

HIV and Aging: Time for a New Paradigm

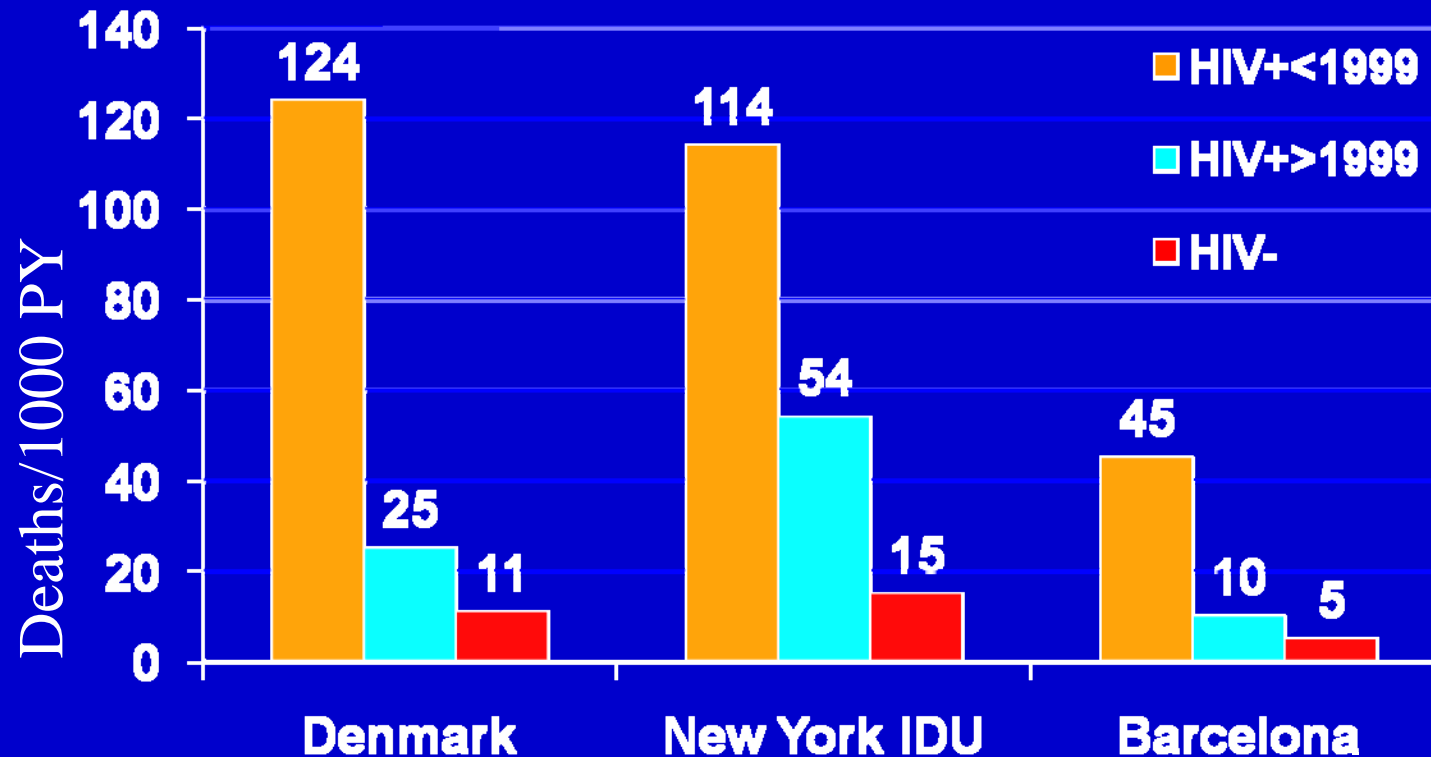
Amy C. Justice, MD, PhD
Associate Professor of Medicine and Public Health
Yale University

Overview

- People are aging with HIV and older individuals are becoming infected
- AIDS conditions are less common and variably associated with outcome
- Non AIDS disease (comorbidity) is influenced by HIV, treatment, and behaviors, and conditions associated with HIV infection
- We need a new paradigm for care

People are aging with HIV
and older individuals are becoming
infected.

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 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%

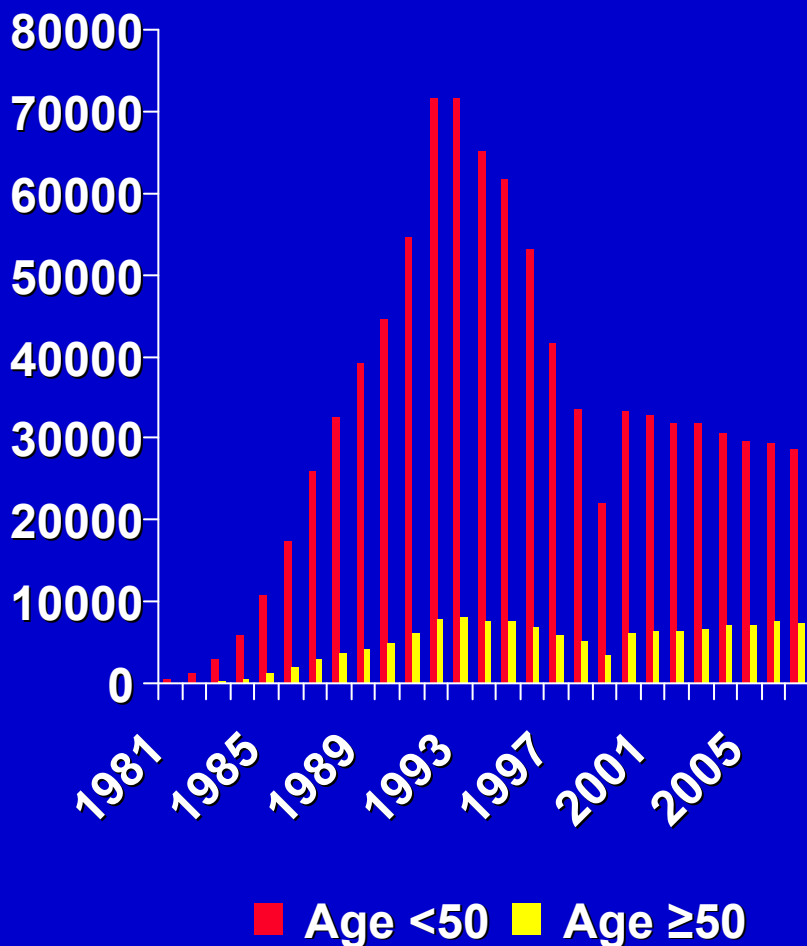
Adapted from *ART-CC, Lancet 2008;372:293-99* by adding additional expected survival to age at treatment initiation.

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

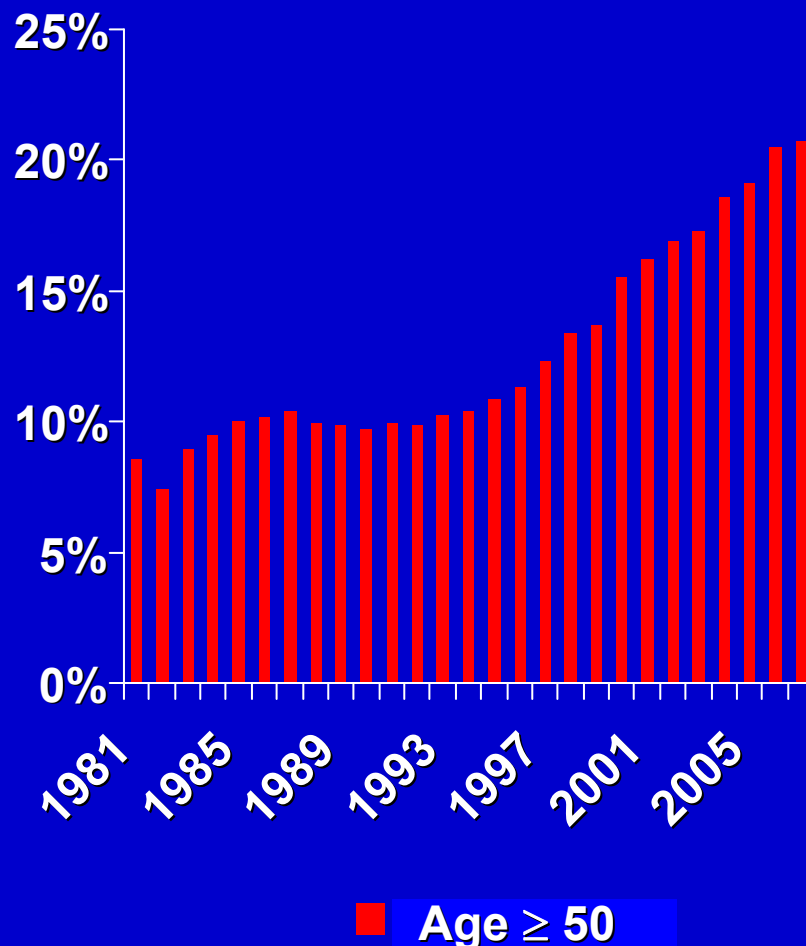
Aging Hearing: HIV over fifty, exploring the new threat.
Senate Committee on Aging. Washington, DC. 2005.

Older People are Becoming Infected: New US AIDS Cases

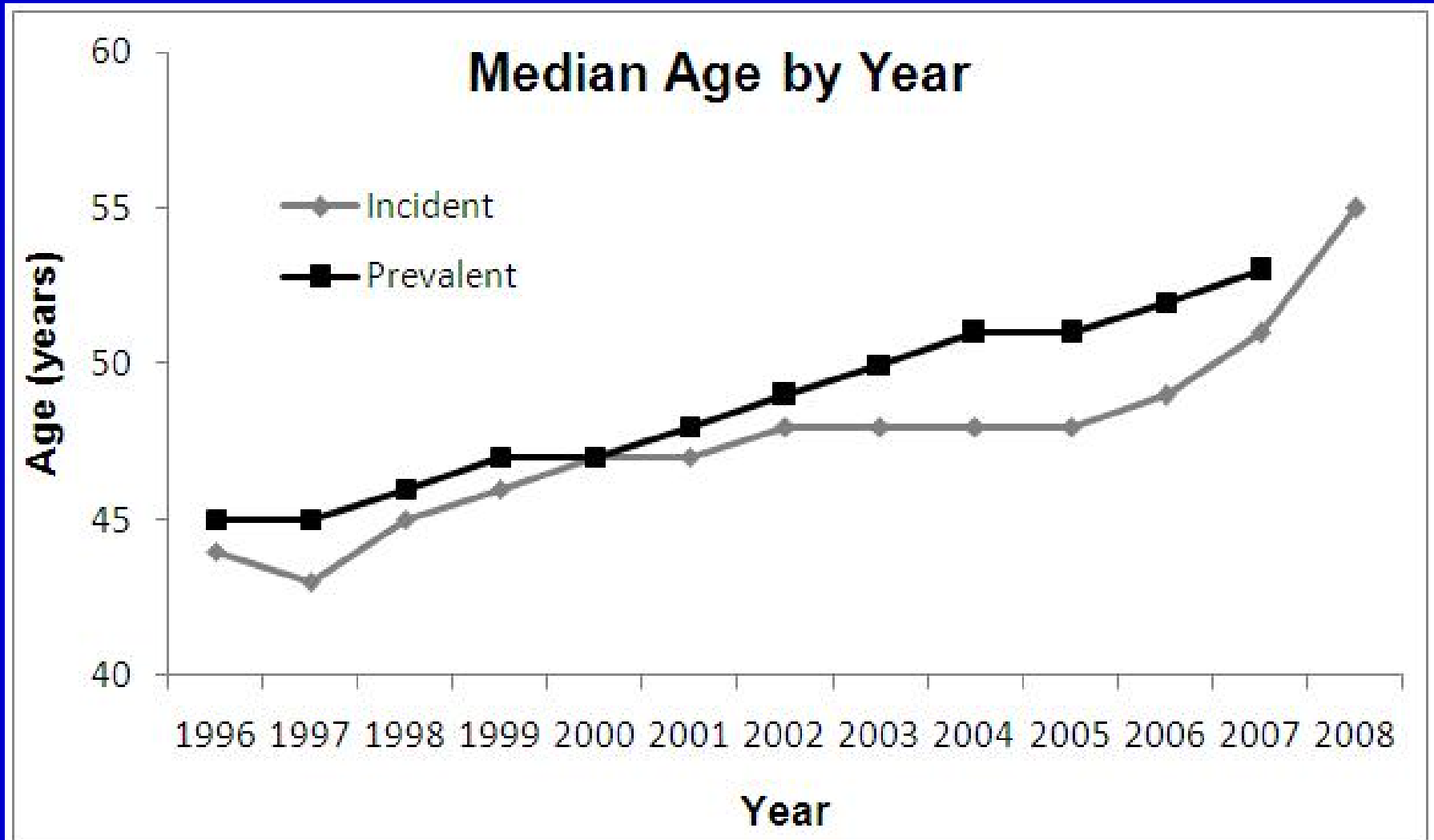
Number of New Cases per Year



Distribution of New Cases



The VA is Ahead of the Curve



Age Associated Response to cART

- Viral Response
 - Older patients have better virologic response
 - Explained by superior adherence
- CD4 Response
- 1 year improvement not as good
- 3 year similar to younger pts.

AIDS conditions are less common
and variably associated with
mortality.

AIDS Events Are Decreased on cART

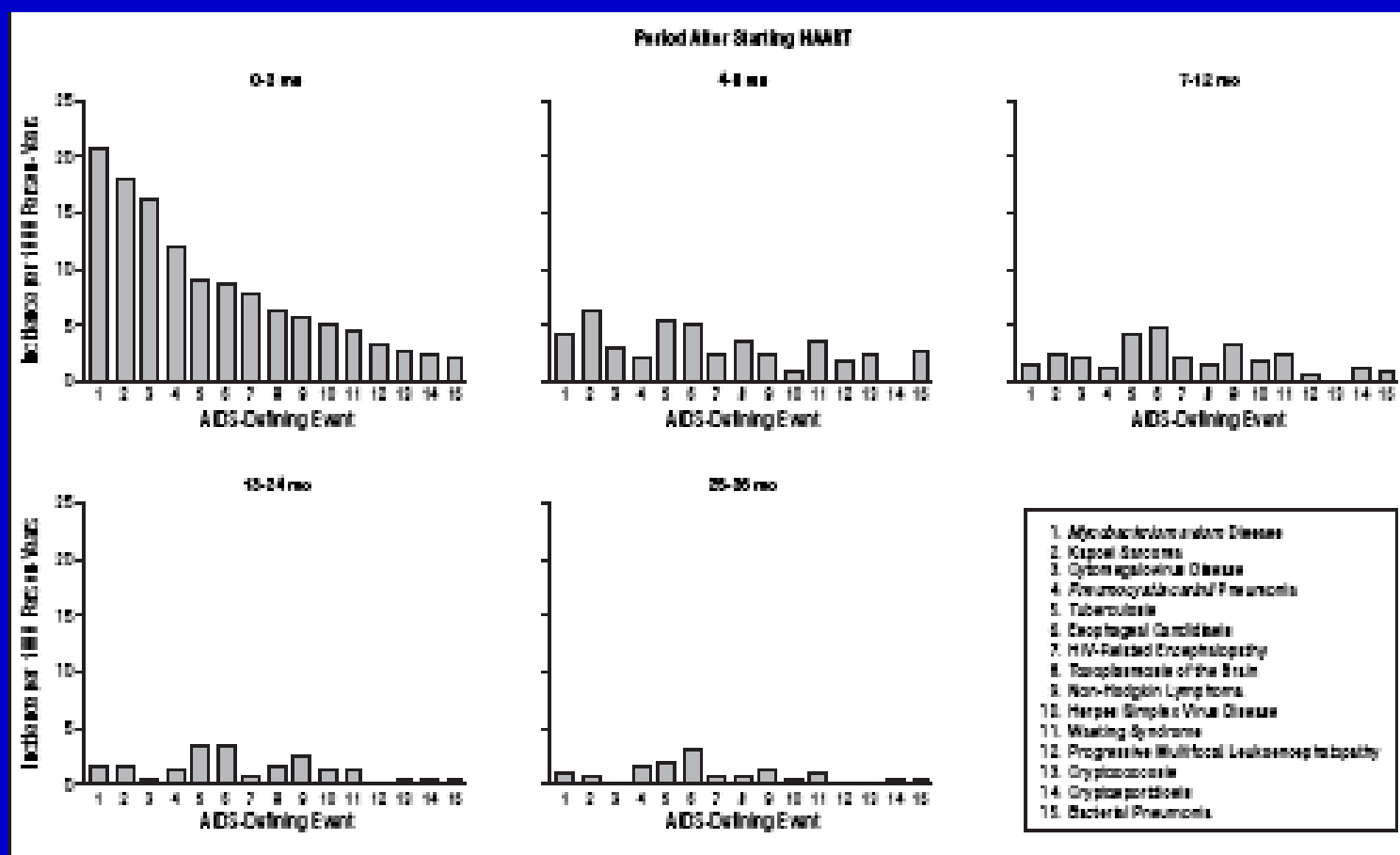
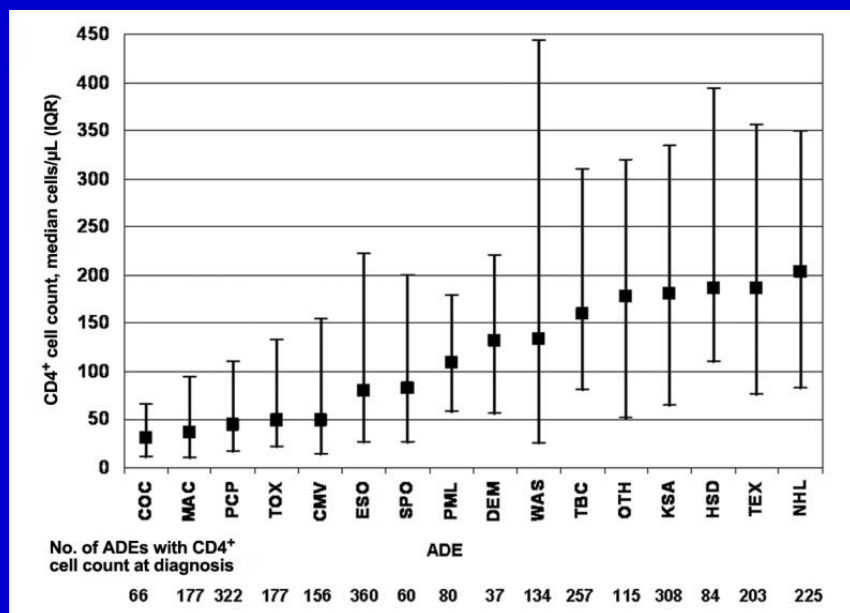


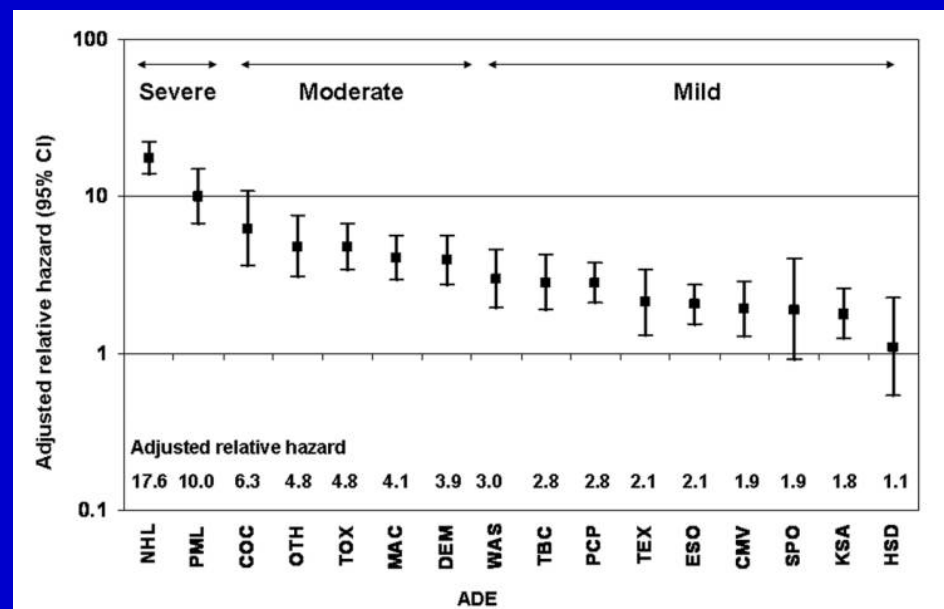
Figure 1. Incidences of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART).

AIDS Events are Variably Associated with CD4 and Survival

By Median (IQR) CD4



By Relative Hazard of Death



“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

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

Non AIDS disease is influenced by HIV, treatment, and behaviors and conditions associated with HIV infection.

Case History: Liver Disease

- 52 year old, past intravenous drug user
- HIV/HCV
- cART (8 yrs) undetectable virus
- CD4 count 250
- Dies with hepatocellular carcinoma
- Was this an 'AIDS death'?

One Condition, Multiple Etiologies

- Substance use

- Drugs, **ALCOHOL**
- Cause of nonadherence

- Viral hepatitis

- Chronic Hepatitis C and B

- Medication toxicity

- **Antiretrovirals (nevaripine, D drugs)**
- Non-HIV medications

- **HIV infection**

- Chronic inflammation
- Immune compromise with deregulation

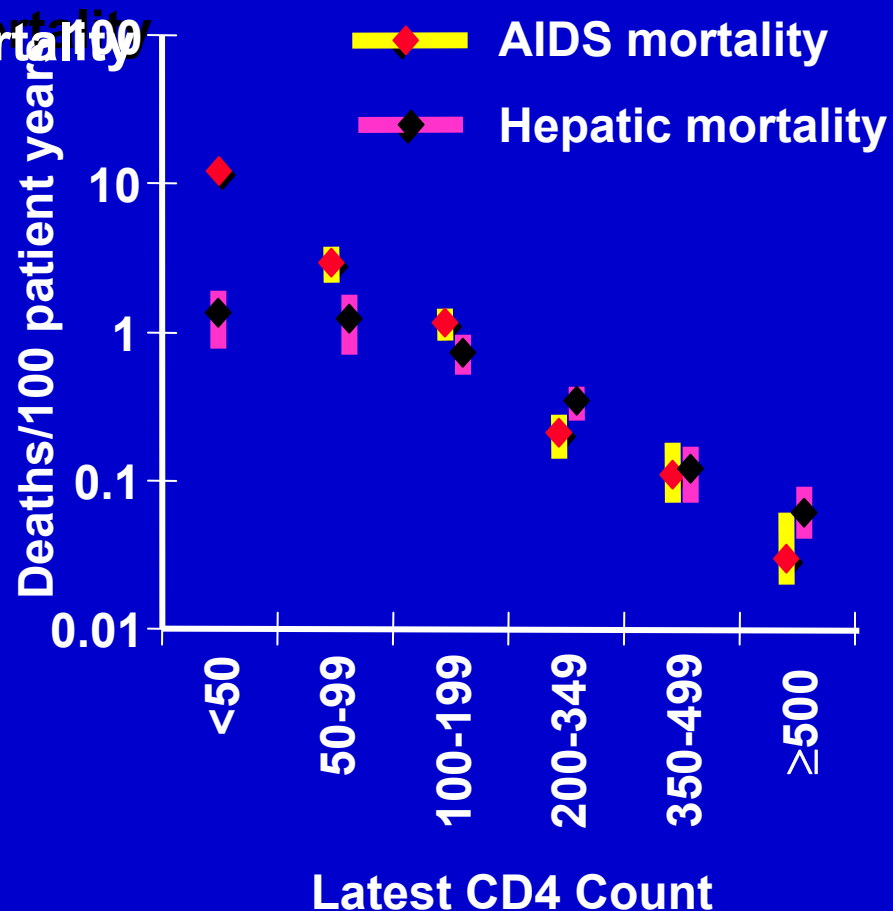
Liver
Disease

HIV and Hepatic Mortality

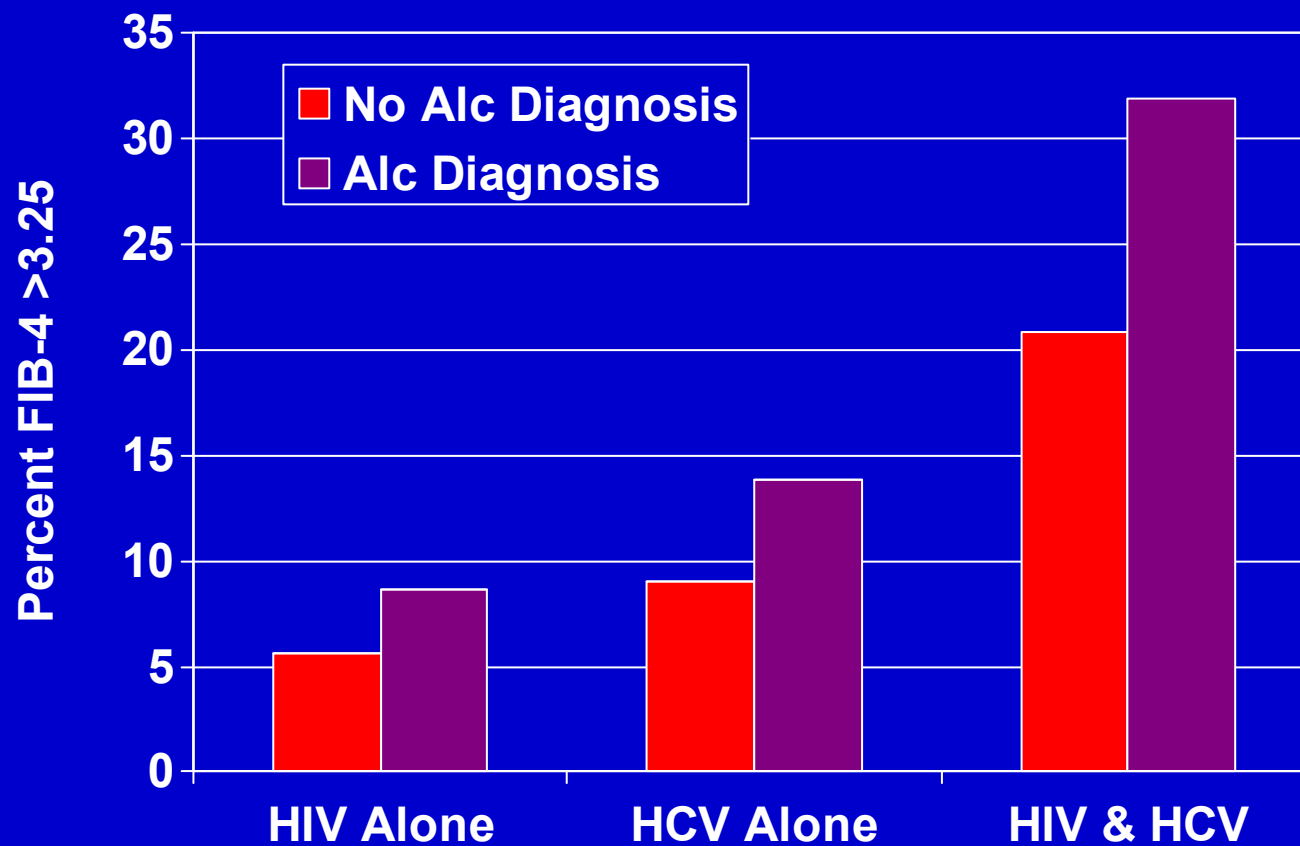
Risk Factors for Hepatic Mortality

	Relative Rate
Risk per 2x ↓ CD4	1.23
Risk per 1.0 log ↑ VL	1.27
Risk per 5 yr ↑ age	1.32
IDU	2.01
Active HBV infection	3.73
HCV infection	6.66

vs CD4 Count



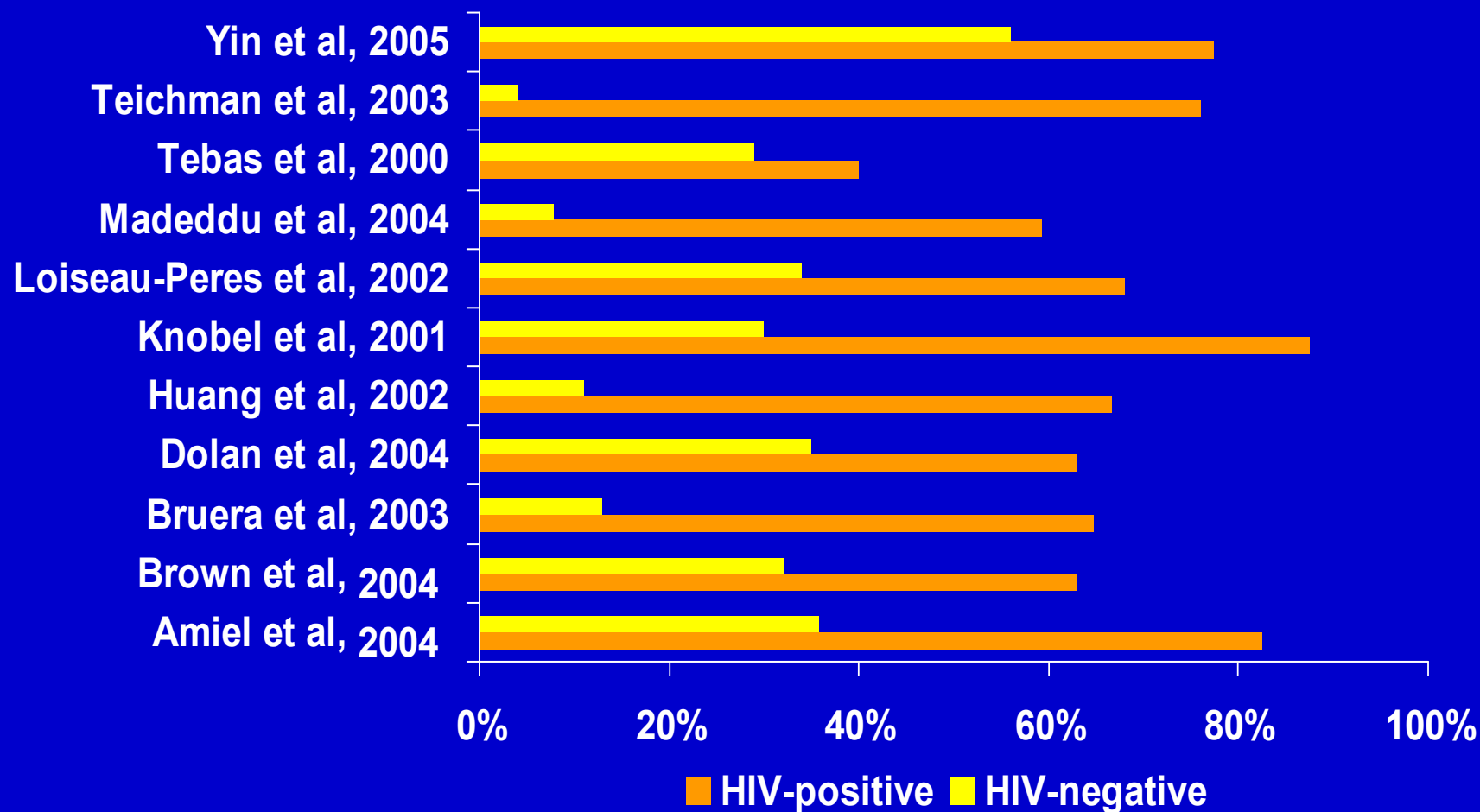
Alcohol & Liver Disease



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

Bone Mineral Density (BMD)

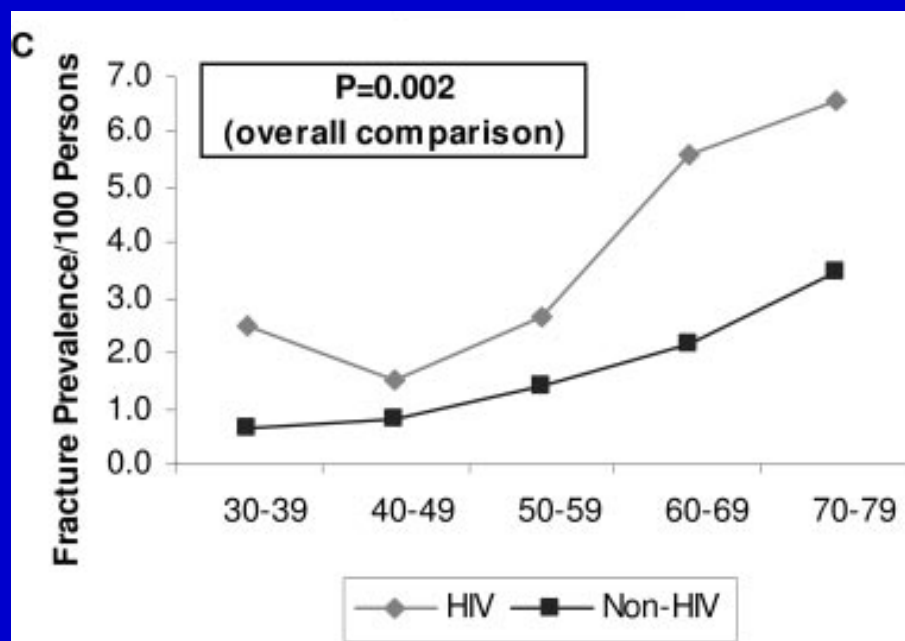


BMD Vs. Fragility Fracture

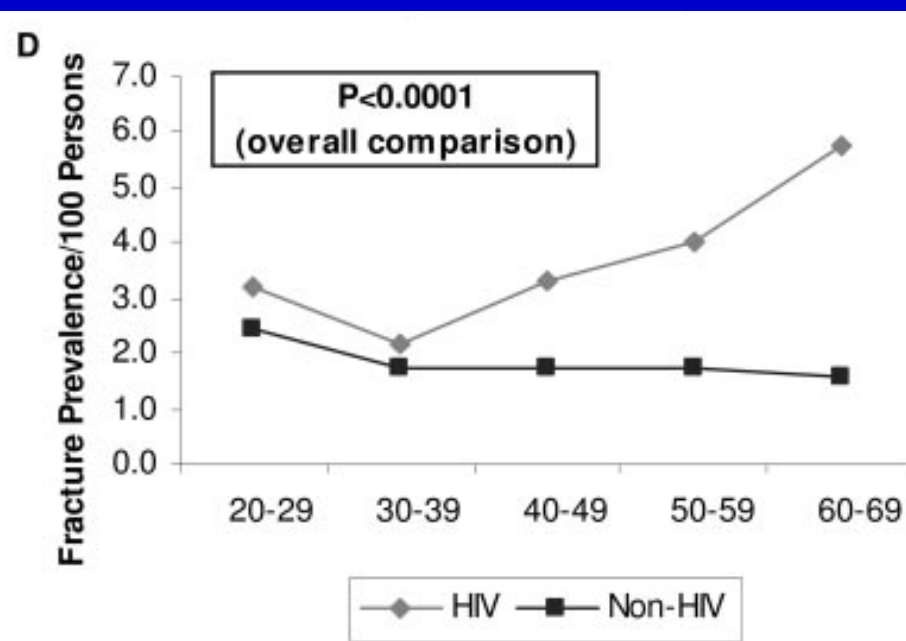
- Low BMD is a risk factor for vertebral, wrist, or hip fracture (fragility fracture)
- HIV and time on cART is associated with low BMD
- One age, race and gender, adjusted study has shown an increased risk of fragility fractures
 - 3.1 vs. 1.8 per 100 PY for HIV+/- men (72% increase)
 - 2.5 vs. 1.7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

'Fragility Fractures' by Sex, Age, and HIV Status

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*

Prevention of Fragility Fractures

- Behavior
 - Smoking and alcohol cessation
 - Weight bearing exercise
- Nutrition
 - Calcium
 - Vitamin D
- Bisphosphonates (Alendronate, Risedronate, etc.)
 - Toxicities: GI reflux, ulcers, esophageal cancer and jaw osteonecrosis
 - No efficacy demonstrated in HIV

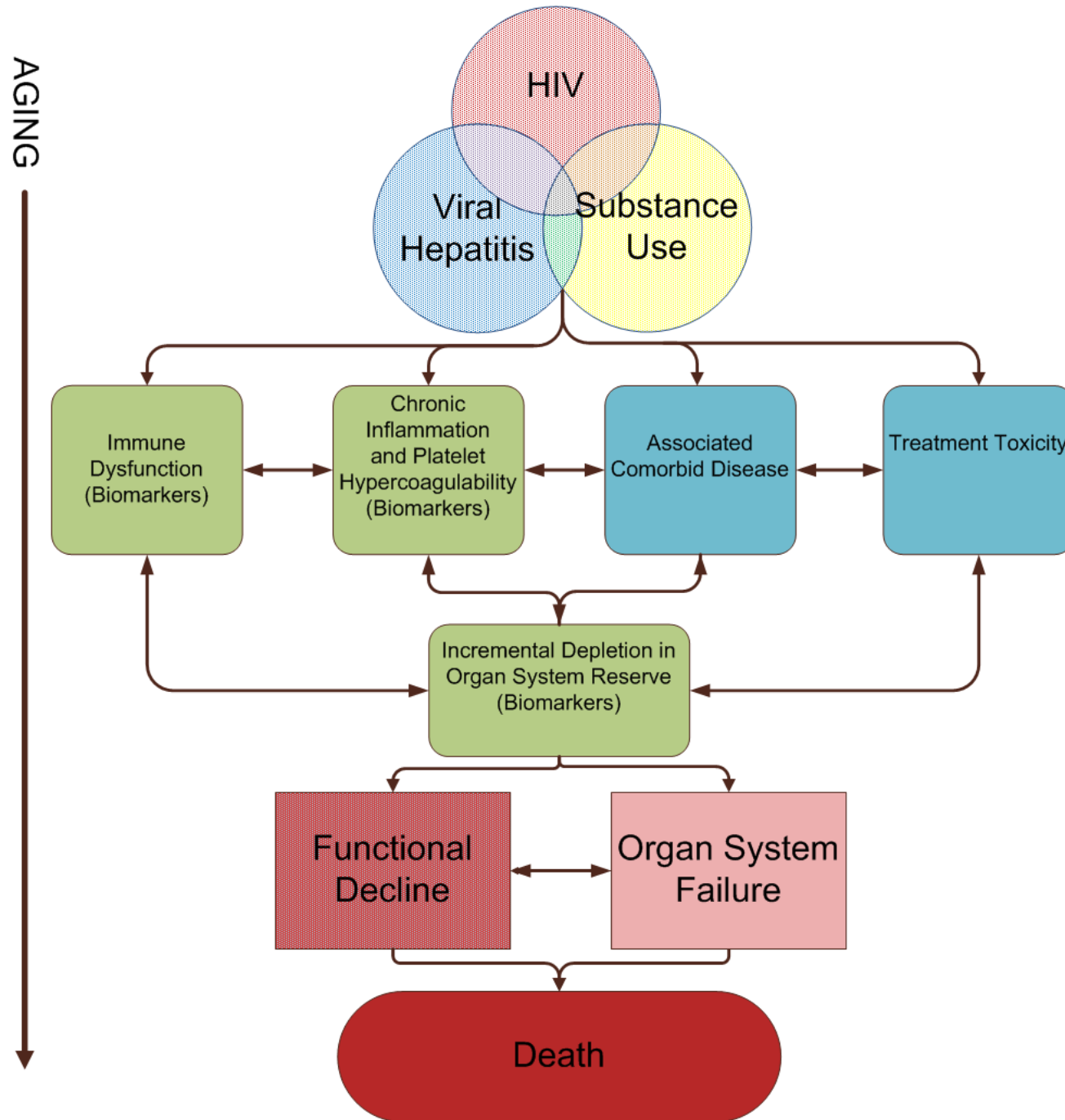
Why Does It Matter?

- If a condition is more likely or progresses rapidly due to HIV infection- *Early HAART may be indicated for those with or at high risk for the condition*
- If a condition is more likely or progresses rapidly due to a specific ARV or class- *Other ARVs or classes might be selected*
- If a condition is independent of HIV or its treatment- *Conventional approaches to management can be adapted to those with HIV*
- But, what if the condition is associated with all three?

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
- How can we assess total burden of disease and susceptibility to bad outcome?

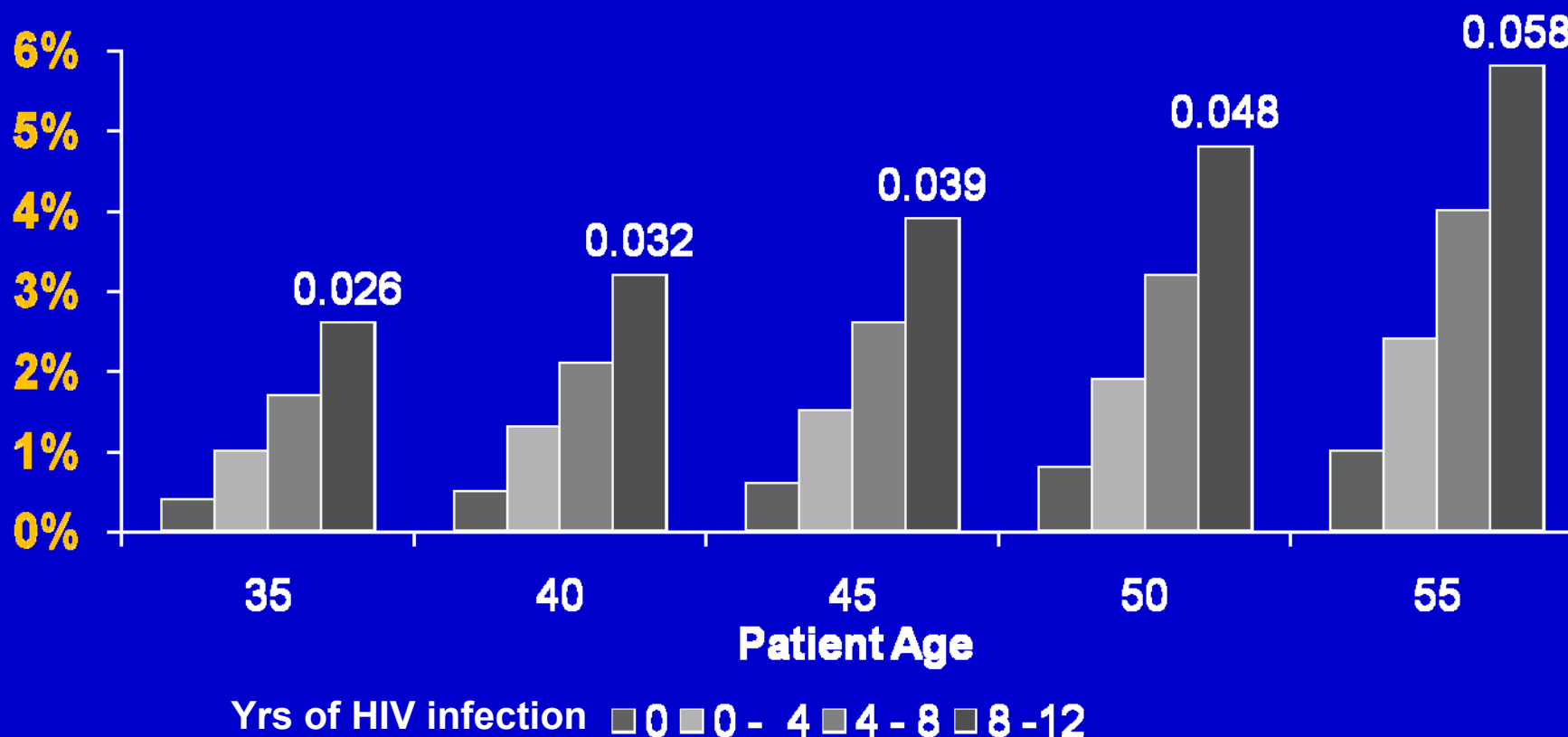
We need a new paradigm to effectively address important causes of morbidity and mortality for those aging with HIV infection.



Frailty Phenotype

- Developed in Cardiovascular Health Study
- Requires presence of 3/5:
 - Physical shrinking (weight loss $\geq 5\%$ in 1 yr)
 - Weakness (grip strength)
 - Slowness (walking time)
 - Exhaustion (subjective report)
 - Low Activity (subjective report)
- MACS Adaptation (no walking time) 3/4

Frailty Related Phenotype, Age, and HIV Infection



Functional Status

- Can be assessed by direct observation or by self report
- Ranges from activities of daily living (e.g., walking) to extreme exertion (e.g., running)
- Differentiates risk of mortality, but does not provide pathophysiologic insight

Is There a More Generally Applicable Approach?

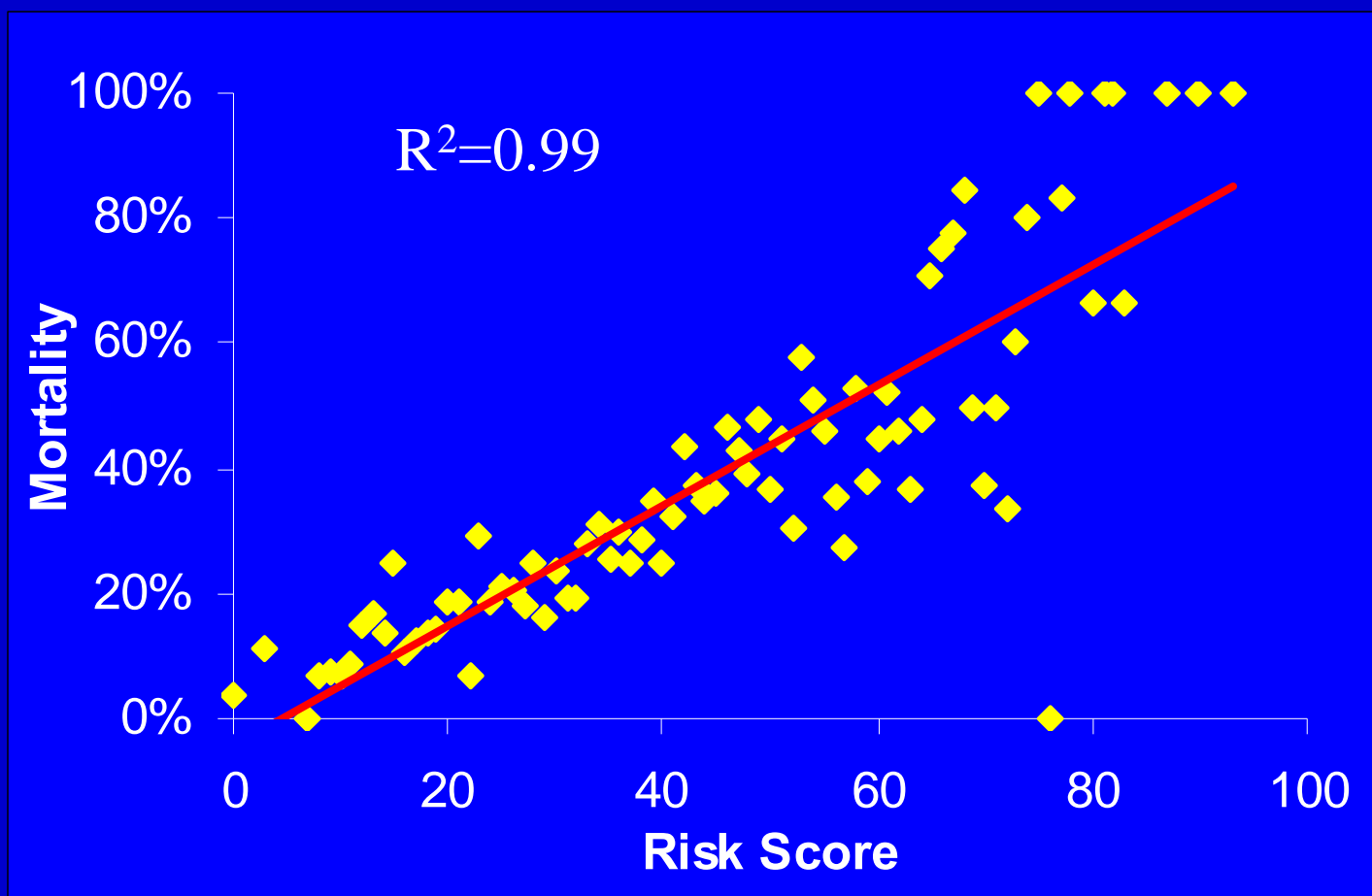
- CD4 and HIV-1 RNA necessary, not sufficient
- Frailty phenotype interesting, but uncommon
- Functional status promising, but does not offer causal insight
- Need a comprehensive risk index

		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

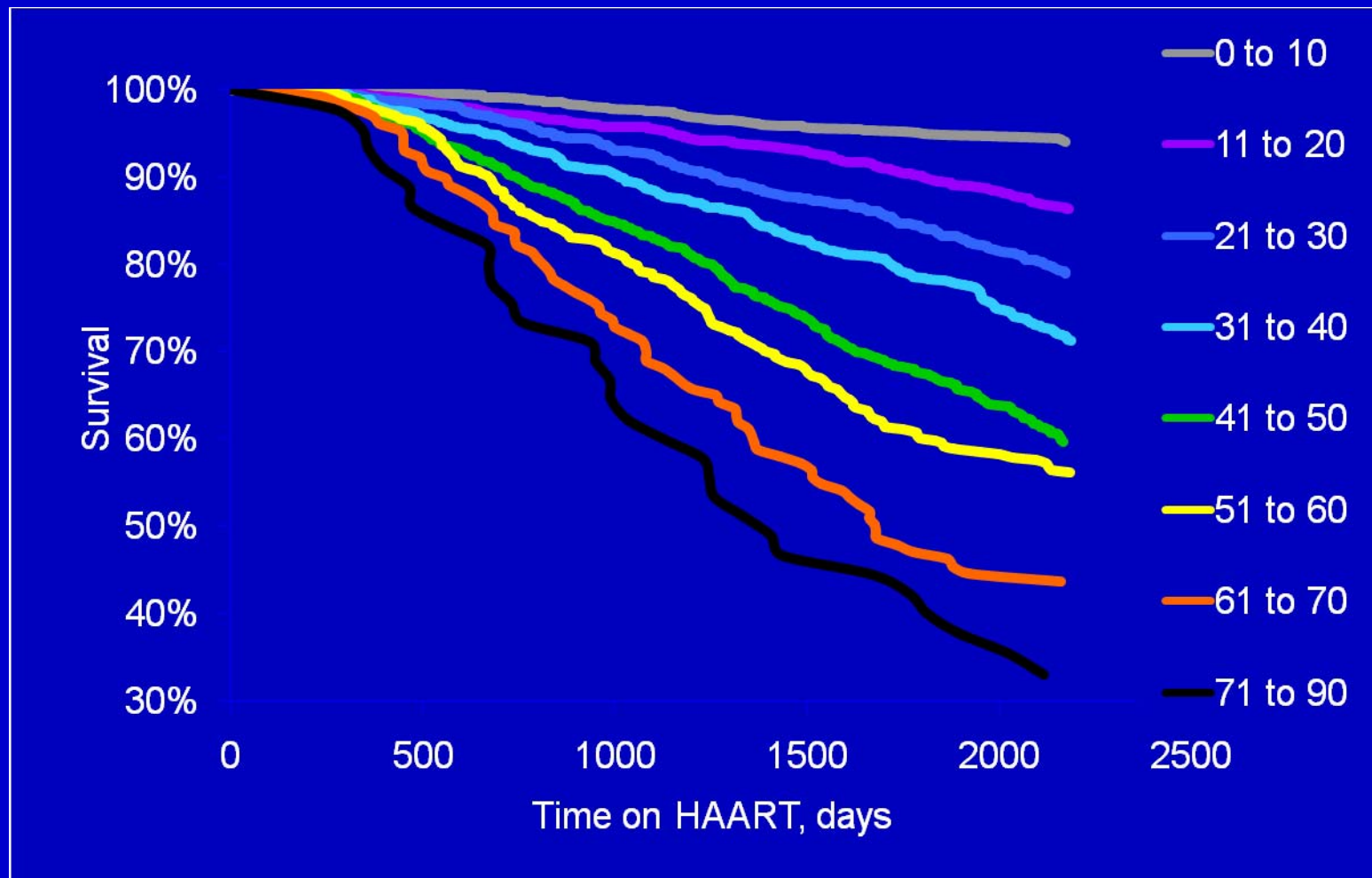
Veterans Aging Cohort (VACS) Risk Index

*Justice 2009 HIV Medicine
published electronically*

Individual Score Pre cART



Survival by VACS Index Score (6 years)



Implications For An Aging Epidemic

- HIV infection increases risk and progression of common infectious and noninfectious 'non AIDS' conditions
- Screening/treatment guidelines for non-AIDS condition must be tailored for those with HIV
- Some non-AIDS conditions may justify earlier or more aggressive ARV treatment
- Selected ARV treatments likely cause/exacerbate some non-AIDS conditions, but effects are often less pronounced than those of HIV itself
- We need a more integrated index of clinical indicators to follow our patient's integrated risk of morbidity and mortality



West Haven/Yale VACS Project Team



National VACS Project Team



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
- **Major Funding by:** National Institutes of Health: NIAAA (U10-AA13566), NIA (R01-AG029154), NHLBI (R01-HL095136; R01-HL090342) , NIAID (U01-A1069918), NIMH (P30-MH062294), 2009 ARRA award; and the Veterans Health Administration Office of Research and Development (VA REA 08-266) and Office of Academic Affiliations (Medical Informatics Fellowship).