# HIV and Aging: Time for a New Paradigm

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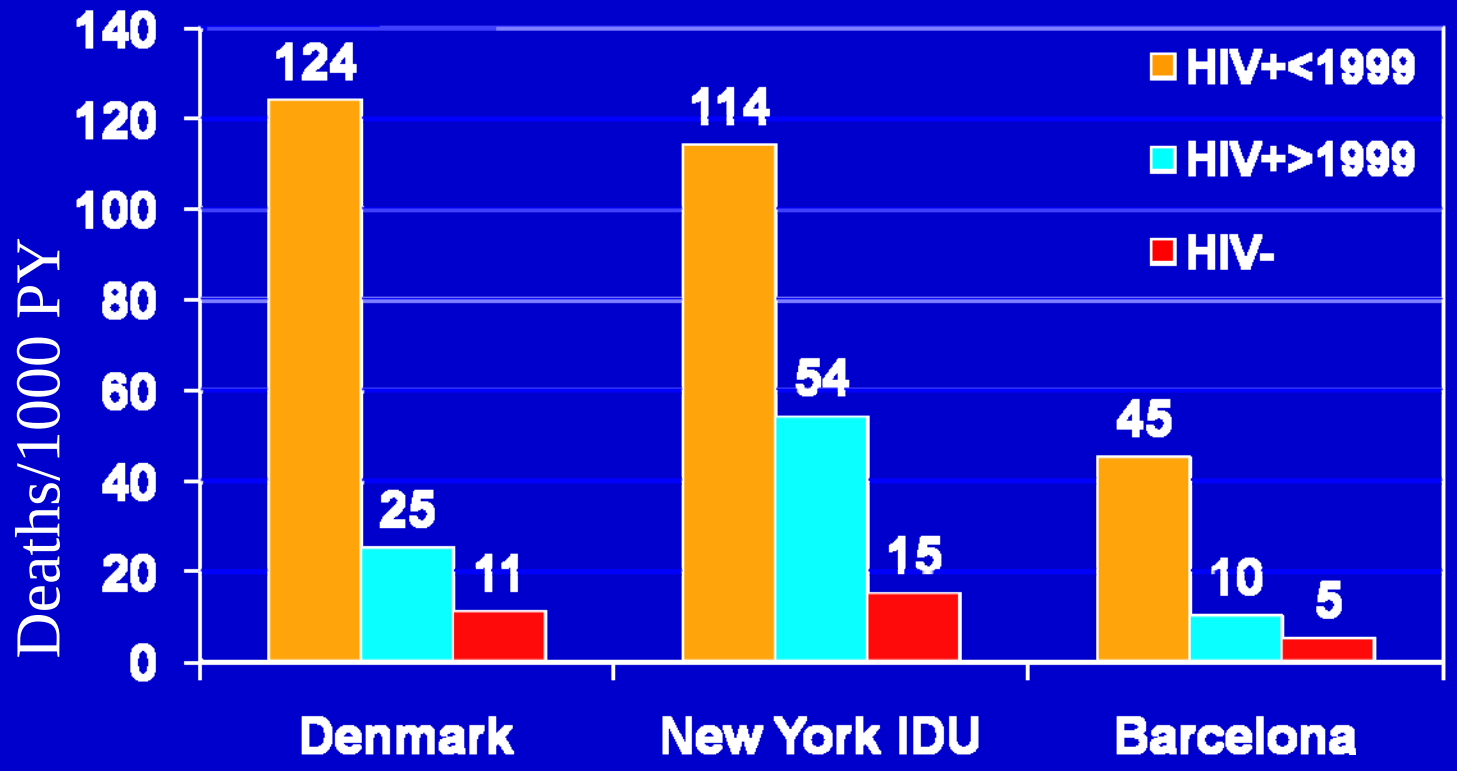
# Overview

- 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"

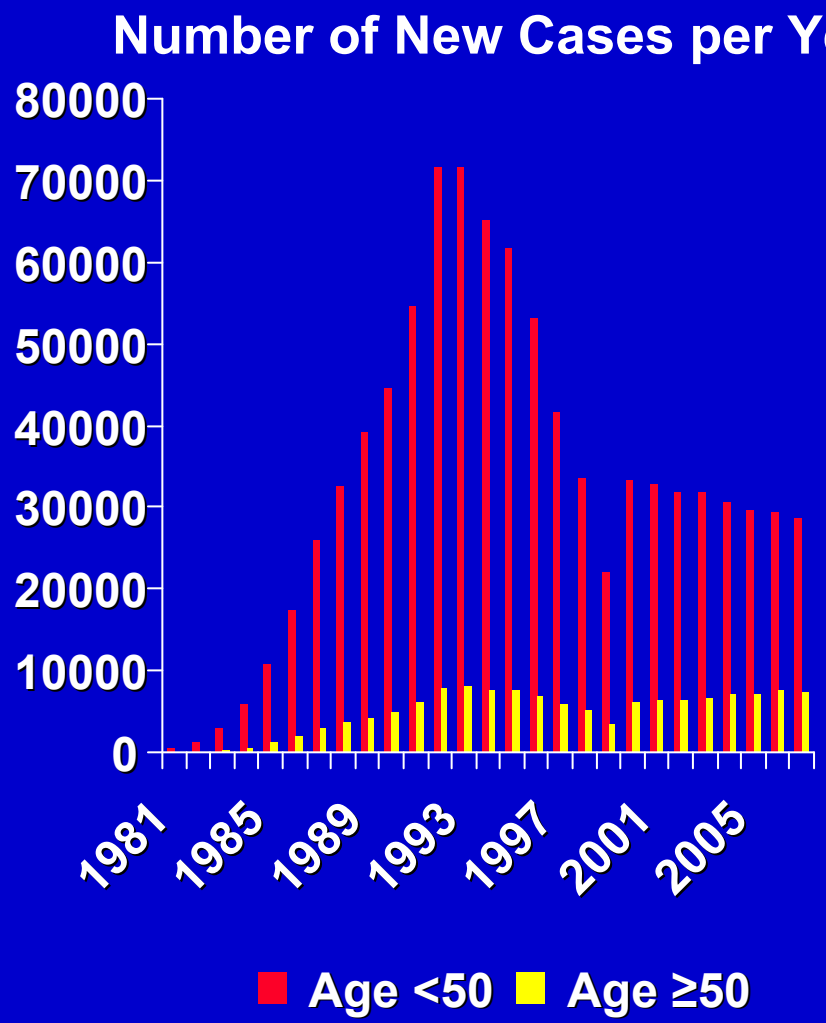
| At HAART Initiation | CD4 Cell Count ($mm^{3)}$ | | |
|---|---|---|---|
| | <100 | 100-199 | ≥200 |
| A 20 yr old will live to | 52 | 62 | 70 |
| A 35 yr old will live to | 62 | 65 | 72 |
| % Remaining Life Lost (all ages) | 46% | 27% | 14% |

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.

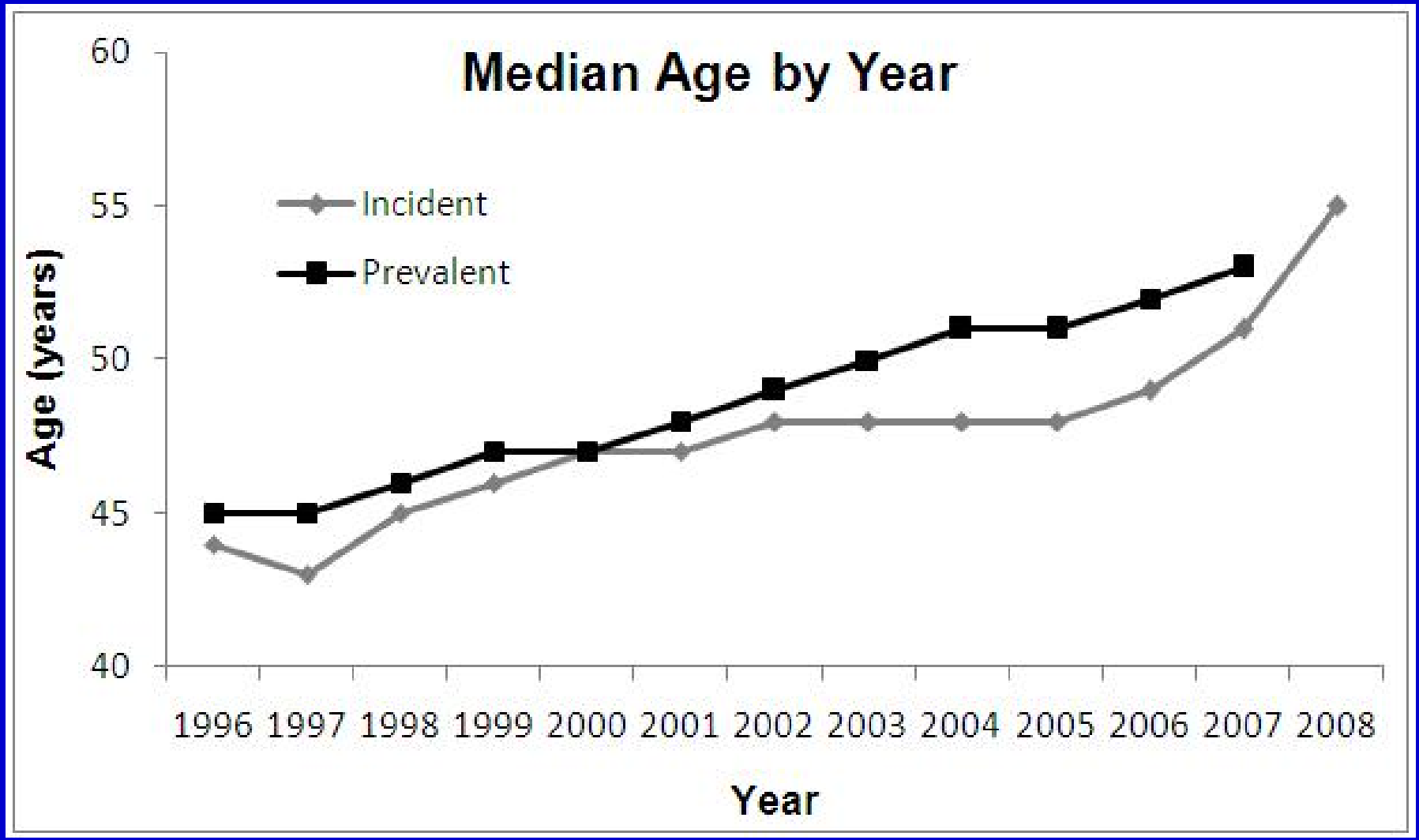
# Older People are Becoming Infected: New US AIDS Cases





*www.cdc.gov/hiv/topics/surveillance/resources/reports/2007report/default.htm*

# 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.

*Silverberg M. et al. Arch Intern Med 2007;167:684-691*

AIDS conditions are less common and variably associated with mortality.

# AIDS Events Are Deceased on cART

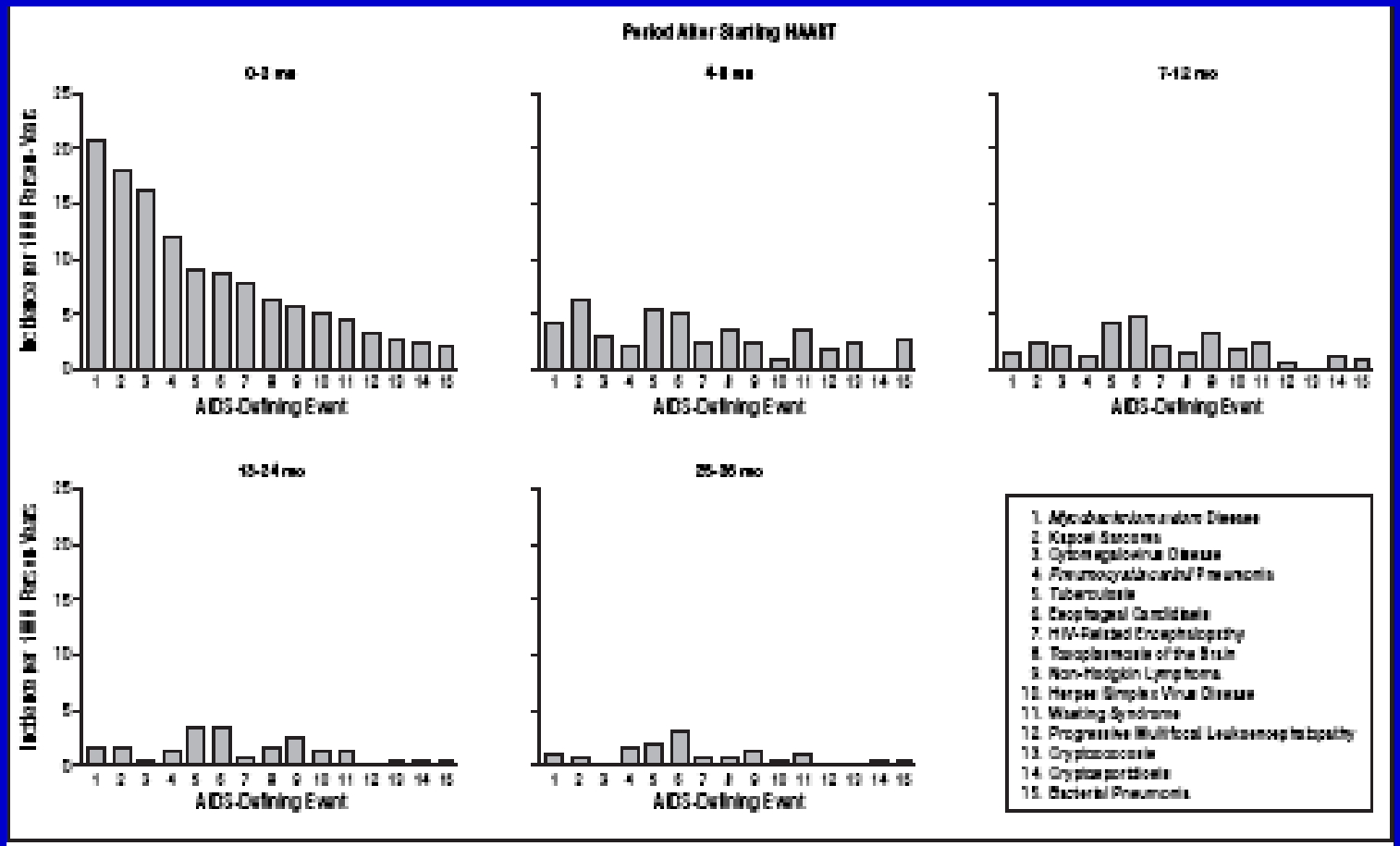
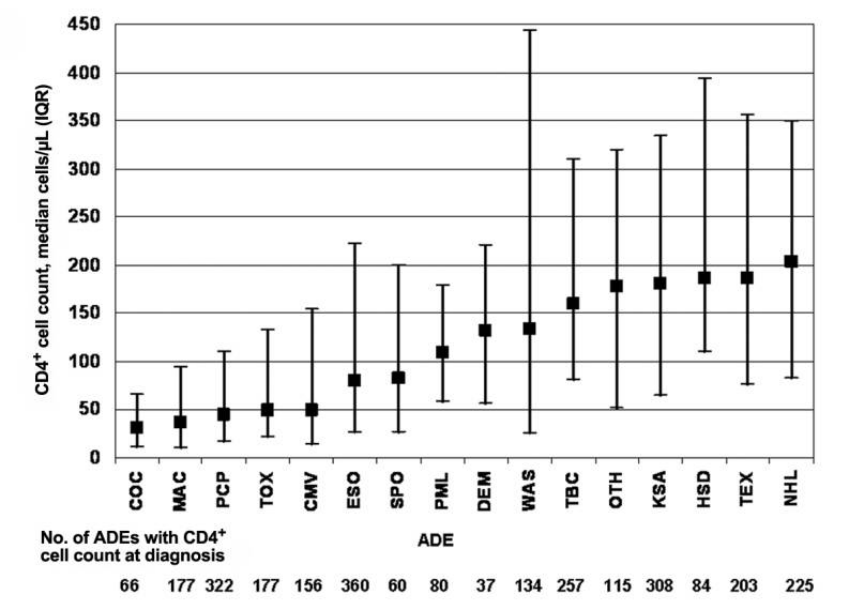



Figure 1. Incidences of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART).

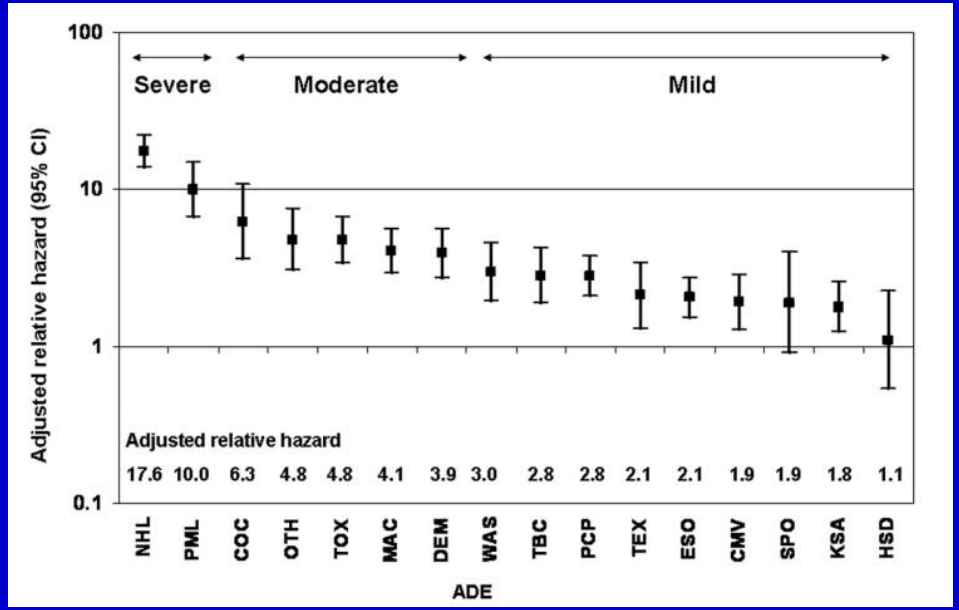
*ART-CC Arch Intern Med 2005 165:416-423*

# AIDS Events are Variably Associated with CD4 and Survival

## By Median (IQR) CD4




## By Relative Hazard of Death




*ART-CC, CID 2009;48:1138-51*

# "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 |

*Strategies for Management of Antiretrivoral Therapy NEJM 2006;355:2283-96*

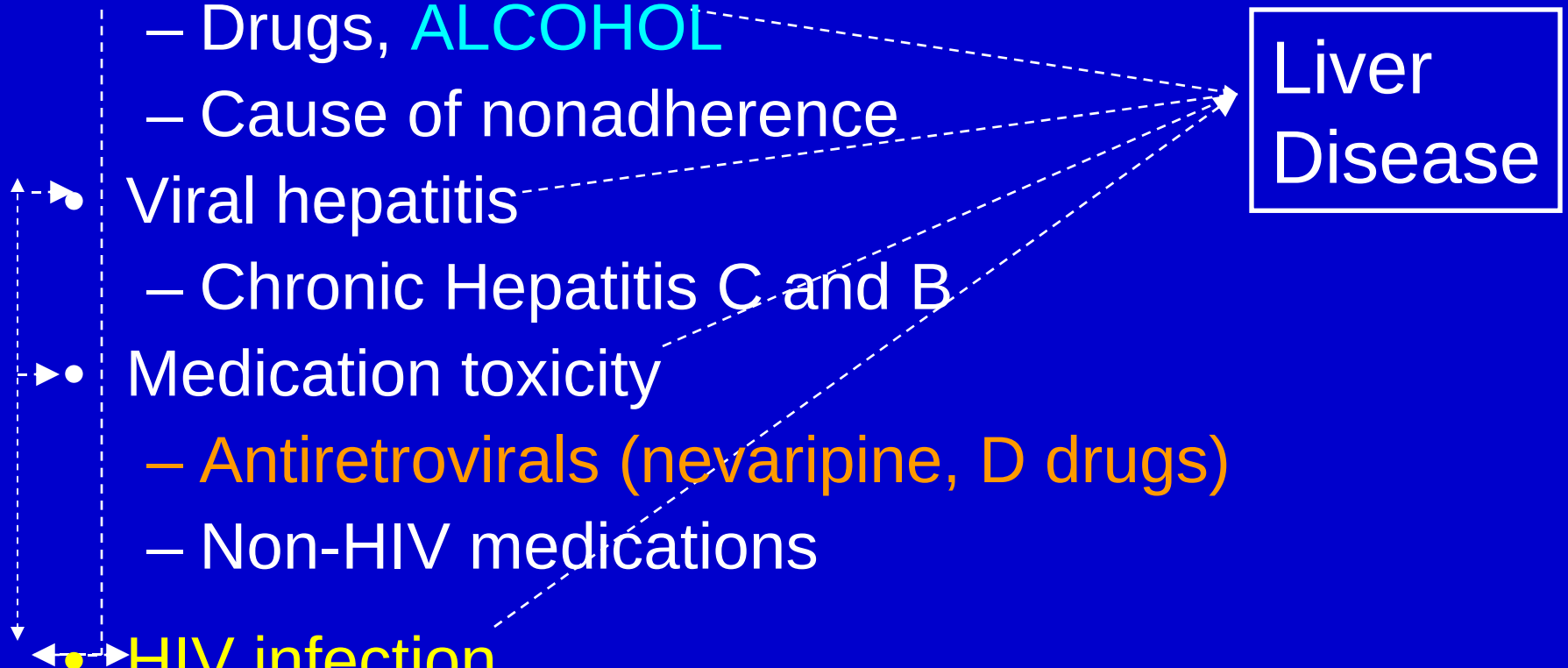
Non AIDS disease is influenced by HIV, treatment, and behaviors and conditions associated with HIV infection.

# 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

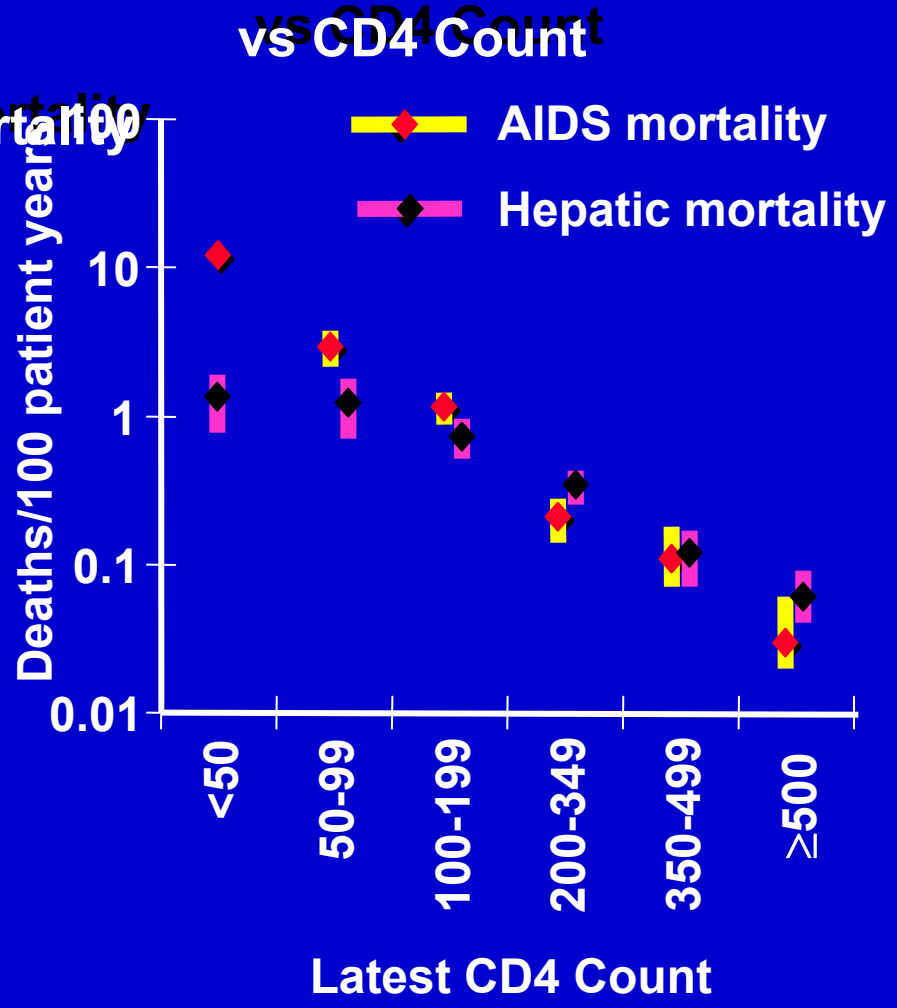
- Substance use
  - Drugs, ALCOHOL
  - Cause of nonadherence
- Viral hepatitis
  - Chronic Hepatitis C and B
- Medication toxicity
  - Antiretrovirals (nevaripine, D drugs)
  - Non-HIV medications
- HIV infection
  - Chronic inflammation
  - Immune compromise with deregulation



# 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 |

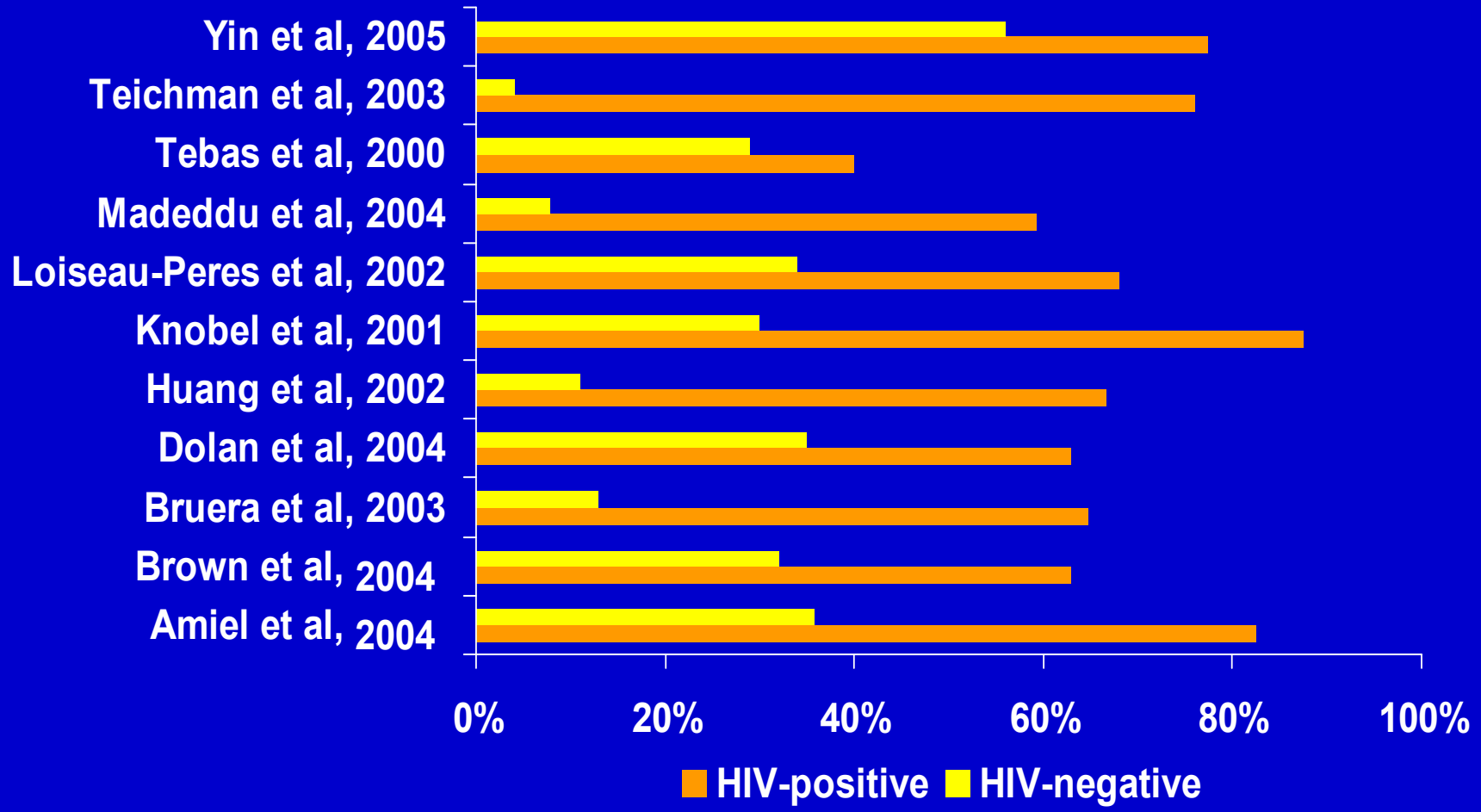



D:A:D study: Weber *et al*, Arch Intern Med 2006

# 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)




*Brown TT & Qaqish RB. AIDS. 2006; 20:2165-2174*

# BMD Vs. Fragility Fracture

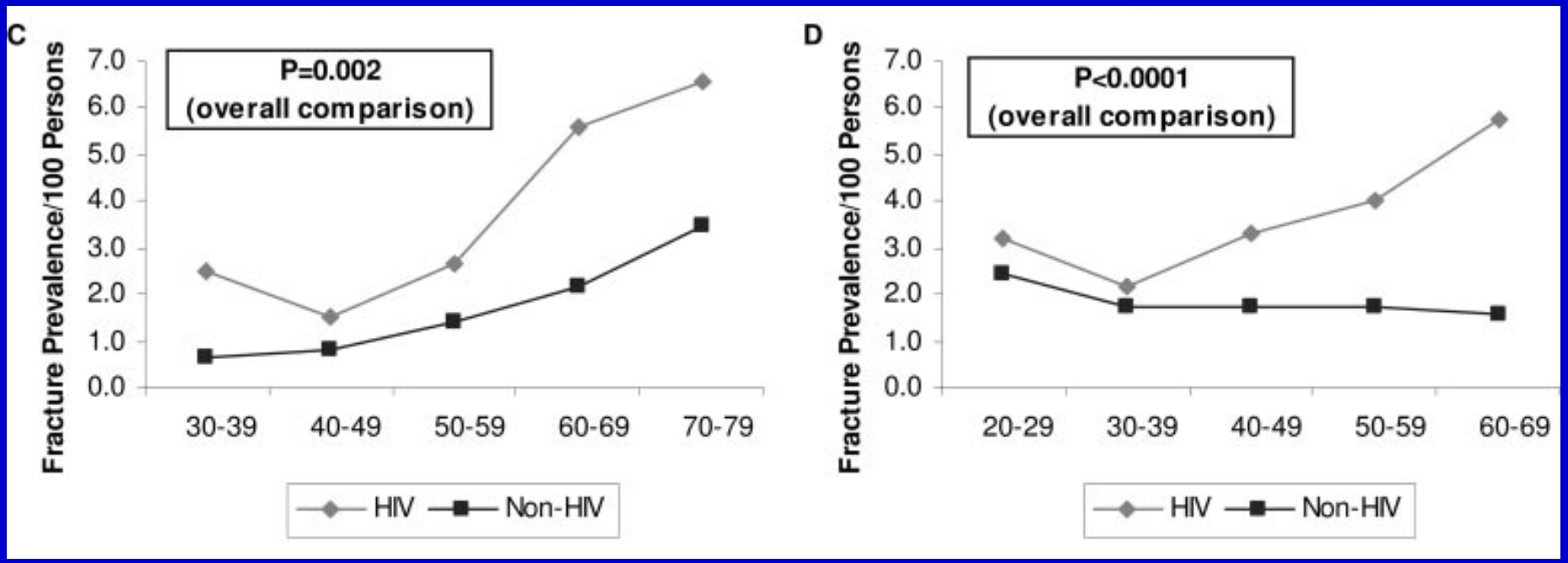
- Low BMD is a risk factor for vertebral, wrist, or hip fracture (fragility fracture)
- HIV and time on cART is associated with low BMD
- One age, race and gender, adjusted study has shown an increased risk of fragility fractures
  - 3.1 vs. 1.8 per 100 PY for HIV+/- men (72% increase)
  - 2.5 vs.1.7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

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

# ‘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 Edocrinol 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

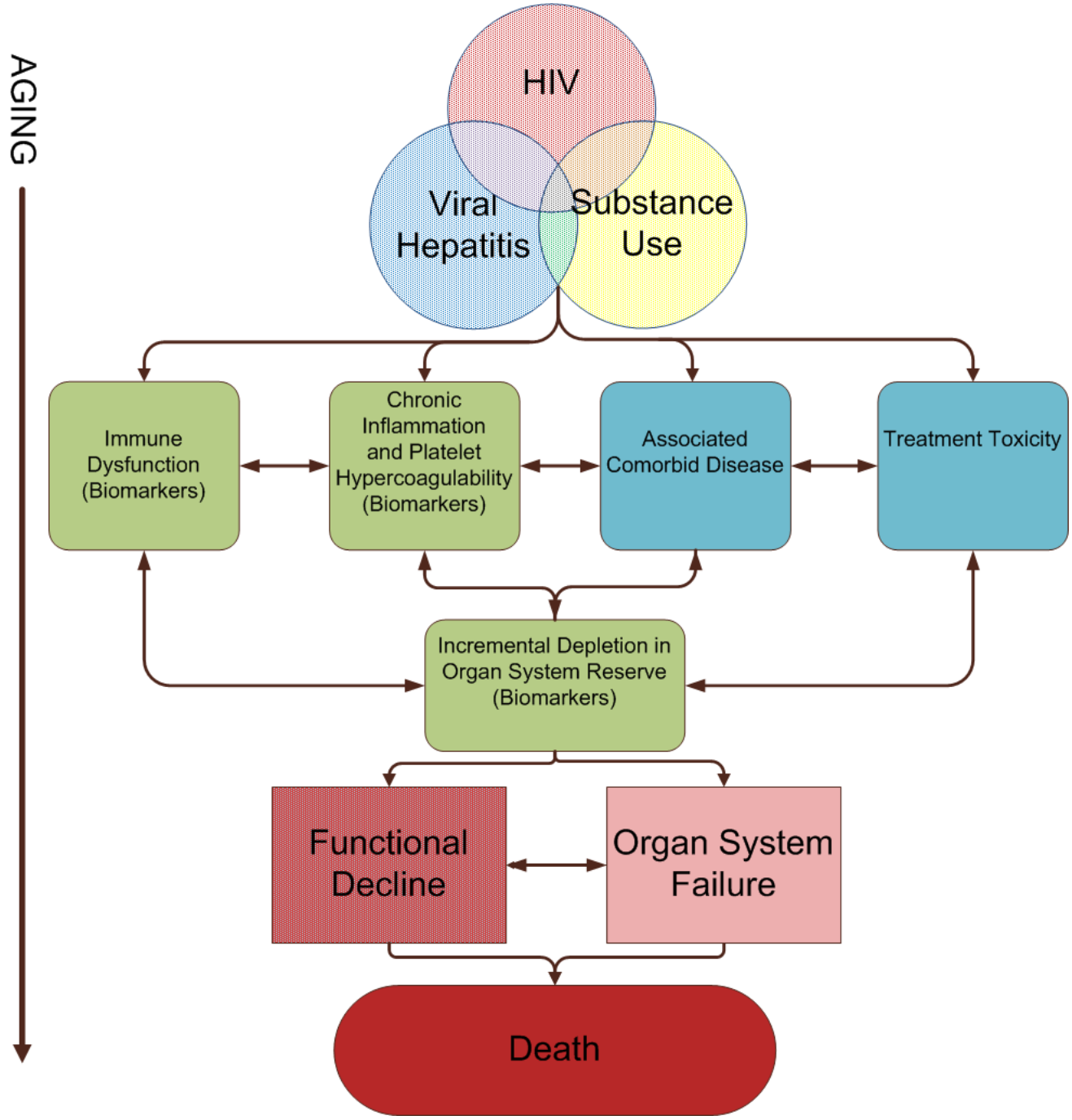
# Why Does It Matter?

- 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?

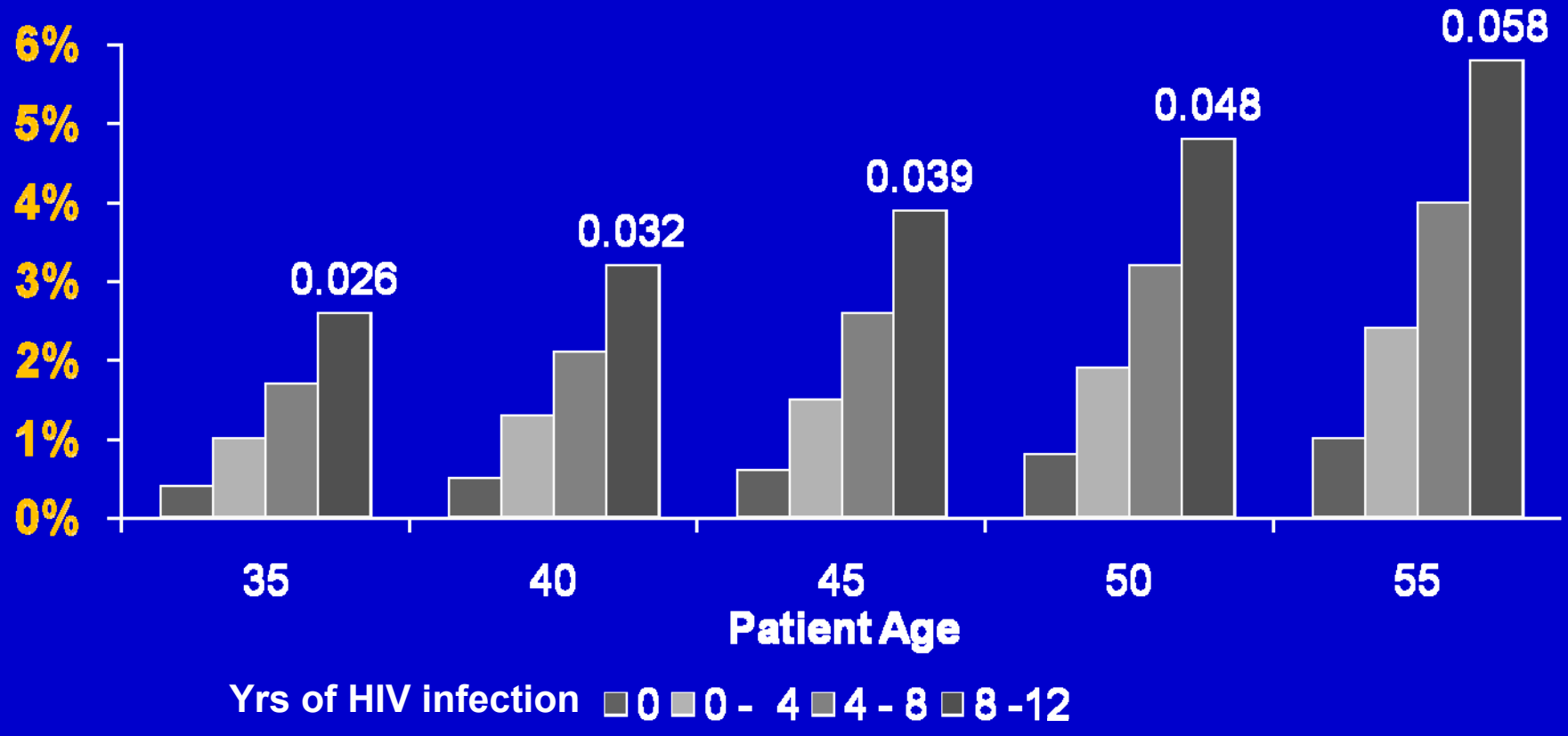
We need a new paradigm to effectively address important causes of morbidity and mortality for those aging with HIV infection.


AGING
HIV
Viral Hepatitis
Substance Use
Immune Dysfunction (Biomarkers)
Chronic Inflammation and Platelet Hypercoagulability (Biomarkers)
Associated Comorbid Disease
Treatment Toxicity
Incremental Depletion in Organ System Reserve (Biomarkers)
Functional Decline
Organ System Failure
Death

# Frailty Phenotype

- Developed in Cardiovascular Health Study
- Requires presence of 3/5:
  - Physical shrinking (weight loss ≥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




*Desquilbet L. J Gerontol Series A. 2007; 62:1279.*

# 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

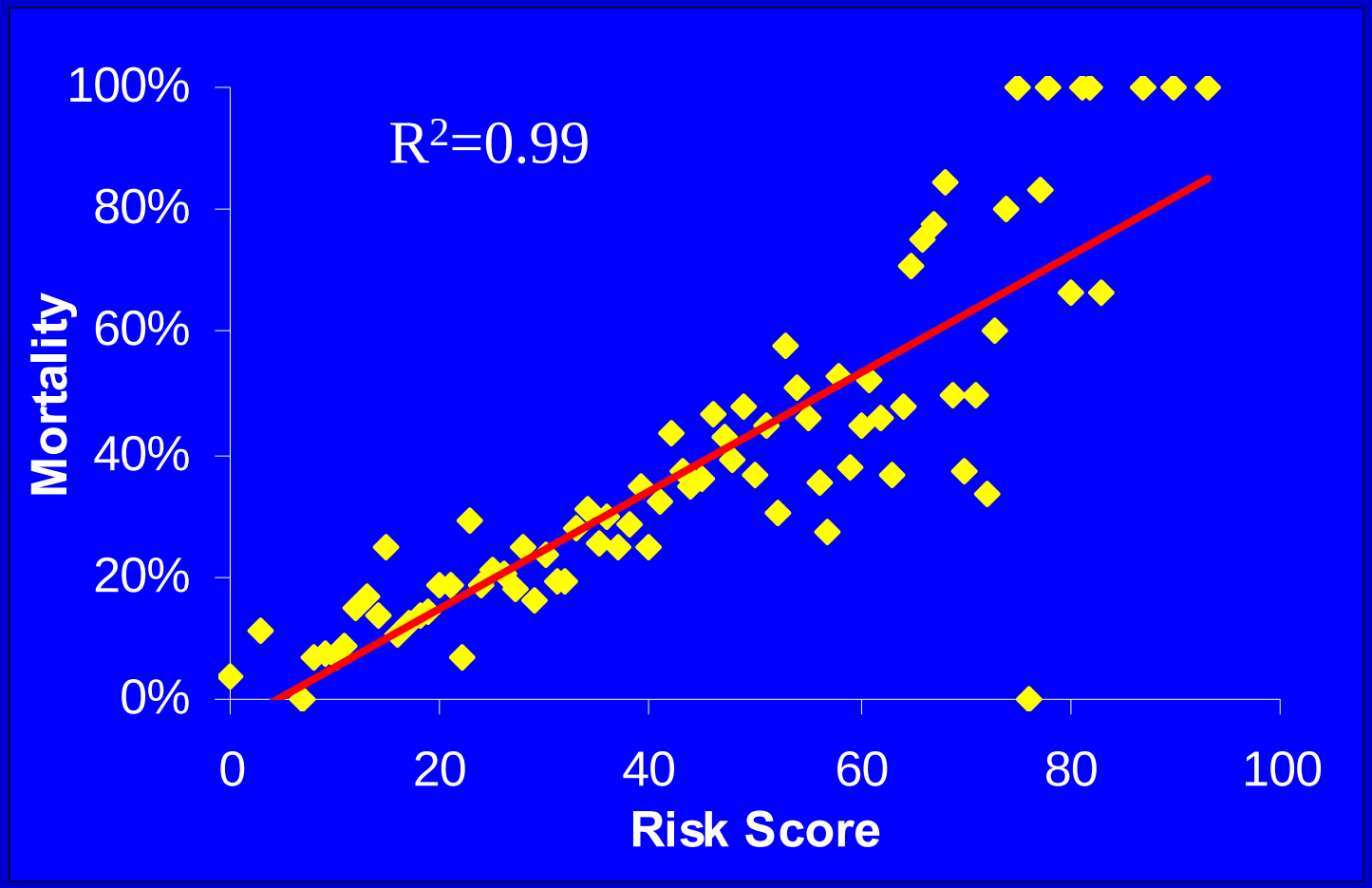
*Justice AC. Top HIV Med 2006;14:159-163*

# Veterans Aging Cohort (VACS) Risk Index

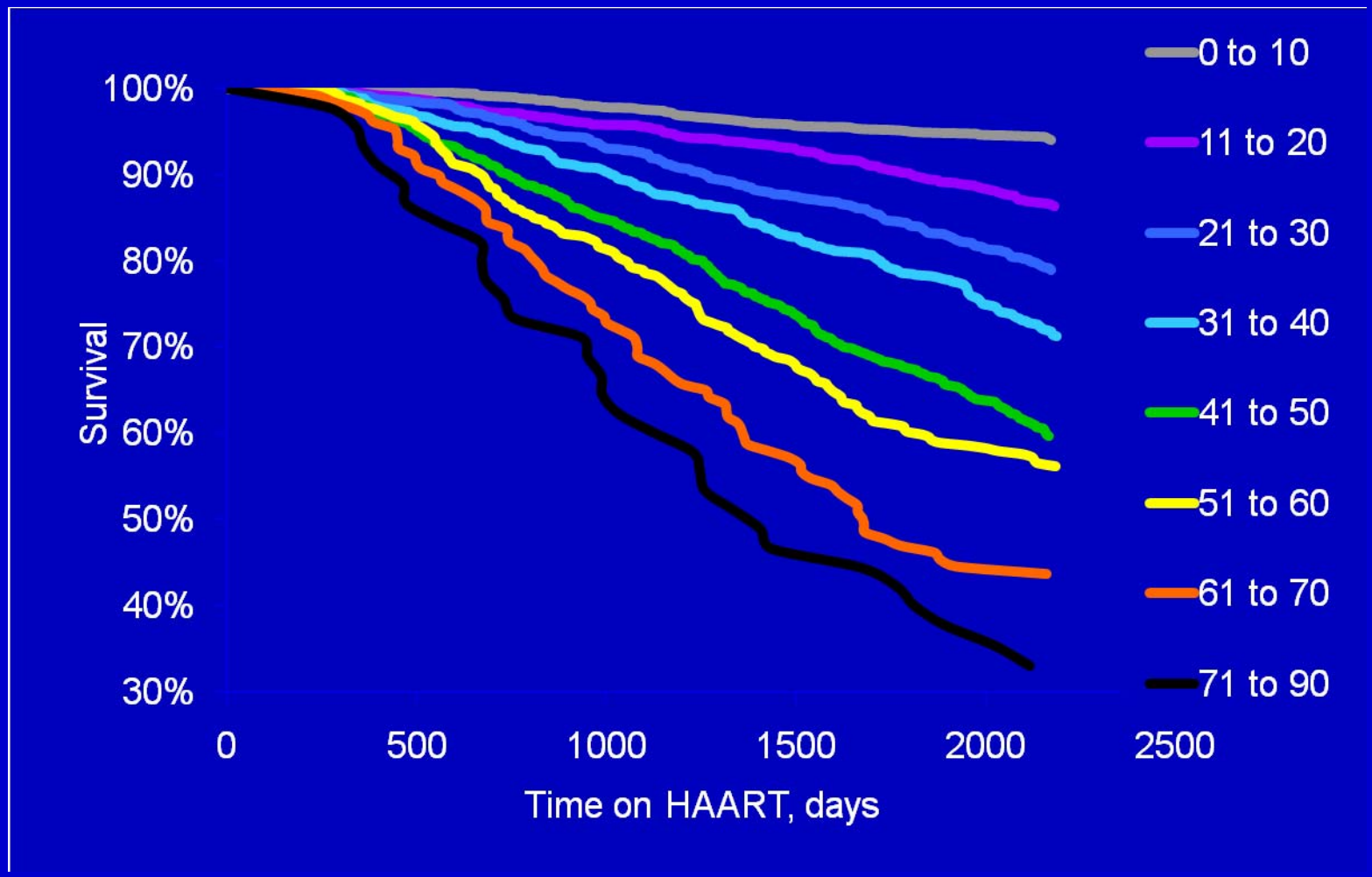
| | | | Points | HR |
|---|---|---|---|---|
| | Age | <50 | 0 | 1 |
| | | 50 to 64 | 9 | 1.45 |
| | | ≥ 65 | 27 | 2.94 |
| | CD4 | <50 | 17 | 1.98 |
| | | 50 to 99 | 14 | 1.72 |
| | | 100 to 199 | 11 | 1.54 |
| | | 200 to 349 | 8 | 1.38 |
| | | >=350 | 0 | 1.00 |
| | AIDS defining condition | | 7 | 1.31 |
| | 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 |

*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
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