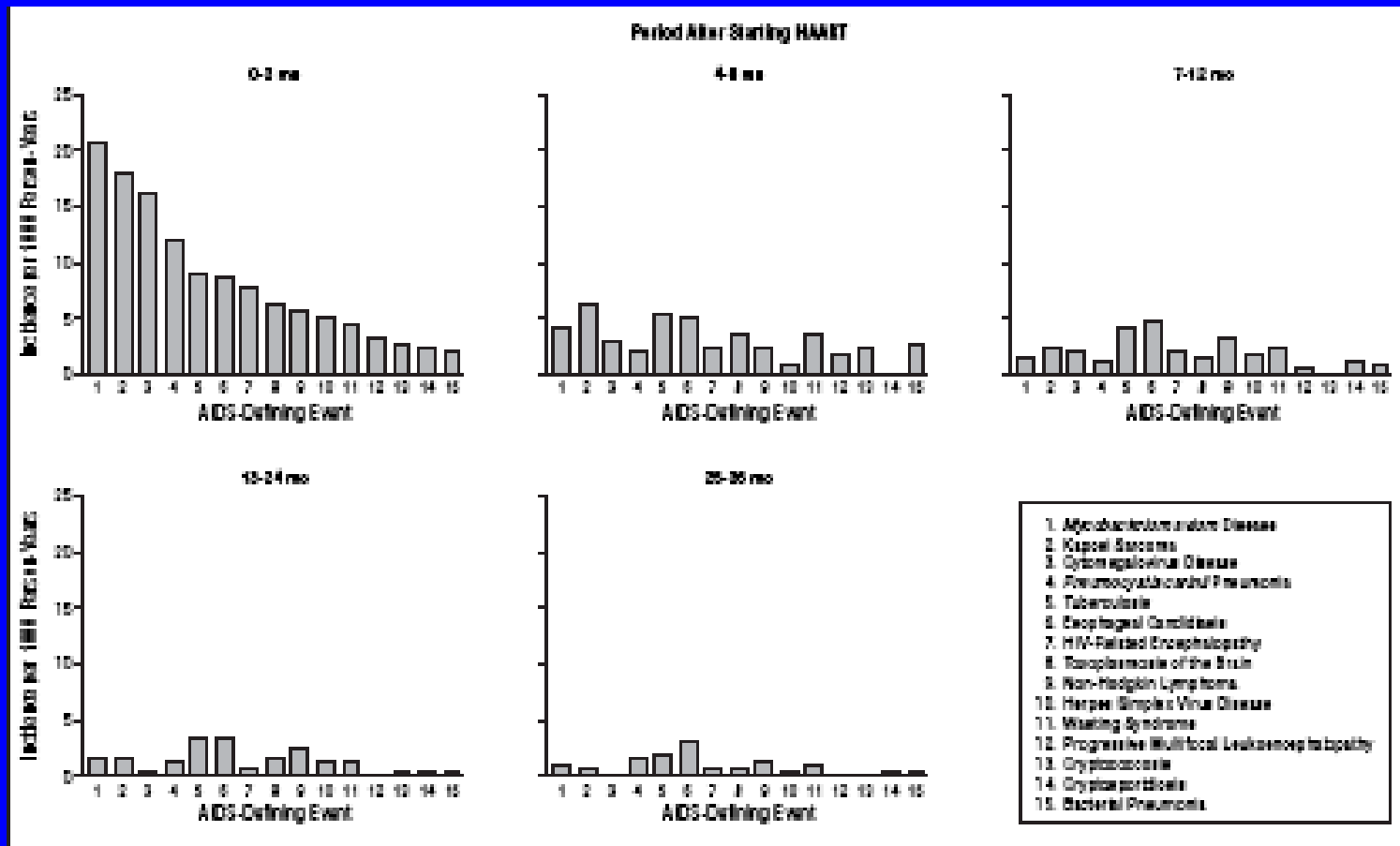
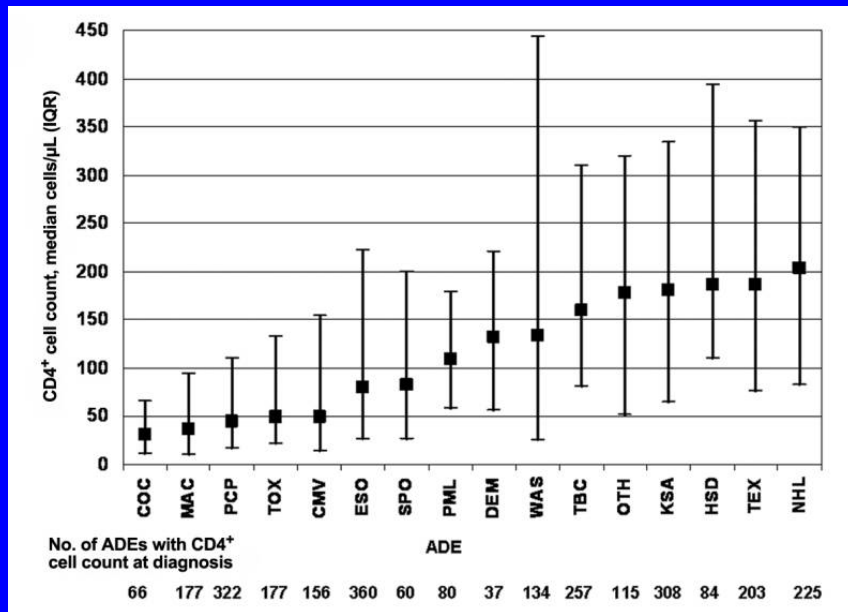


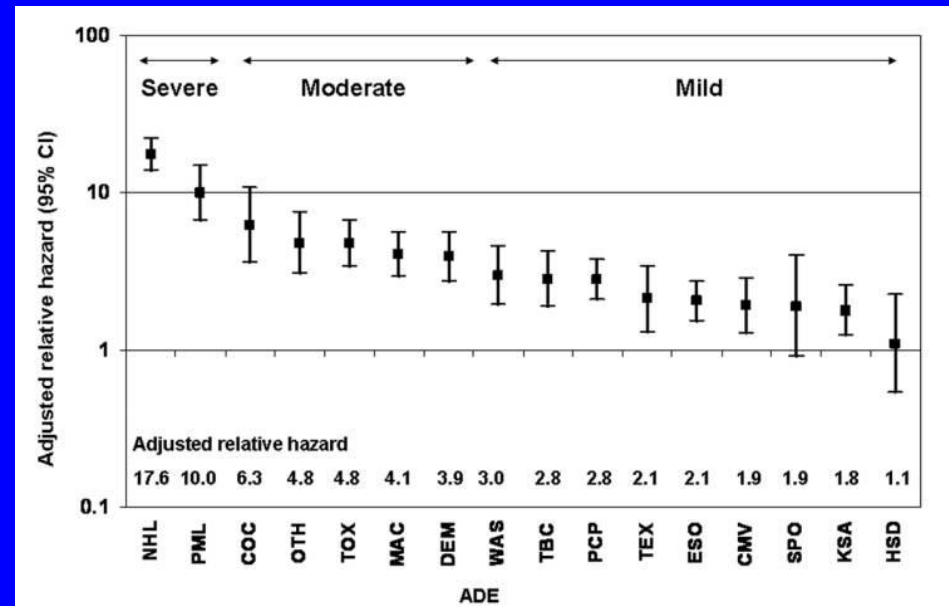
Figure 1. Incidences of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART).

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

We need to adopt our research priorities to better understand the full role of HIV in causing a wide range of clinical diseases.

...Clinicians caring for patients with HIV need to ...become aware of the best means to try to prevent and to monitor for early signs of these [non-AIDS] outcomes.

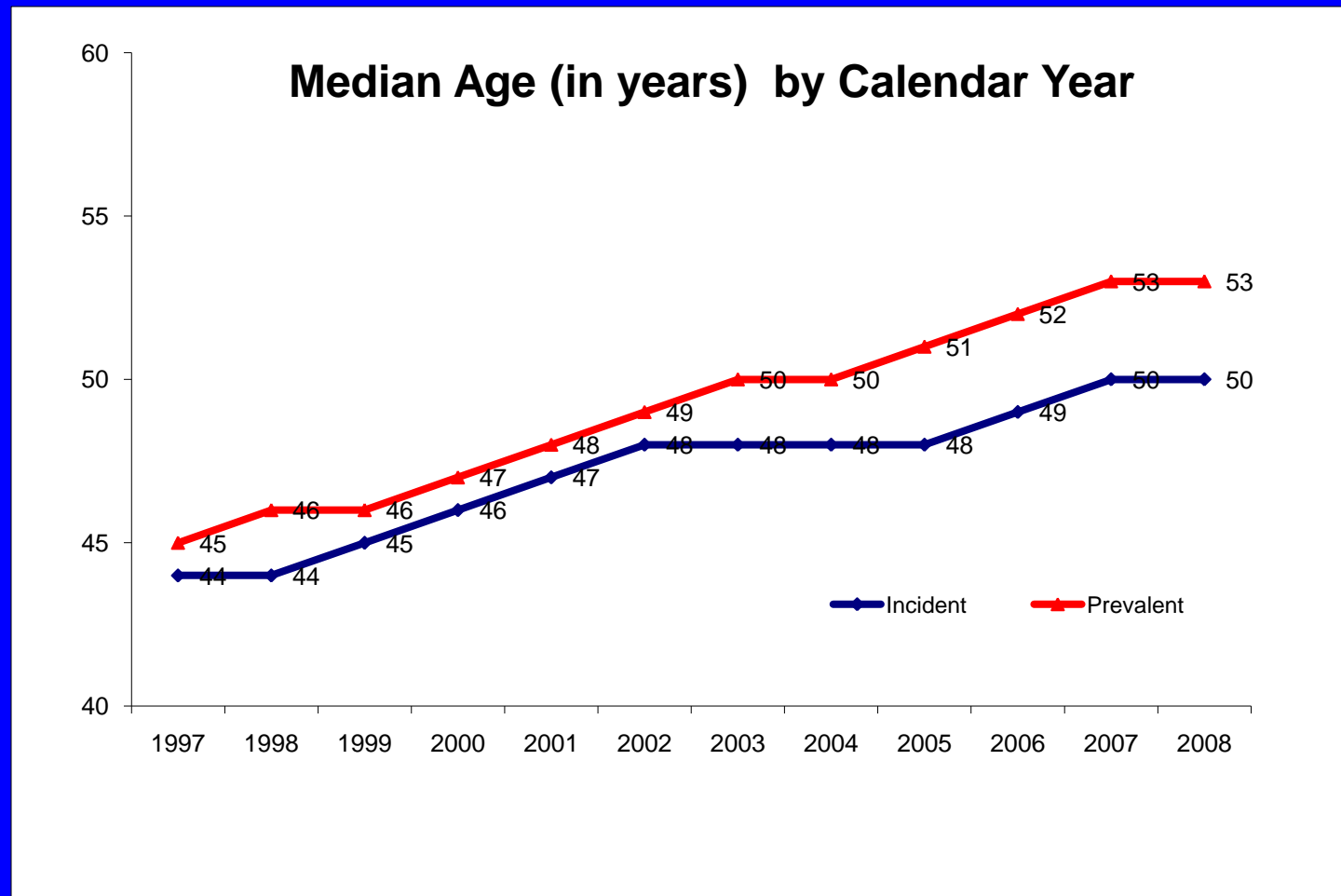
--SMART Investigators

AIDS 2008, 22:2409-2418

Where Can We Find Answers?

- Many questions can't be addressed in RCTs
 - Sample size
 - Interval of observation
 - Ethics
- Need large observational studies with demographically similar controls
 - Health systems with EMRs (VA, Kaiser, Pilgrim, etc)
 - Cross cohort collaborations (ART-CC, NaACCORD)

The VA is Ahead of the Curve



What is the Veterans Aging Cohort Study?

Two nested Veteran cohorts,
funded by the NIH



Three Assumptions

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

Goals

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

and

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

One Example in Detail

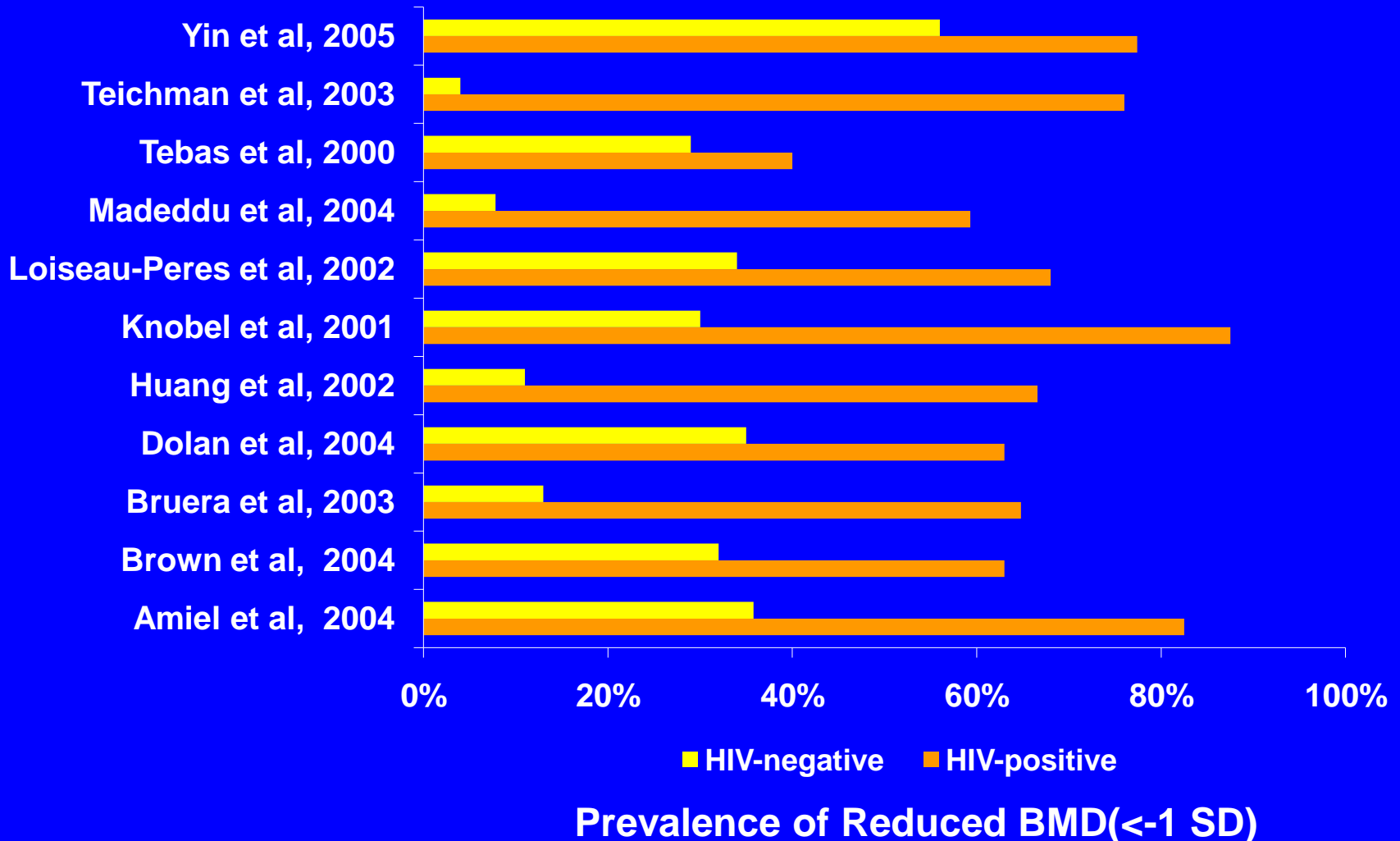
Osteoporosis among Men Aging with HIV Infection and Demographically Similar Controls

Oral Presentation CROI 2010

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 active alcohol abuse
- Long term active smoker

HIV is Associated with Decreased Bone Mineral Density



BMD and Fragility Fracture

- Fragility fractures (vertebral, wrist, or hip fracture)
 - Are the clinical concern when low BMD is detected
 - Occur spontaneously or with minor trauma
- Note, of fragility fractures in general population:
 - 50% occur among those with $BMD < -2.5$ SD
 - 95% are associated with a fall
- Two studies have found increased fractures among HIV infected vs. uninfected
 - Triant *found 72% increase in fractures HIV+/-
 - Arnstein** found 38% increase --not statistically significant

*Triant et al *J Clin Endo and Metabolism* 2008 93:3499-504

**Arnstein et al *AIDS* 2007;21(5):617-23

Virtual Cohort (VC)

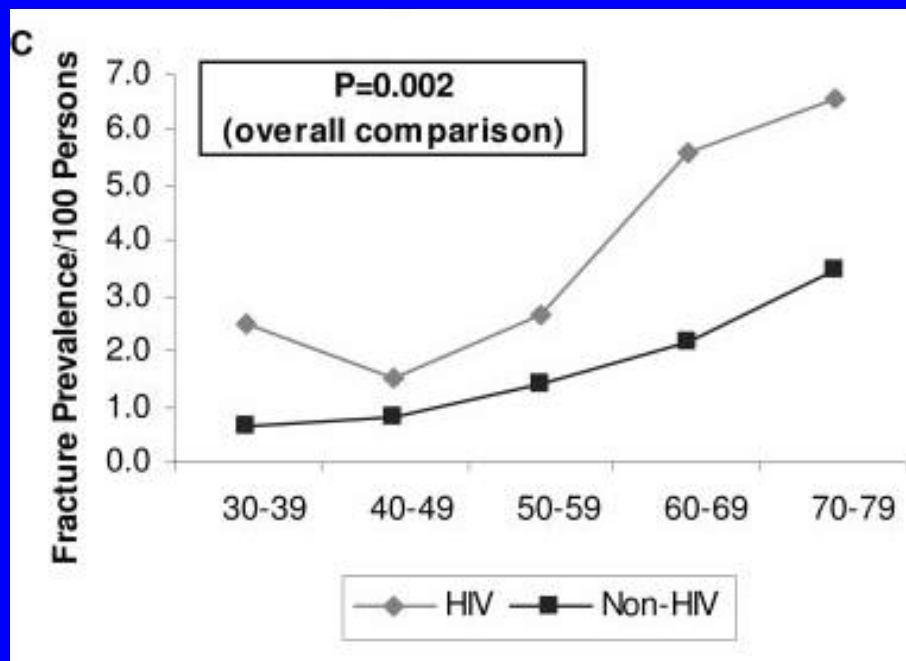
- **CURRENT DATA SOURCES:** National administrative, laboratory, pharmacy, cancer registry, MI quality of care, and all cause mortality (requesting Medicare)
- **SUBJECTS:** 41,753 HIV infected; 83,506 uninfected
 - All individuals with HIV diagnoses
 - Age, race/ethnicity, region 2:1 matched controls
 - 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

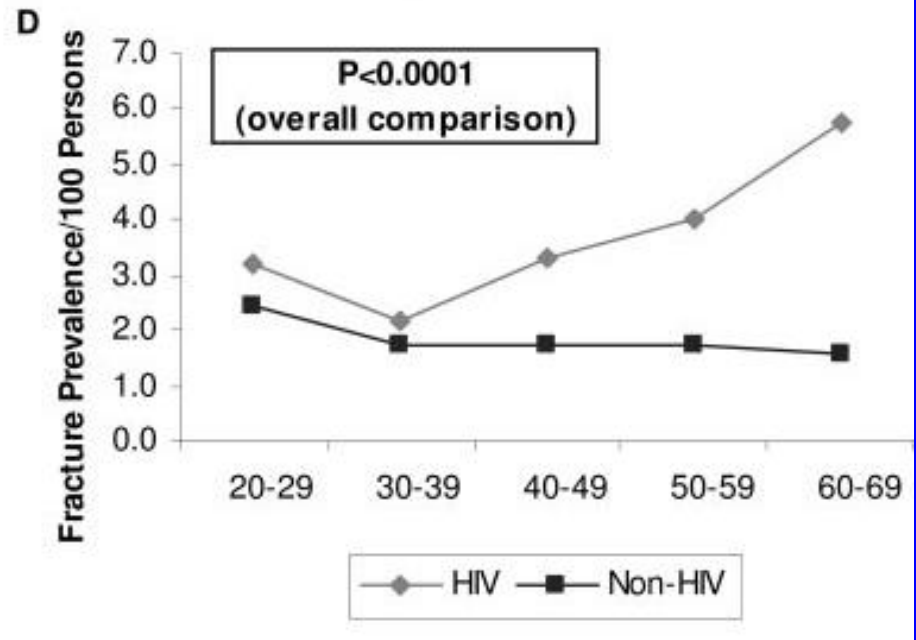
- CURRENT DATA SOURCES (VC sources plus)
 - Consented for all clinical data
 - Records for sentinel events requested outside VA
 - All VA Electronic medical records including text fields
 - DNA and tissue bank
 - Annual self completed surveys
- SUBJECTS: 3,600 HIV infected; 3,600 uninfected
 - Group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

Fragility Fracture Cumulative Incidence

Women

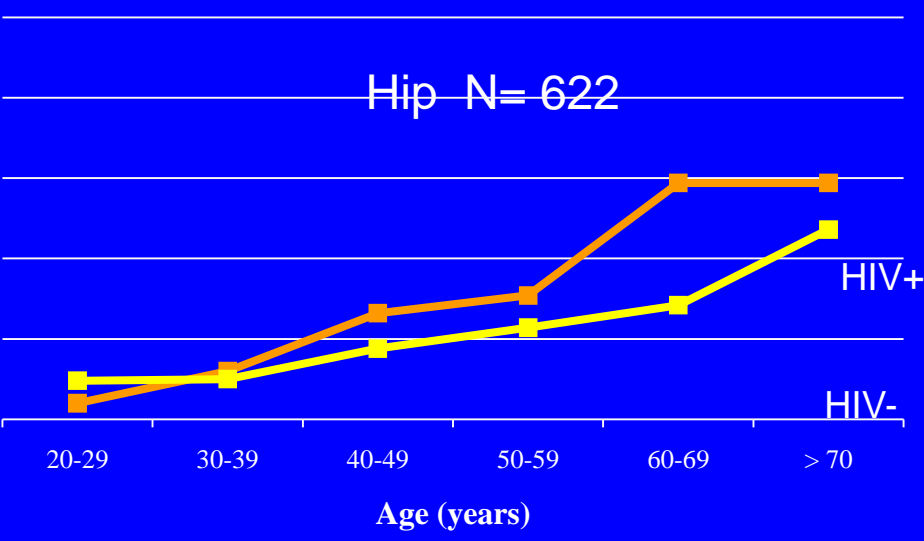
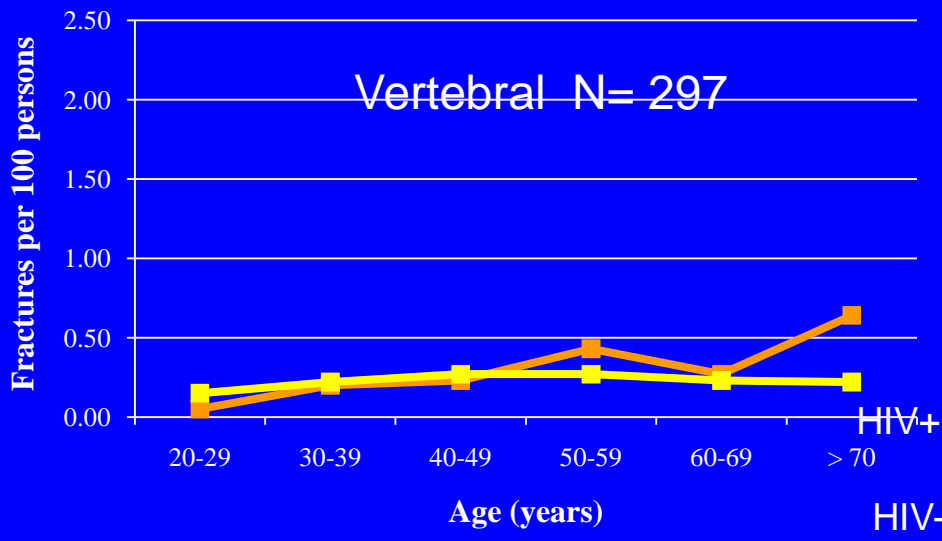
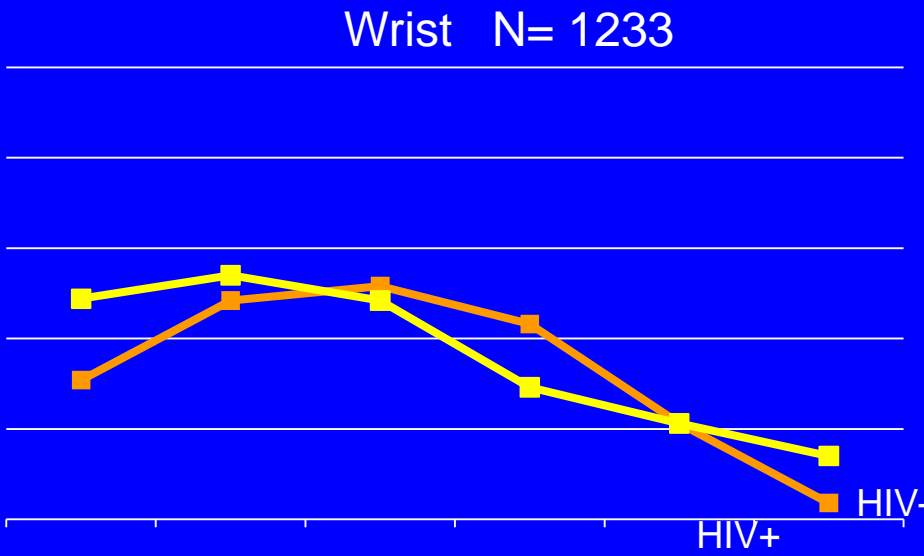
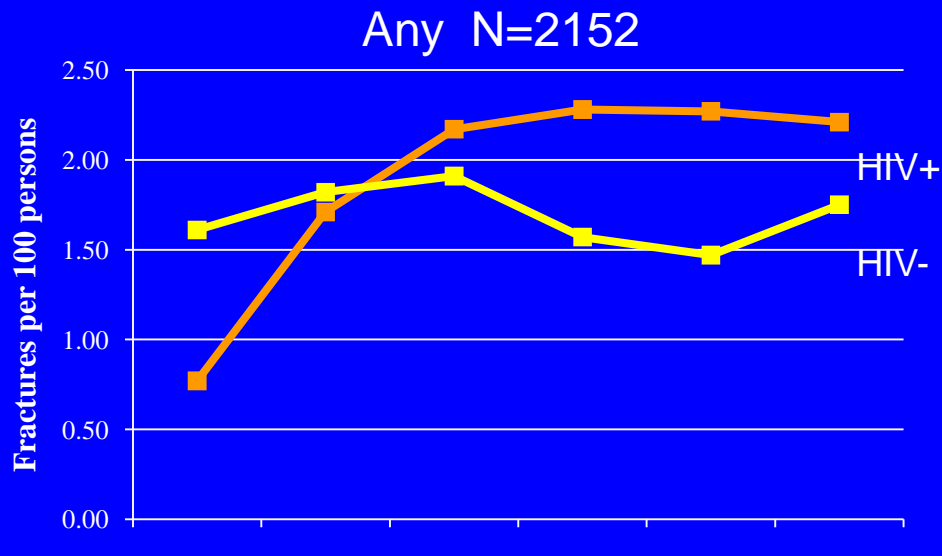


Men



Includes fractures caused by violent injury. Not adjusted for Body Mass Index, smoking, alcohol, prior fracture, functional status or BMD.

VACS VC Cumulative Incidence in Men



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)
HIV	1.53 (1.34, 1.75)	1.38 (1.18, 1.60)	
Cachexia (BMI<19)		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 before 1999		0.75 (0.64, 0.87)	0.89 (0.69, 1.14)
CD4 (per 100 cells/mm ³)			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. *Womack J. et al. Abstract #129 CROI 2010*

Prevention of Fragility Fractures

- Behavior
 - Alcohol and smoking cessation
 - Exercise and weight maintenance
 - Falls prevention in the home
- Nutrition
 - Avoidance of wasting
 - Calcium, Vitamin D
- Bisphosphonates (Alendronate, Risedronate, etc.)
 - Likely indicated for those with BMD -2.5 SD
 - Unknown efficacy /toxicity in HIV
 - Toxicities: reflux, ulcers, esophageal cancer osteonecrosis

Implications For An Aging Epidemic

- HIV infection increases risk of 'non AIDS' conditions
- HIV associated risk is modest compared to most established risk factors
- Care guidelines for non-AIDS condition may require adaptation for those with HIV
 - Some conditions may justify earlier ARV treatment
 - Selected ARV treatments likely cause some conditions, but effects are often less than those of HIV itself

“Short List” of Aging Conditions More Common Among those with HIV

- Lung diseases (COPD, pulm. hypertension, cancer)
- Liver diseases (fibrosis/cirrhosis and cancer)
- Renal diseases (insufficiency, failure)
- Vascular diseases (MI, stroke)
- Hematologic diseases (anemia, thrombocytopenia)
- Neurological diseases (dementia, neuropathy)
- Bone diseases (osteoporosis, avascular necrosis)

How Do We Prioritize Care?

- List of conditions of concern overwhelming
- Impact of prevention and treatment varies
- How do we compare effectiveness of many available interventions to prioritize care?

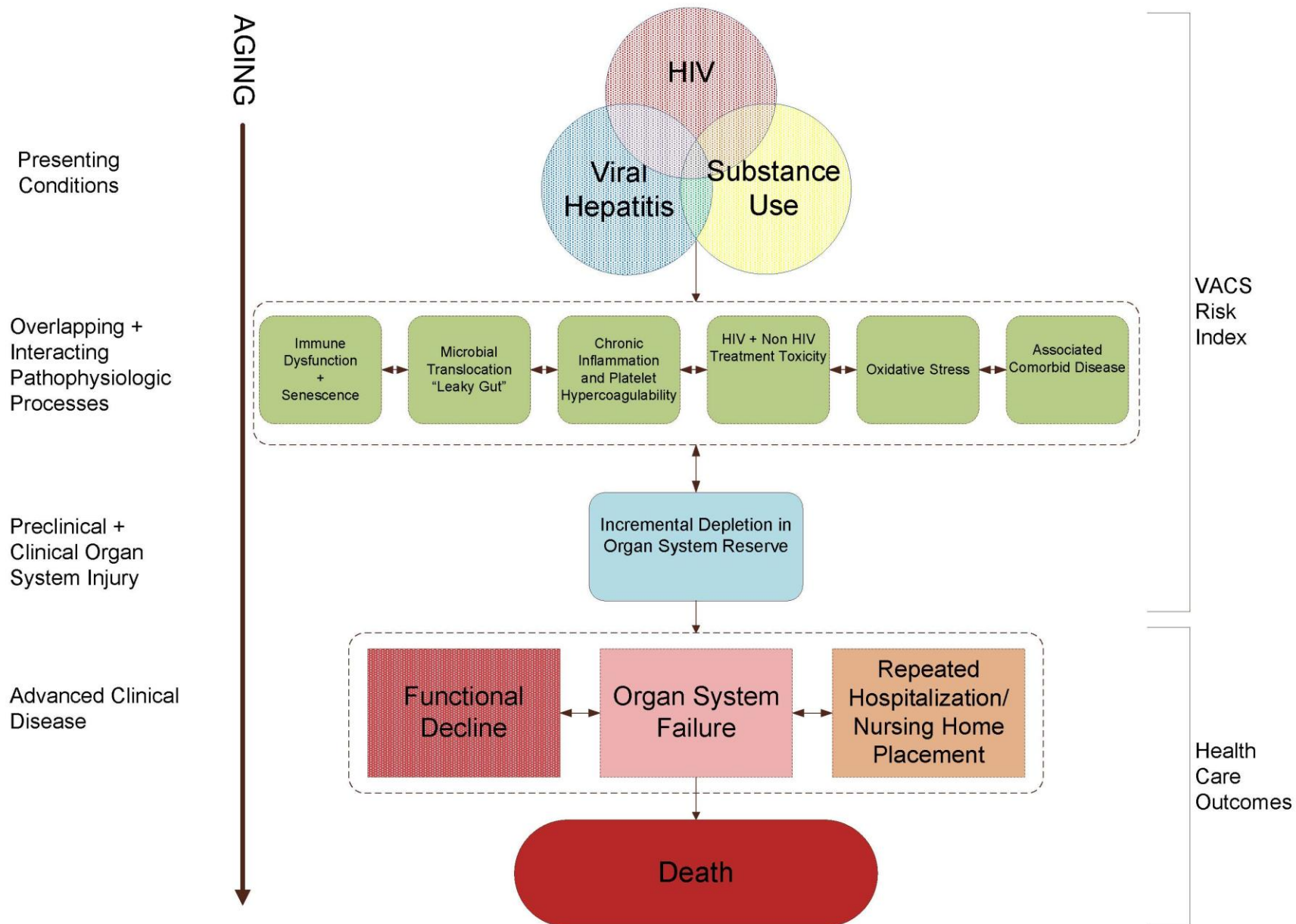
Comparative Effectiveness

- Rank interventions according to effectiveness among those with HIV infection
- Requires a consistent measure of benefit
 - Survival (no longer an option)
 - CD4 cell count, HIV-1 RNA (do not capture all important effects)

We Need a Comprehensive Index

- That reflects
 - Risk of morbidity and mortality
 - Changes in risk over time
 - Due to behavior change (alcohol, tobacco, & drugs)
 - Due to treatment (cART, HCV Rx, etc)
- To
 - Motivate behavior change
 - Monitor effectiveness of care
 - Compare cost effectiveness of interventions
 - Individually tailor and prioritize care

Aging, HIV Infection and Outcomes



VACS Risk Index

An index composed of routinely collected laboratory values that accurately predicts all cause mortality and morbidity among those with HIV infection

Components of VACS Risk Index

- Age
- HIV-1 RNA
- CD4 Count
- Hemoglobin
- Composite Biomarkers for
 - Liver Injury: FIB 4
 - Renal Injury: eGFR

Composite biomarkers

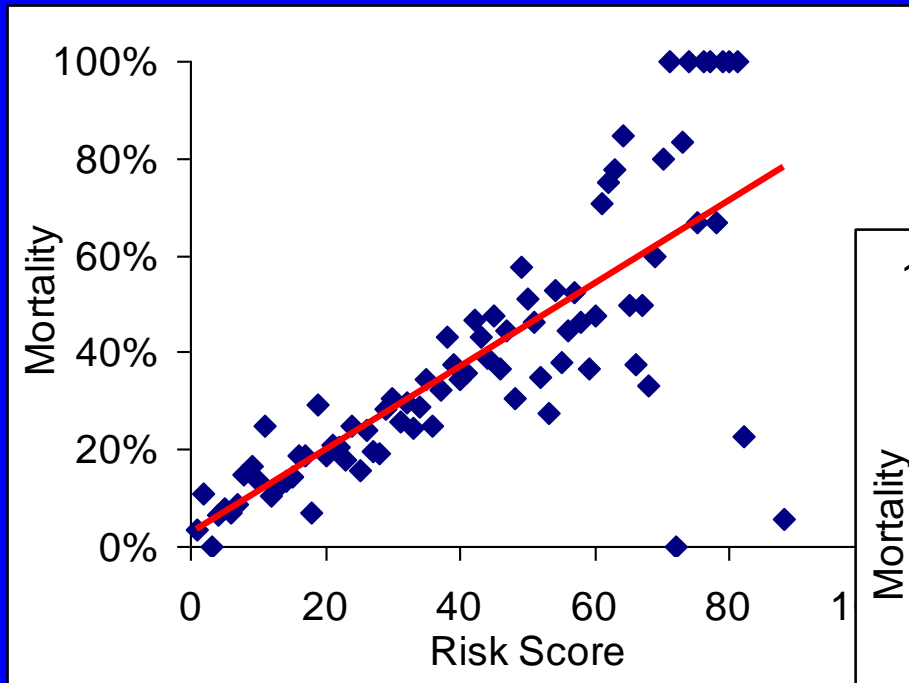
$$\text{FIB 4} = \frac{\text{AGE} * \text{AST}}{\text{PLT} * \text{sqrt}(\text{ALT})}$$

$$\text{eGFR} = 186.3 * \text{CREAT}^{-1.154} * \text{AGE}^{-0.203} * \text{FEM_VAL} * \text{BLACK_VAL}$$

FEM_VAL = 0.742 if female, 1 if male

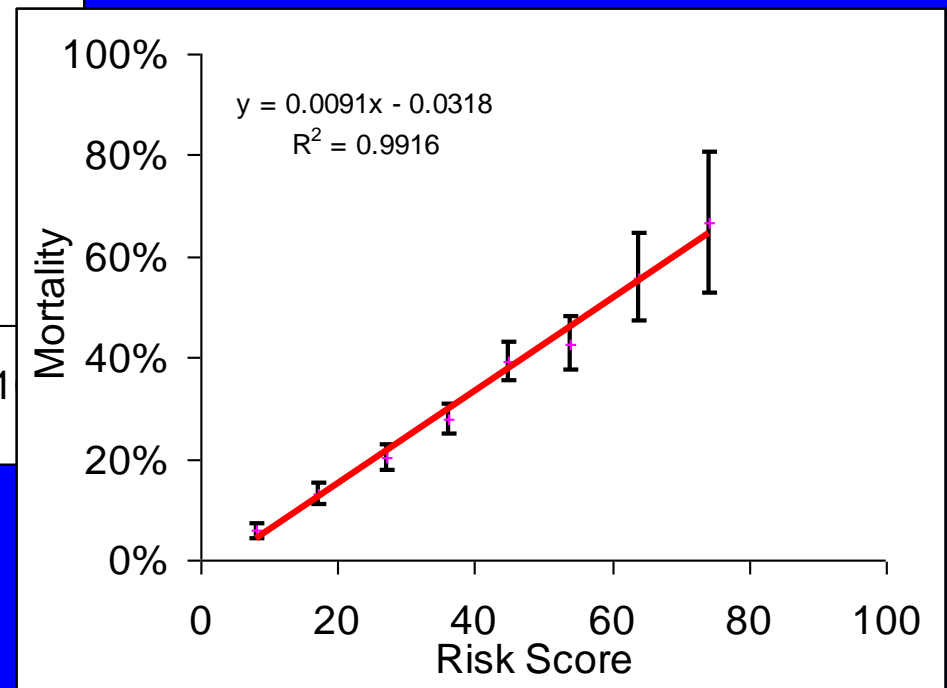
BLACK_VAL = 1.21 if black, 1 otherwise

VACS Index Highly Predictive of Long Term (5 Year) All Cause Mortality

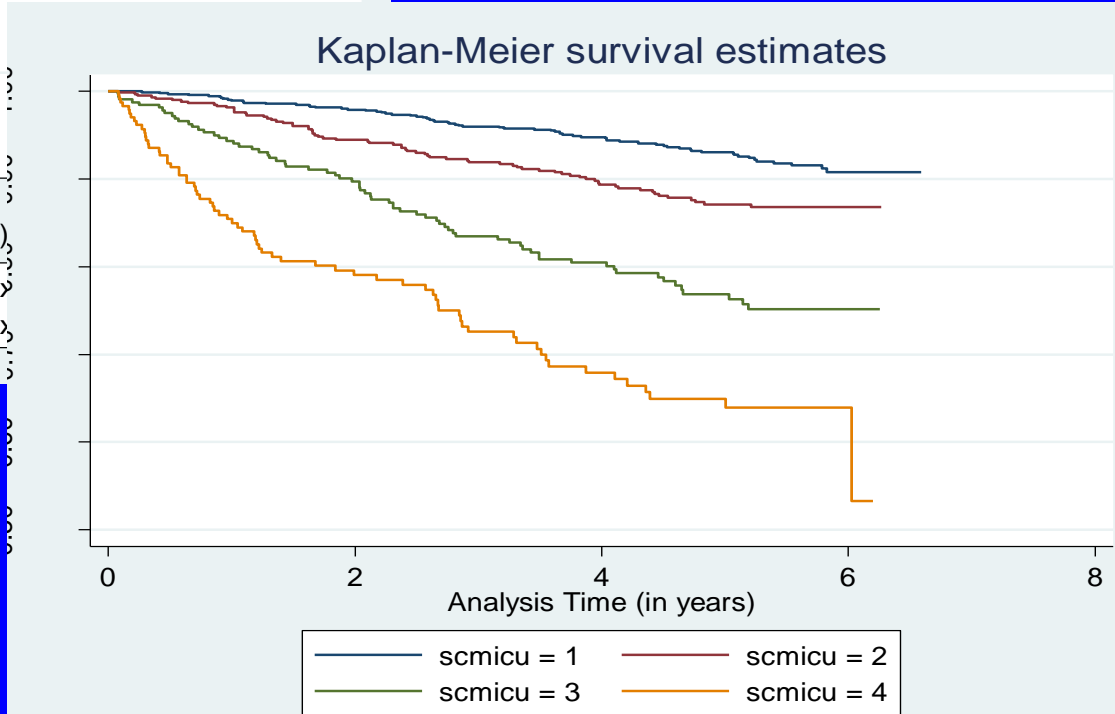
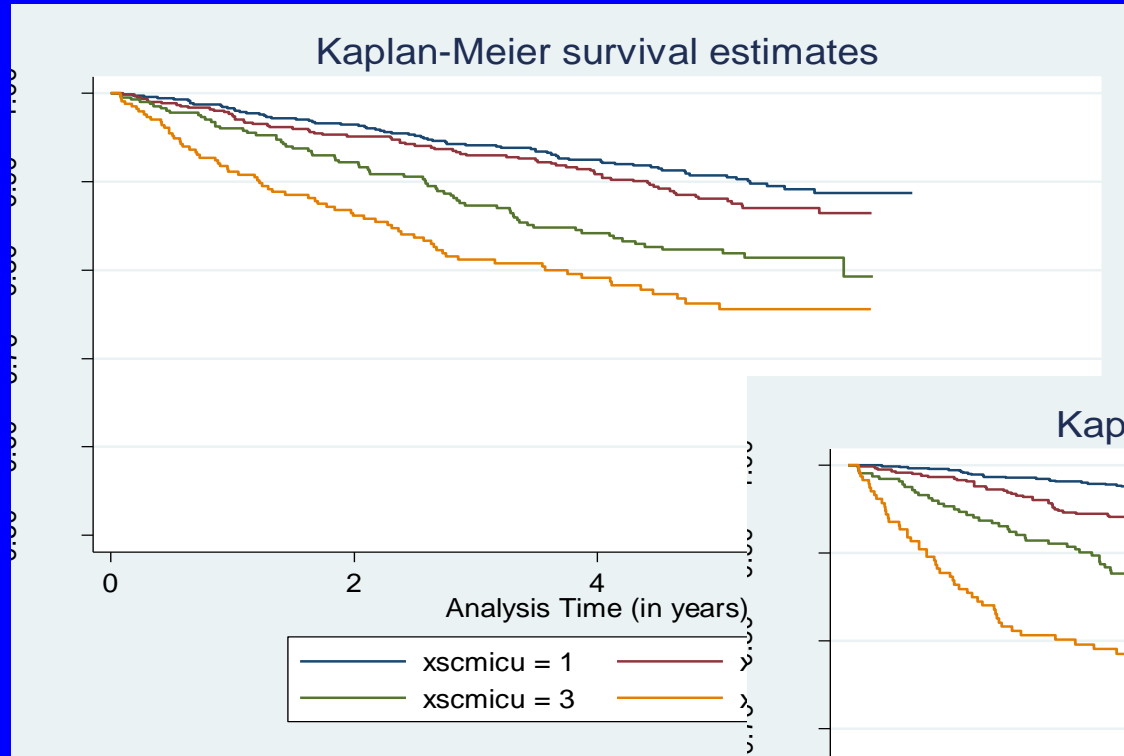


Individual Scores

Aggregated Scores



VACS Index Predicts MICU-Admissions Better than CD4 and HIV-1 RNA Alone



Akgun K. et al. American Thoracic Society 2010 . A5199

ARS Question

Validation Work Nearing Completion

- Determined weights to use after cART
 - CD4, HIV-1 RNA, and hemoglobin increase
- Demonstrated Index generalizes outside VA
 - ART-CC, beginning work in NA ACCORD
- Demonstrated Index works as a surrogate
 - See poster, 2010 International AIDS Meeting

Major Next Steps for Index

- Correlate with markers of inflammation
- Test responsiveness to change (behavior and treatment)
- Test morbidity prediction
 - Hospitalization, MICU admission, nursing home
 - Health related quality of life
 - Disability



National VACS Project Team 2010

An Example...

55 yr. old male (HCV -, HIV +) with undetectable viral load, a cd4 count of 250, a normal AST, ALT, platelets, and creatinine who has a normocytic hemoglobin of 10 mg/dL with inappropriately low reticulocyte count. He has been on the same cART regimen for 5 years. What do you do

A.



Veterans Aging Cohort Study

- **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
- **Staff:** D Cohen, A Consorte, K Gordon, F Kidwai, F Levin, K McGinnis, J Rogers, M Skanderson, J Tate, Harini, T Boran
- **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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