Aging and HIV infection: looking at two facets of the infection

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Outline

- What is aging?
- HIV infection in older patients
- HIV/ART as aging

What is aging?

WHO Definition of Elderly

- Lacking an accepted and acceptable definition, in many instances the age at which a person became eligible for statutory and occupational retirement pensions has become the default definition.
- The ages of 60 and 65 years are often used, despite its arbitrary nature
- The cutoff age of 50 years is often used for HIV patients

What is aging?

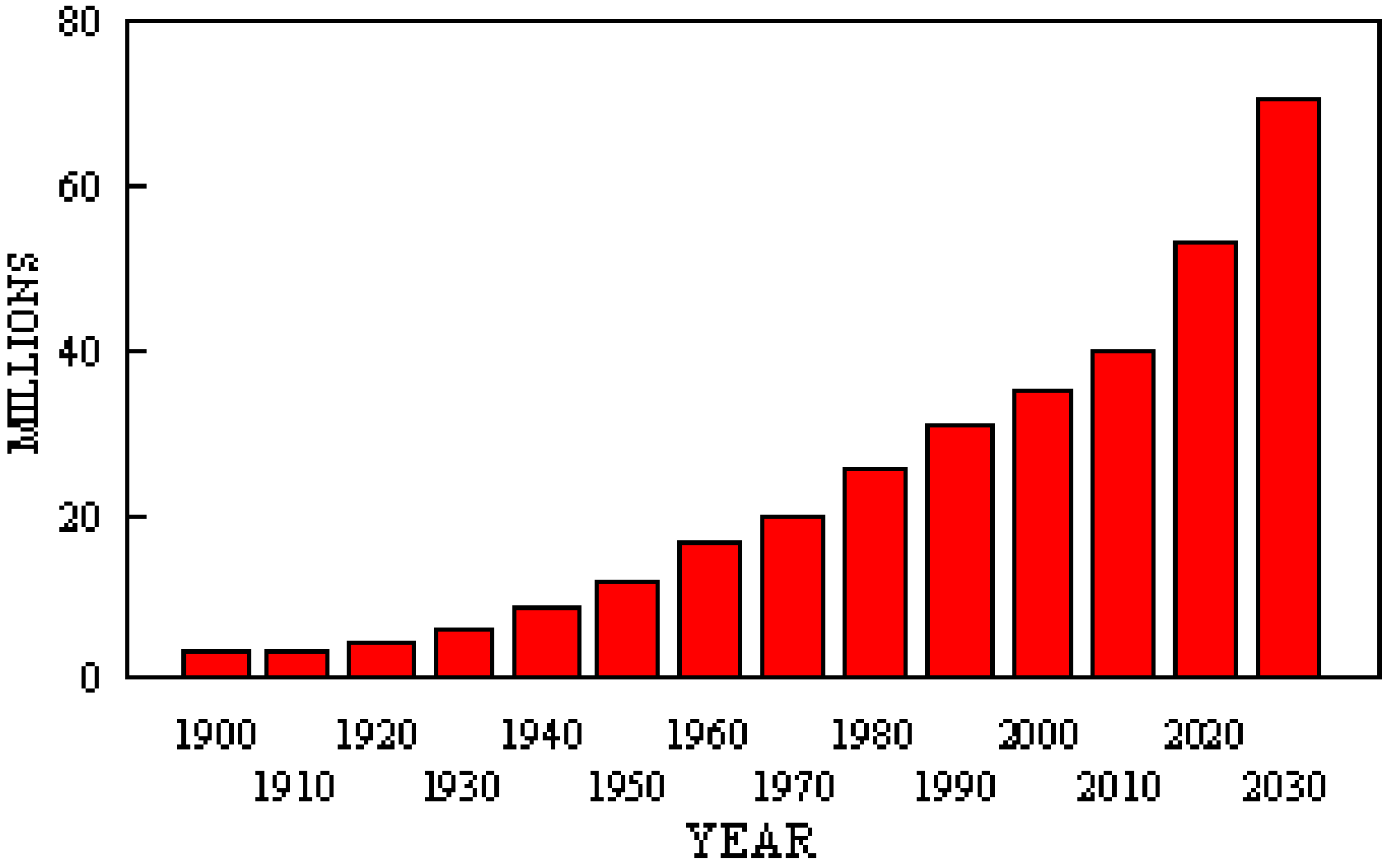
- Progressive deterioration in physiologic function that accrues as a consequence of cumulative molecular, cellular and organ damage

- Impaired ability to maintain physiologic equilibrium with stress

- These changes invariably result in increased susceptibility to disease and death

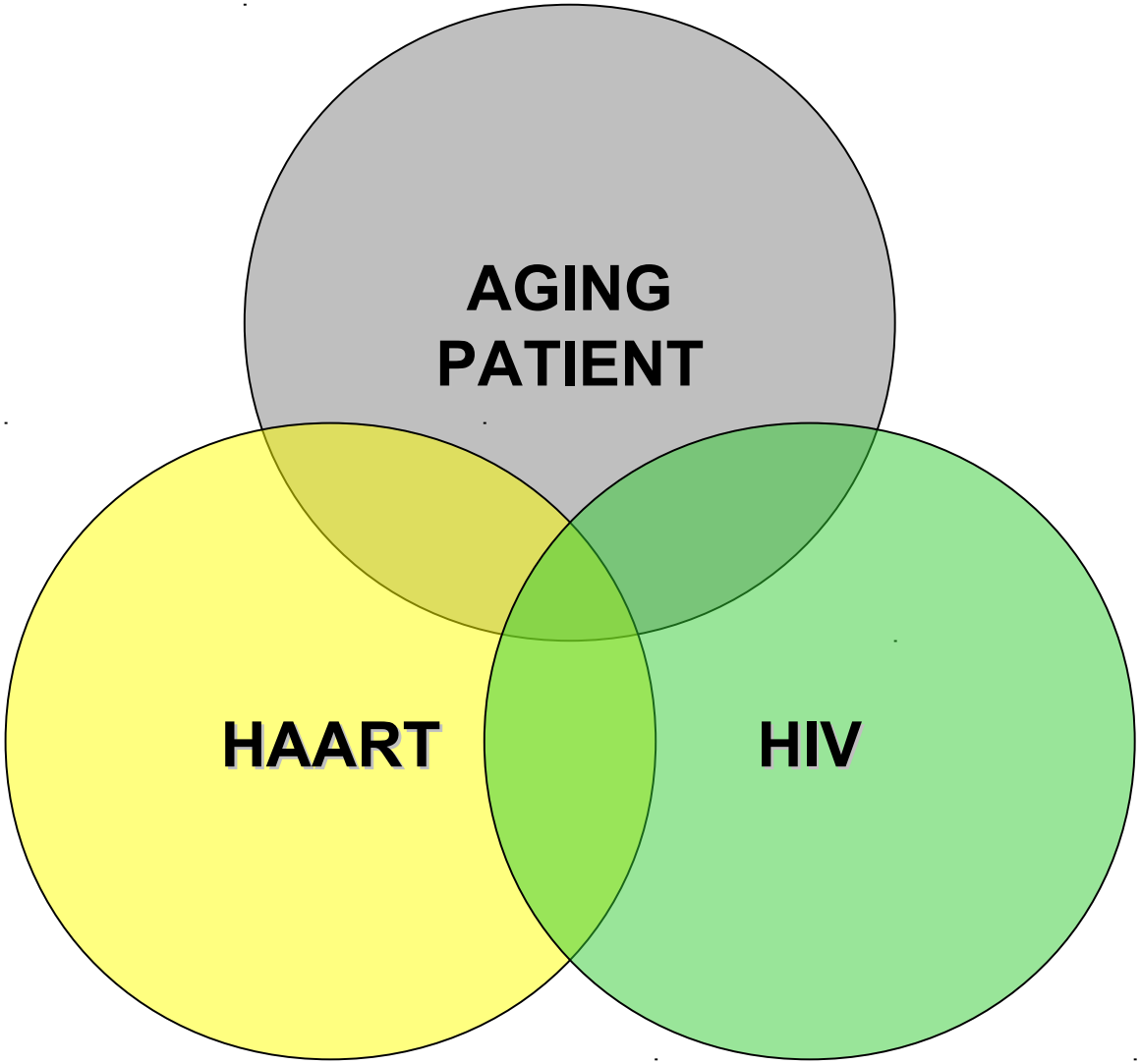
Growth of the Elderly Population

1900 to 2030



Source: U.S. Bureau of the Census

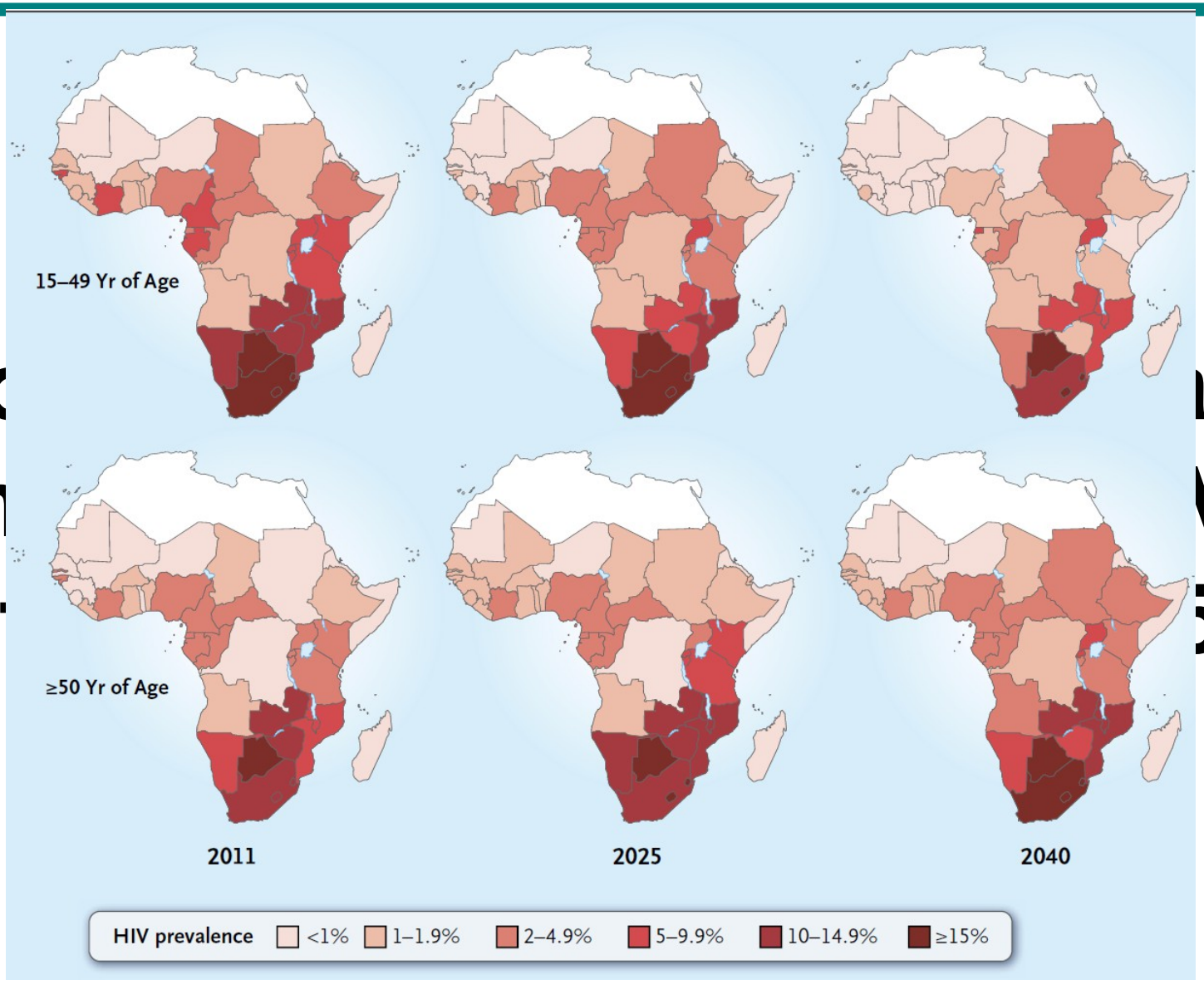
An intersecting problem



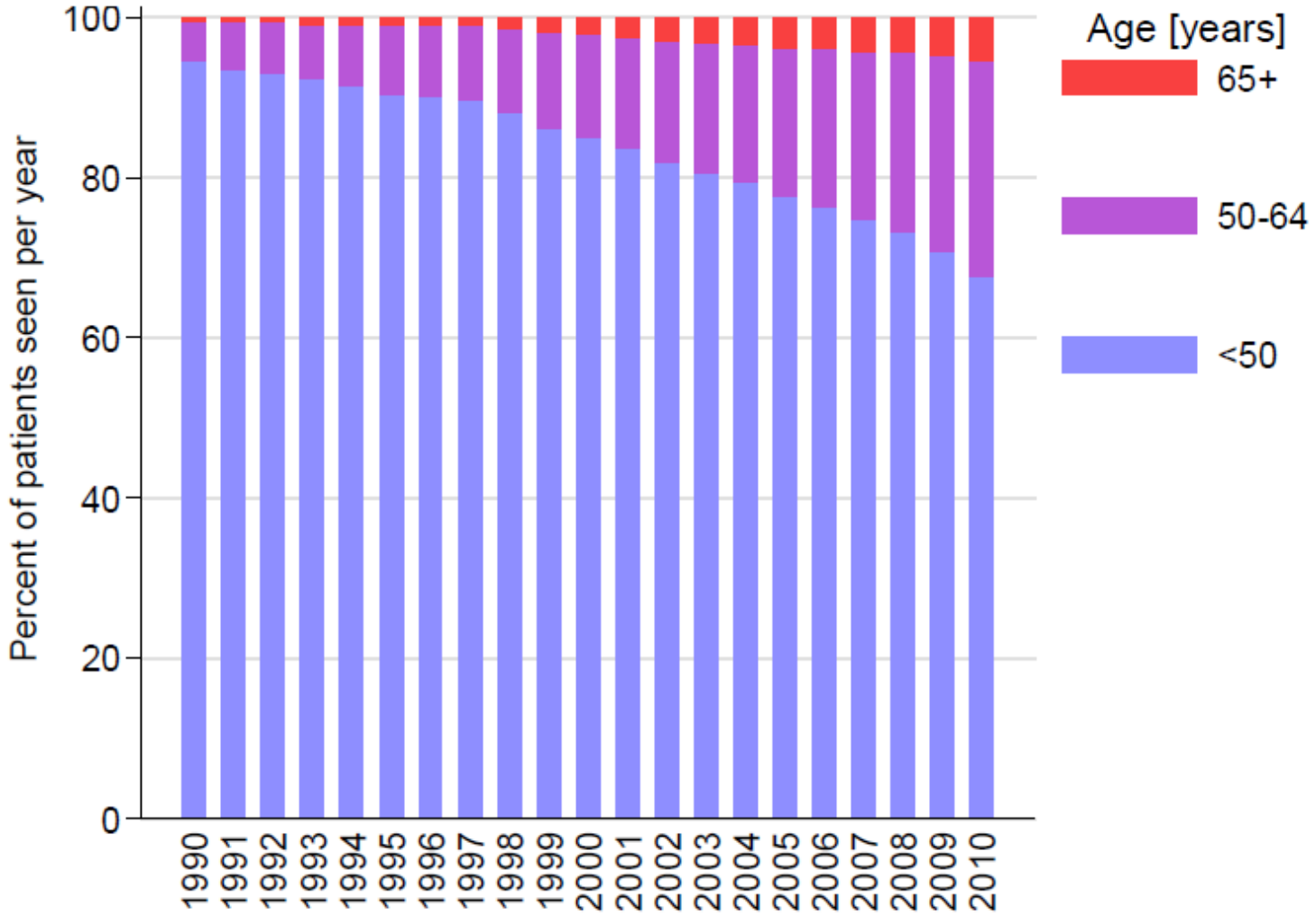

HIV in older patients
HIV/ART as aging agents

HIV infection in older patients

The magnitude of the problem



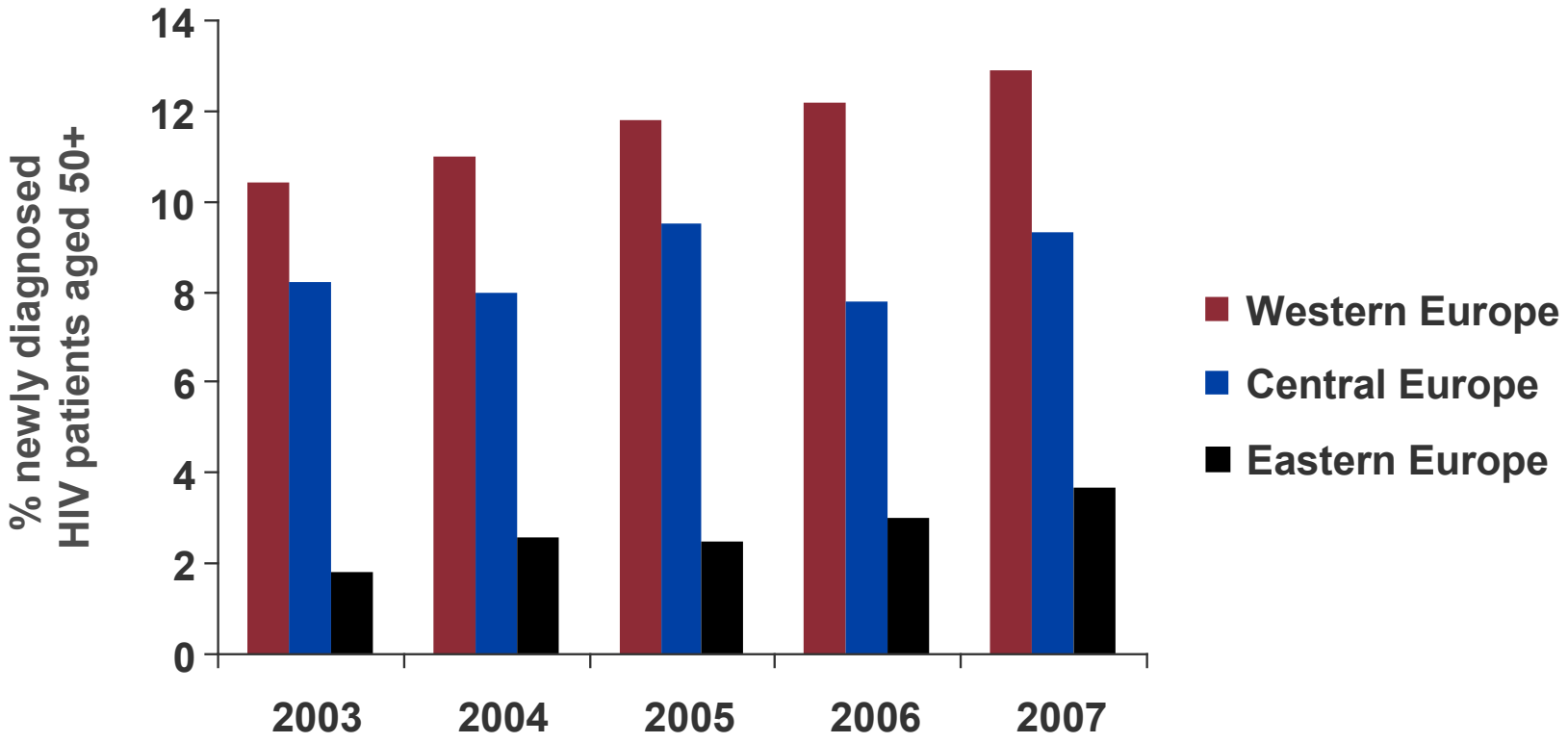
Aging of HIV population Swiss Cohort



Hasse et al, CID 2011

Epidemiology: A growing proportion of HIV diagnoses are in the over 50s

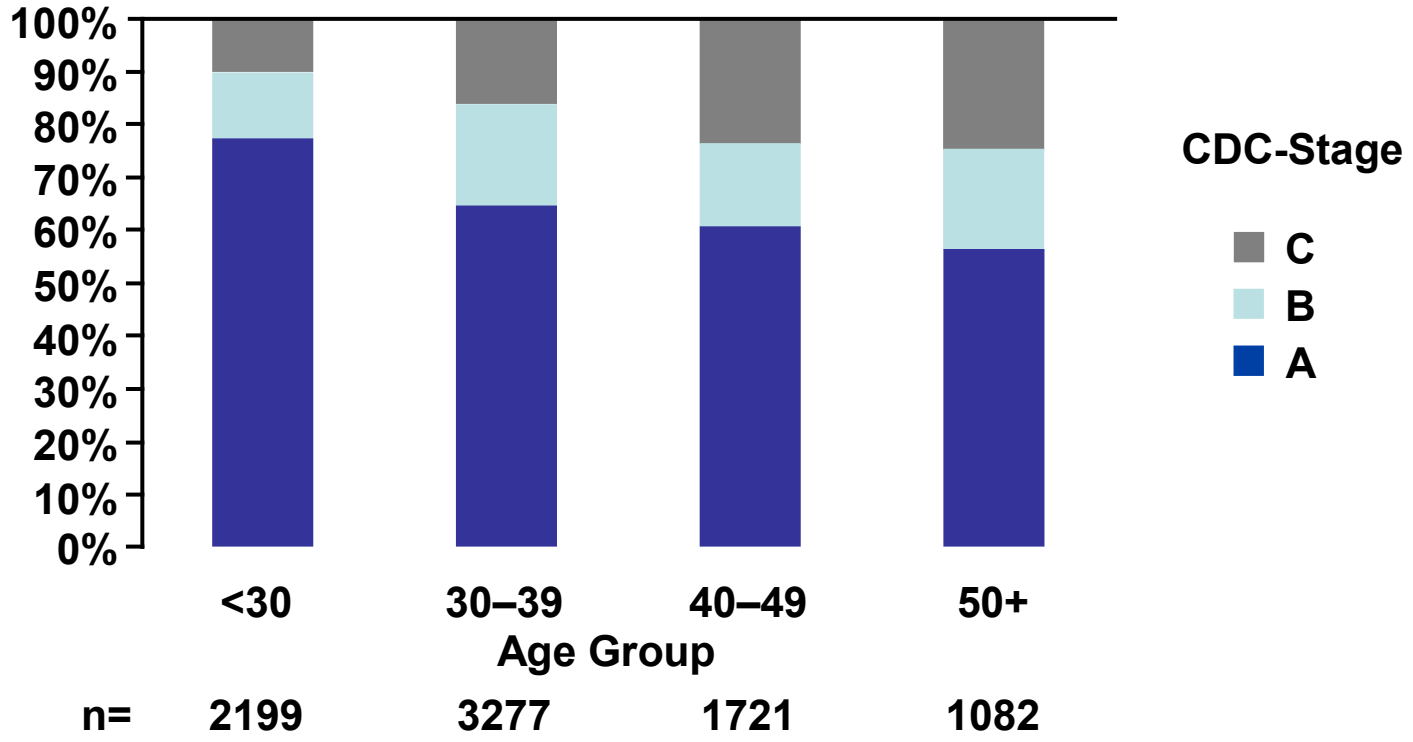
12.9% of newly reported cases of HIV infection in Western Europe in 2007 were in people aged 50 years or older



Lazarus JV and Nielsen KK, *HIV Medicine* 2010

Persons 50+ more often present with symptomatic HIV disease

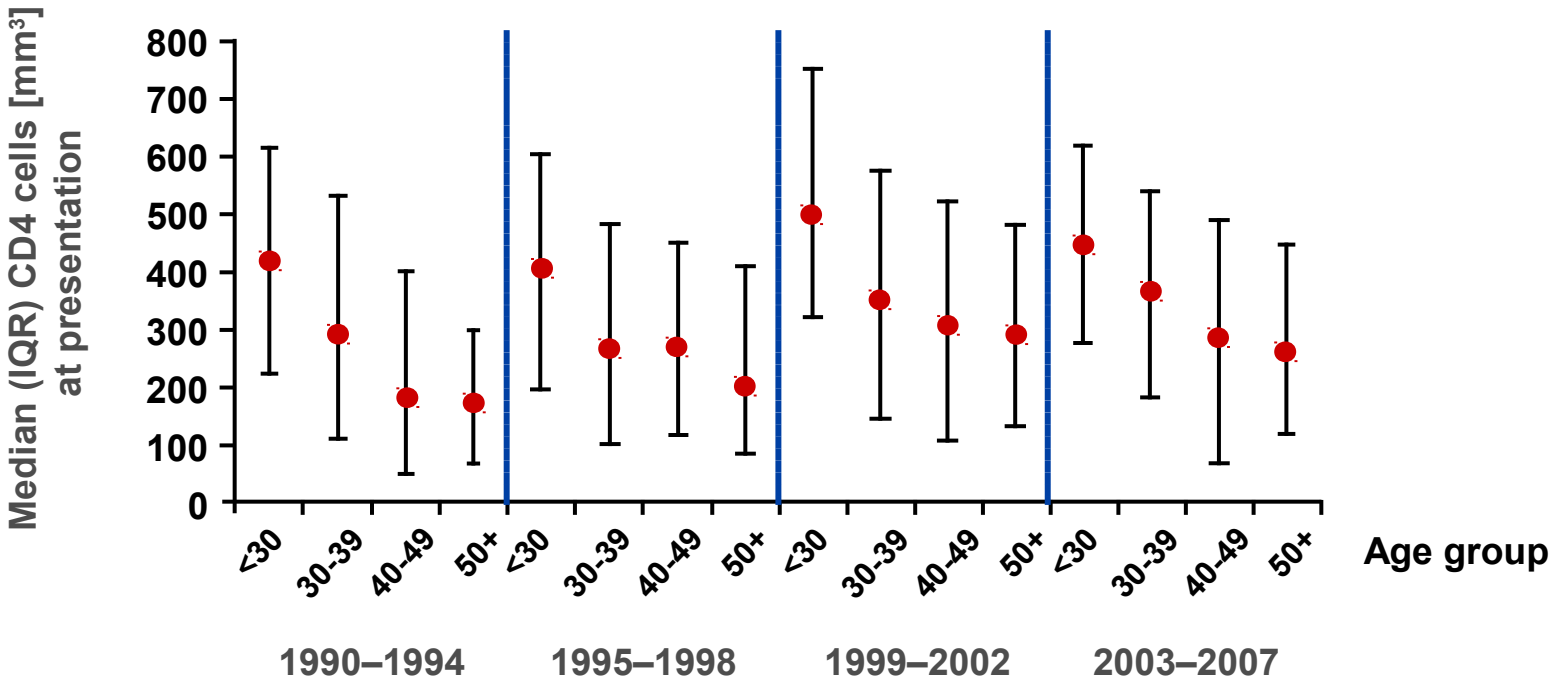
Clinical stage at presentation of non-IDUs since 1990



Unpublished Swiss Cohort HIV Study

...and more often with a lower CD4 cell count

CD4 cell count at presentation of Caucasian heterosexually-infected persons (n=2877)



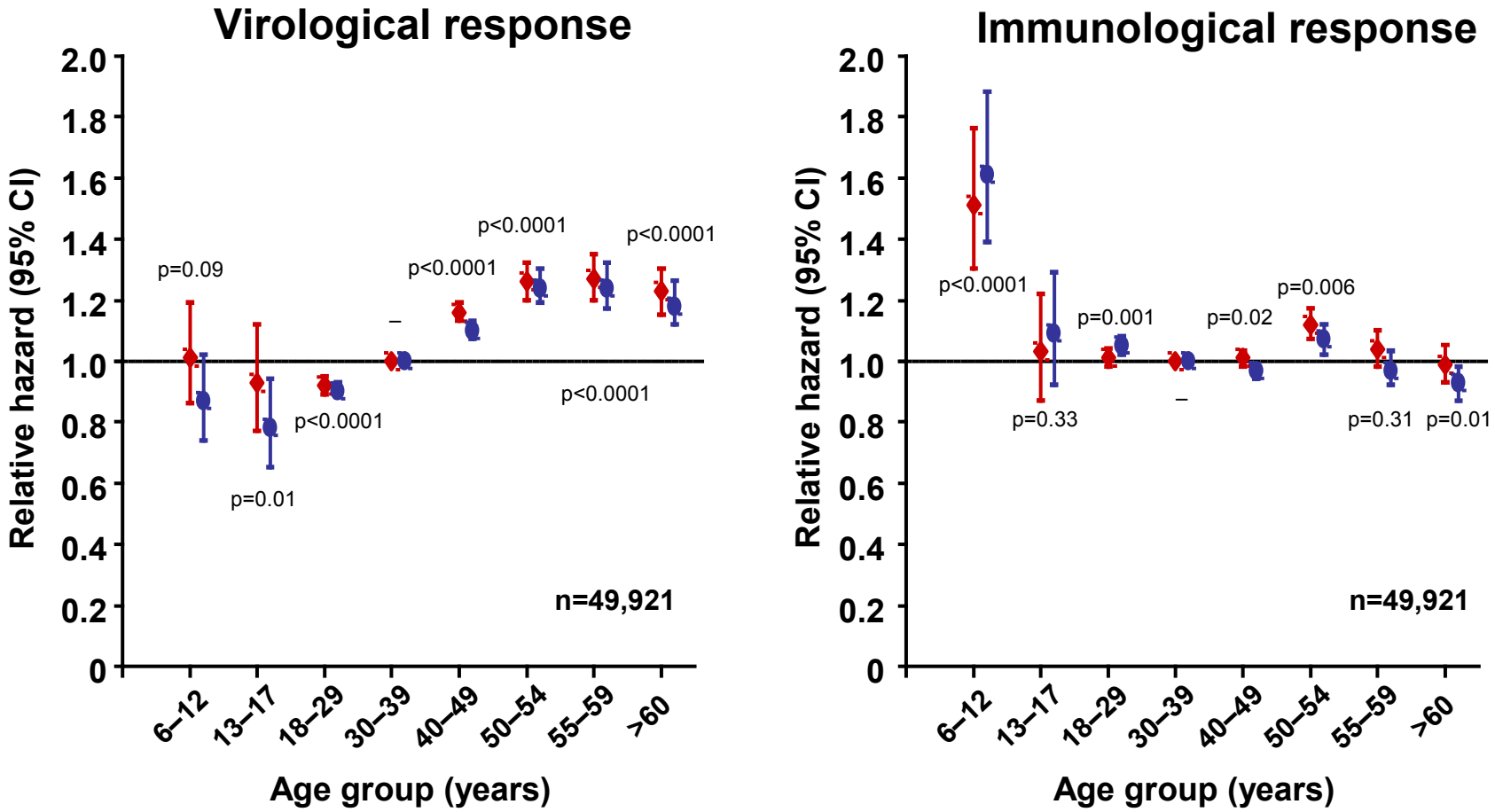
Unpublished Swiss Cohort HIV Study

Why do older patients appear to be at higher risk of HIV disease progression?

- Tendency to be diagnosed at a later stage
- More rapid progression in natural course of HIV
- Higher risk of complications
- Greater potential for worsening ARV toxicity
- Slower immunological response to ART

Grabar S, et al., *J Antimicrob Chemother* 2006, 57:4–7.

Effect of age on ART response: COHERE 2006

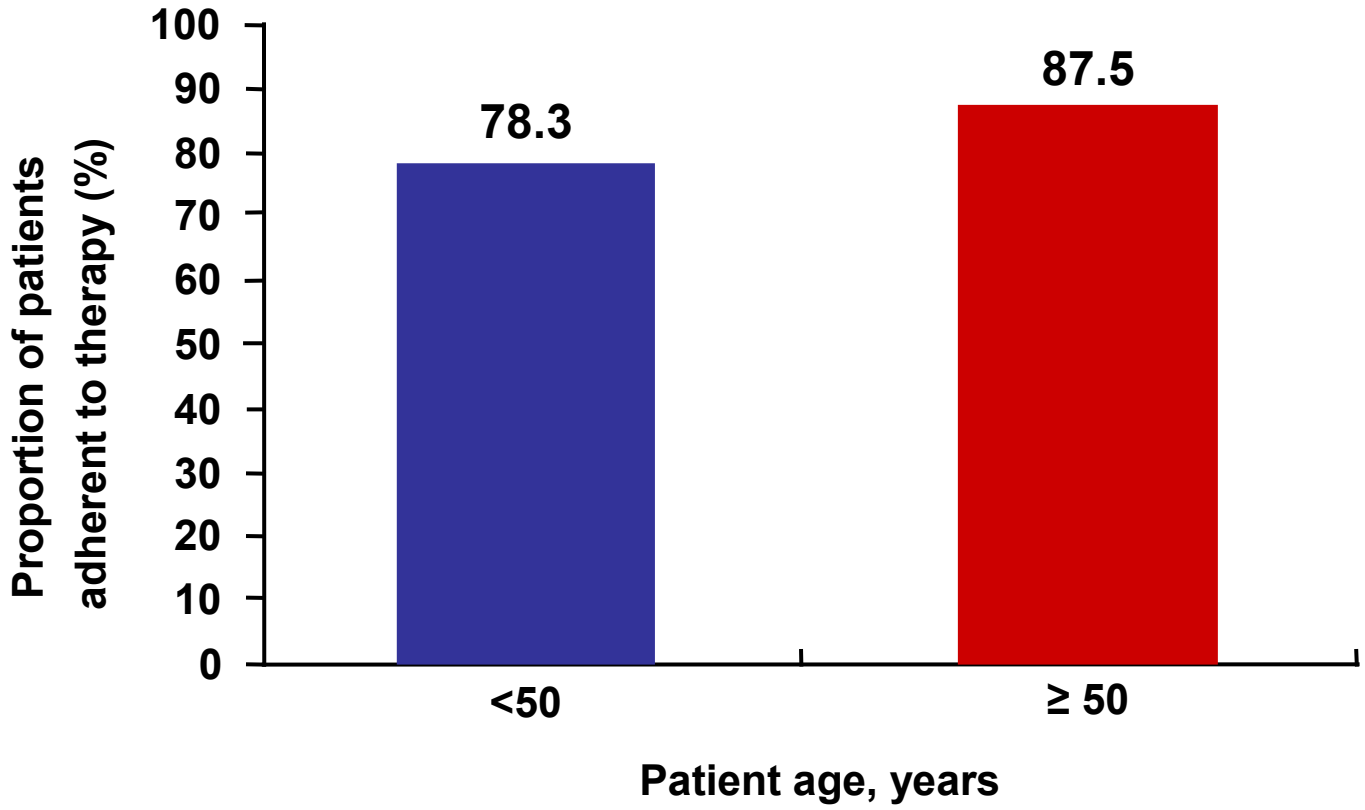


Unadjusted (red) and adjusted (blue) relative hazards for confirmed virological and immunological responses in the different age groups. Estimates are adjusted for year of starting cART, pre-cART CD4 and VL, AIDS, gender, ethnic origin and initial cART regimen.

COHERE: Collaboration of Observational HIV Epidemiological Research Europe

COHERE Study Group. *AIDS* 2008, 22:1463–73.

Adherence in younger vs. older HIV patients



p=0.01

Hinkin CH, et al., *AIDS* 2004, 8 (Suppl. 1):S19–S25

Challenges in treating older patients

- Older patients often take concurrent medications for other conditions
- Vigilance is needed to avoid drug–drug interactions
  - Overlapping toxicities
  - Altered plasma drug levels, necessitating dose adjustments
  - Increased metabolism of ARVs, decreasing bioavailability
- Commonly used drugs that may interact include
  - Statins, antiarrhythmics, gastric acid inhibitors, warfarin, SSRIs, erectile dysfunction agents, anticonvulsants

Simone MJ et al., *Geriatrics* 2008.

Age impact on ART tolerability

- **Pharmacological handling:**
  - Decreased hepatic and renal function with age
  - Decreased CYP450 concentrations[1]
- **Predisposition to toxicities:**
  - Increased cardiovascular risk
  - Lower bone mineral density
  - Increased renal disease
- **Polypharmacy**
- **Patient perception of health and medicines:**[2]
  - Increased adherence, stoicism
  - Less concerns about theoretical toxicity
  - Less concerns with experiencing side-effects

1. Sotaniemi EA et al., *Clin Pharmacol Ther* 1997.
2. 2. Sherr et al., *Psychology, Health & Medicine* 2009.

Toxicity in the first year of cART

- 8,708 treatment-naïve patients initiating HAART between 1998–2005 in 13 UK centres
- 2,650 (30%) discontinued at least one drug for non-virological failure reasons
- Discontinuing was associated with:
  - Younger age (<30; RH 1.12, 95% CI 1.01, 1.24)
  - Older age (>50; RH 1.14, 95% CI 1.00, 1.31)
- Strong association between older age and:
  - Increased cholesterol
  - Decreased haemoglobin
  - Increased triglycerides (although triglycerides were also higher in older patients before HAART)

Sabin CA et al., *HIV Medicine* 2009, 10:35–43.

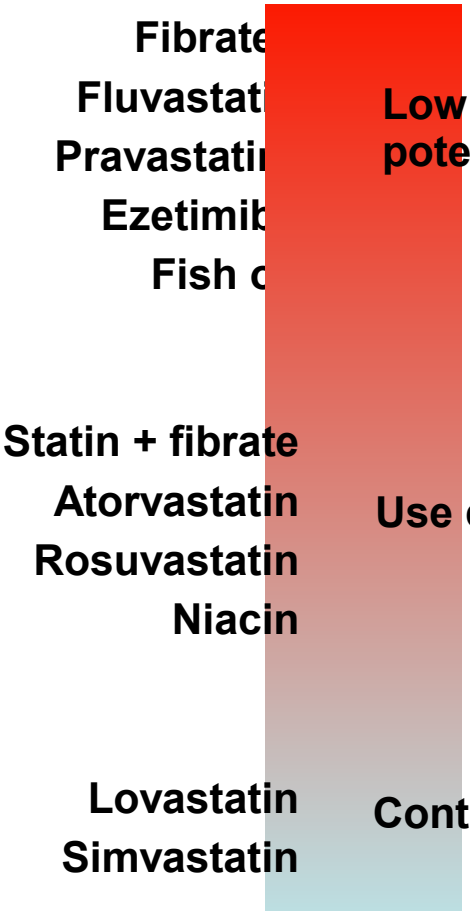
Antiretroviral Tolerability Decreases With Age

- Kaiser Permanente of Northern California chart review study of all members who initiated antiretroviral therapy from 1995-2004 (N = 5090)
- ≥ 18 years of age
- Starting ≥ 3 antiretrovirals in combination
- Labs available in year before and year after HAART initiation
- Excluded patients with laboratory abnormality in year before HAART
- Analysis of those who developed grade 2-4 abnormality while on HAART

Parameter	% With Abnormality				
	All Patients	18-39 Yrs	40-49 Yrs	≥ 50 Yrs	*P* Value
TC or LDL cholesterol	26.6	21.0	26.4	34.0	.0001
Glucose	9.7	6.0	11.4	14.4	< .001
Creatinine	5.2	3.2	5.8	8.3	< .001

Silverberg M, et al. IAC 2006.

Lipid-Lowering Agents and PIs: Drug-Drug Interactions



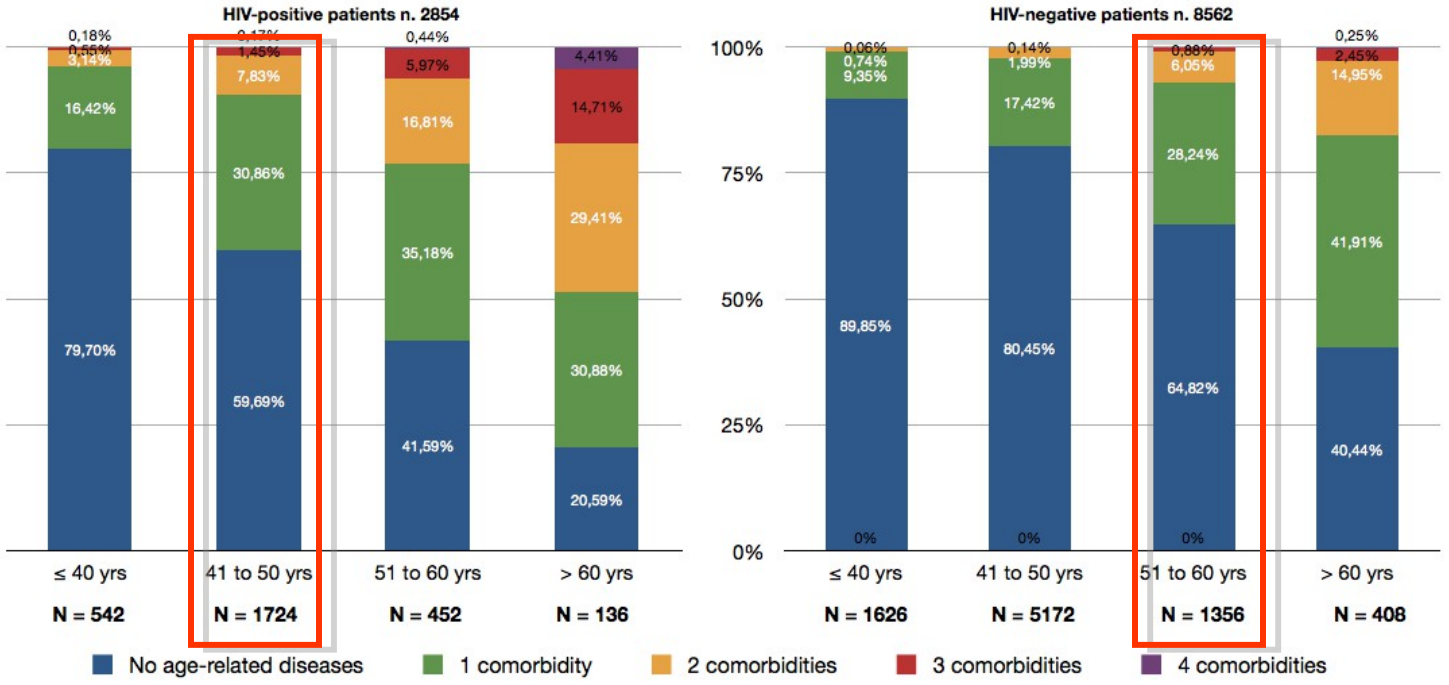
*AUC ↑↑↑ with DRV.

Aptivus [package insert]; 2005. Carr RA, et al. ICAAC 2000. Abstract 1644. Fitchenbaum CJ, et al. AIDS. 2002;16:569-577. Gerber JG, et al. CROI 2004. Abstract 603. Gerber J, et al. IAS 2003. Abstract 870. Hsue PH, et al. Antimicrob Agents Chemother. 2001;45:3445-3450. *Lexiva* [package insert]; 2007. *Prezista* [package insert]; 2006. *Reyataz* [package insert]; 2007.

Age and Comorbidities in HIV Infection

- Cardiovascular disease
- Metabolic syndrome
- Body composition changes
- Renal dysfunction
- Bone disease
- Cancer

Incidence of Multiple Comorbidities Increases With Age in HIV-Infected patients

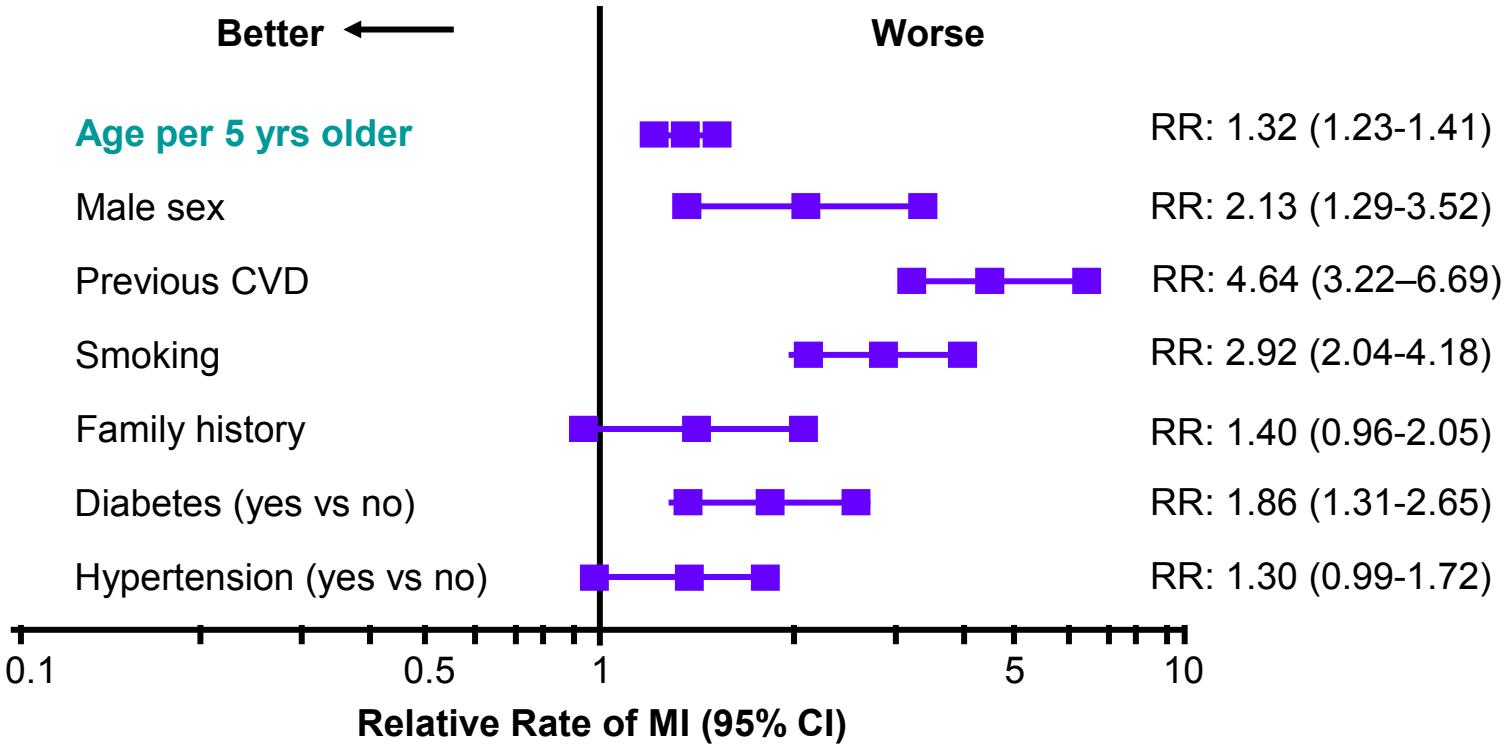


Pp prevalence was higher in cases than controls in all age strata (all p-values <0.001)

Pp prevalence seen cases aged 41-50 was similar to that observed among controls aged 51-60 controls (p=0.282)

Guaraldi G, et al. Glasgow 2008.

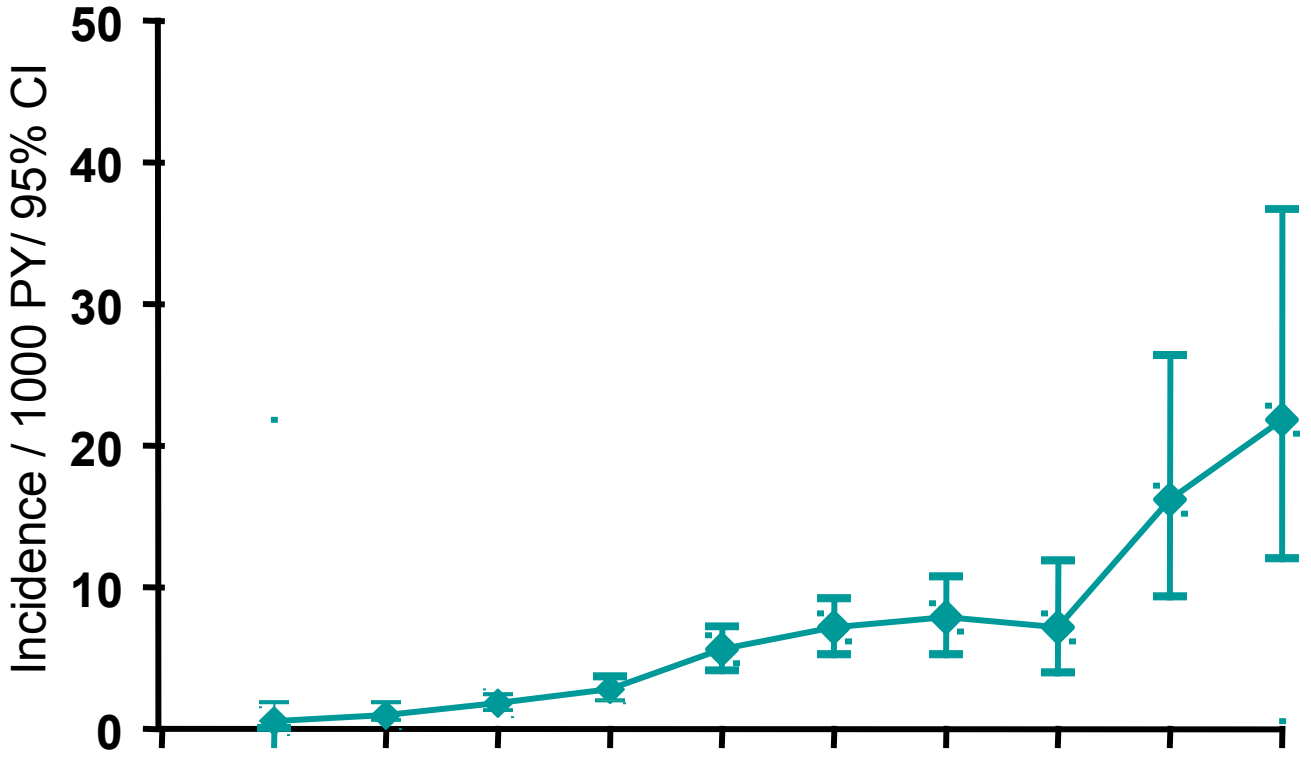
D:A:D: Risk Factors for CHD in an HIV-Infected Population



Multivariable Poisson model adjusted for age, sex, BMI, HIV risk, cohort, calendar year, race, family history of CVD, smoking, previous CVD event, TC, HDL, HTN, DM.

Friis-Møller, et al. N Engl J Med. 2007.

MI Incidence according to age in the D:A:D study

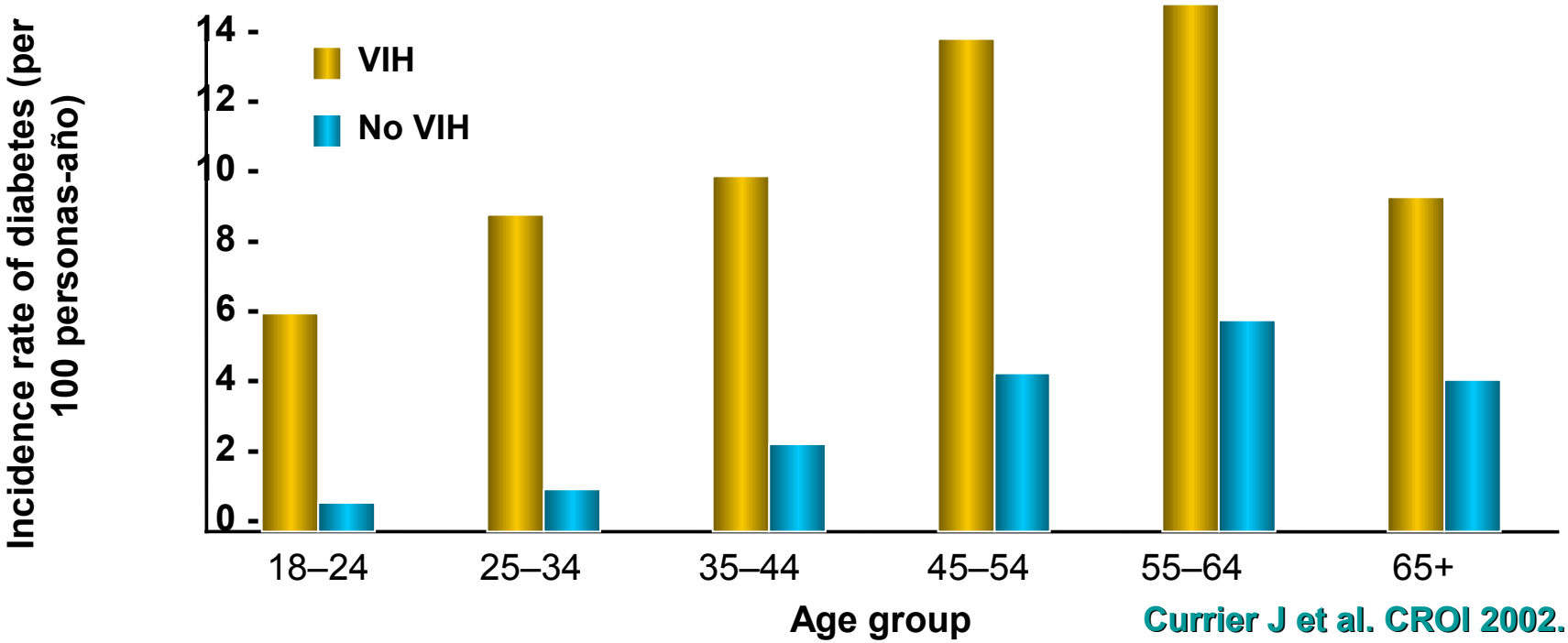


Age groups	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	>70
Events	2	11	36	48	55	48	31	15	16	14
PYFU	3834	10801	20075	16900	9741	6687	3899	2093	989	641

Friis-Moller N et al. AIDS 2003

The risk of diabetes in HIV patients is greater than in controls

- Medi-Cal database explored between July 1994–June 2000, age-specific incidence rate of diabetes
- Diabetes mellitus diagnosed by ICD-9
- 7219 VIH (61% men) and 792 971 non-VIH (30% men) individuals, for 7 101 180 persons-year

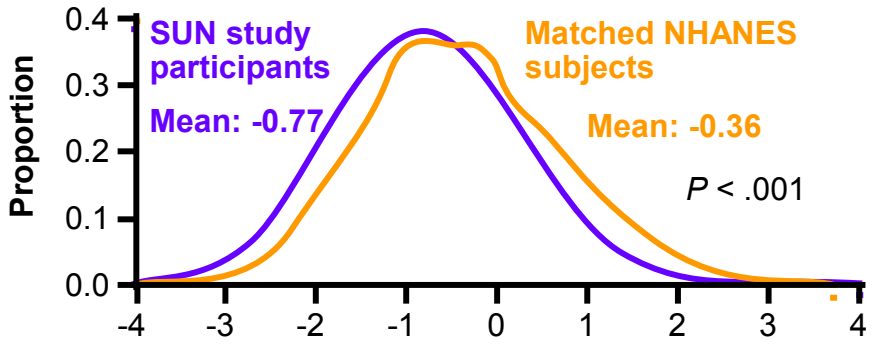


Currier J et al. CROI 2002.

SUN: Prevalence of Osteopenia/ Osteoporosis in HIV-Infected Patients

- **Prospective study of 525 HIV+ pts with baseline DEXA bone densitometry compared with matched pairs from NHANES**
  - **Longitudinal follow-up ongoing**
- **Higher rates of reduced bone density at the femoral neck in HIV+ vs controls**
  - **Osteopenia: 51.7% vs 29.1%**
  - **Osteoporosis: 9.8% vs 1.0%**

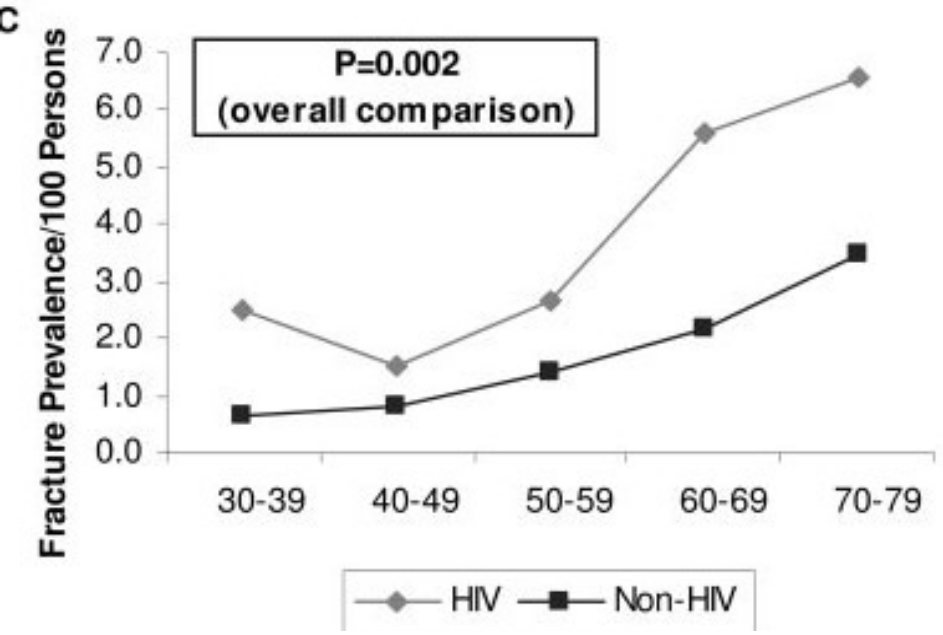
Comparison of Femoral Neck T-Scores Among SUN Study Participants and Matched Controls

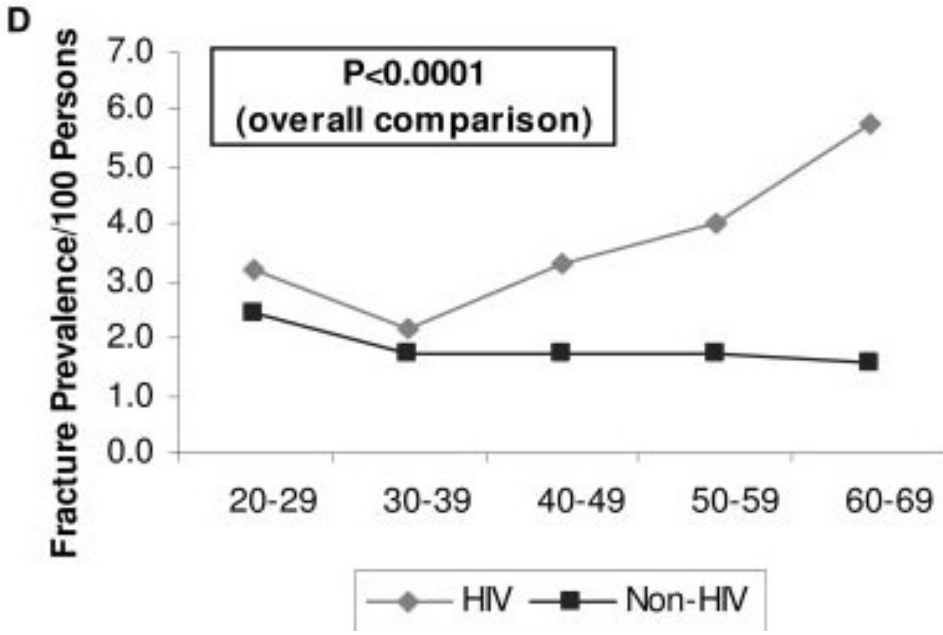


Multivariate Analysis: Factors Related to Osteoporosis		
Factor	**OR (95% CI)**	***P* Value**
BMI < 22.5 kg/m²	**3.01 (2.24-5.69)**	**<.001**
Age > 45 yrs	**2.35 (1.33-4.15)**	**.003**
BL CD4+ < 300	**2.10 (1.16-3.78)**	**.013**
HIV > 97.7 mos	**1.56 (1.09-3.55)**	**.023**

Overton T, et al. CROI 2007.

Fracture Prevalence in HIV-infected and non-HIV-infected Persons





MGH/Partners Healthcare System: 1996-2008

Triant, JCEM, 2008

HIV and Malignancies

- Risk factors for fatal AIDS-defining and non–AIDS-defining malignancies evaluated in D:A:D study
- 1246 deaths in 23,441 subjects (rate: 16.2/1000 person-years)
  - 193 (1.8/1000 person-years) due to fatal nADM
  - 112 (1.1/1000 person-years) due to fatal ADM
- Most frequently affected organs with nADM: lungs, GI tract, hematologic system, anal canal
- Gradually increasing RR of either nADM or ADM with fatal outcome with lower latest CD4+ cell counts
- Risk factors for fatal nADM: older age (relative rate: 1.53/5.00 years older; $P < .0001$), current smoking; active HBV infection

D'Arminio Monforte A, et al. CROI 2007.

HIV and frailty

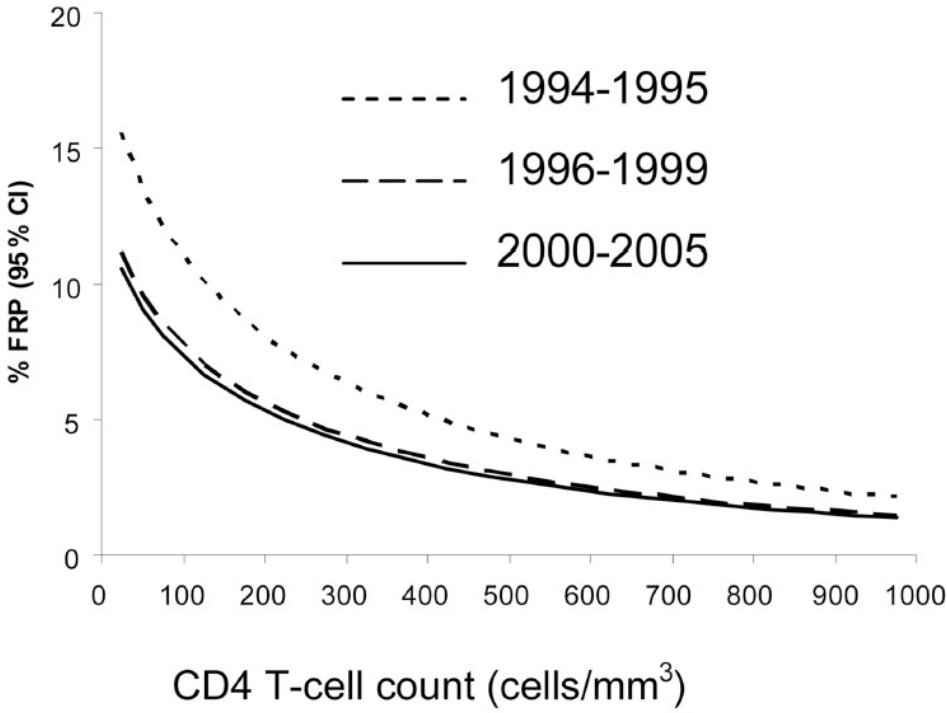
- Frailty: vulnerability to health threats
  - ✓ Accumulated functional defects
  - ✓ Cognitive, physical, social
  - ✓ Exhaustion, muscle weakness, slow gait, weight loss, decreased physical activity

- Can be measured
  - ✓ Fried's Frailty Phenotype
  - ✓ Short Physical Performance Battery
  - ✓ 400 m walk time

Fried J. J Gerontol Biol Sci Med 2001

Increased frailty phenotype in HIV infection

- Three-fold higher prevalence of frailty in HIV+ than in HIV-
- Occurs around 20 years erlier than in HIV-
- Associated with lower CD4 counts, older age and longer duration of Hiv infection



Desquilibet. JAIDS, 2009.

Summary

- HIV infection in old patients is a growing condition in western societies
- Age modifies the natural history of HIV infection
- Management of older HIV-infected patients is complicated by the presence of co-morbidities related to age
  - Cardiovascular disease, Cancer, Diabetes, Renal disease, Hepatic disease, Bone disease
- Not clear to what extent HIV status and ARV exposure contribute to these comorbidities

Summary (cont'd)

- Presence or risk of comorbidities in older HIV patients may influence antiretroviral selection
  - Avoidance of metabolic and other toxicities, drug-drug interactions
- Management of older HIV patients should include
  - Baseline evaluation of cardiovascular risk
  - Regular monitoring of fasting lipids and glucose, renal function, and markers of bone disease

HIV/ART as aging agents

The questions

- Does HIV accelerate the aging process?
- Does HIV accelerate degenerative, aging-related diseases?
- Does ART reverse or accelerate these processes?

Molecular Mechanics of Aging

- Senescence (Telome[illegible]hortening)
- Low degree infl[illegible]
- Chronic imm[illegible]ation
- Mitoch[illegible]unction
- Ar[illegible]
- Reac[illegible] intermediates generation

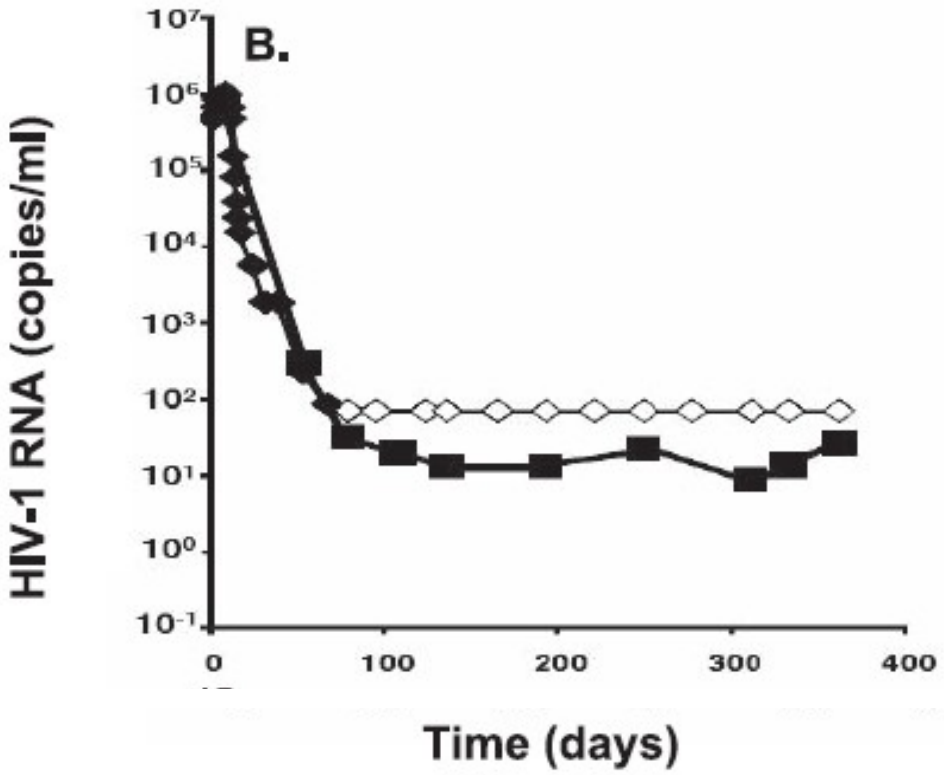
HIV-1/ART

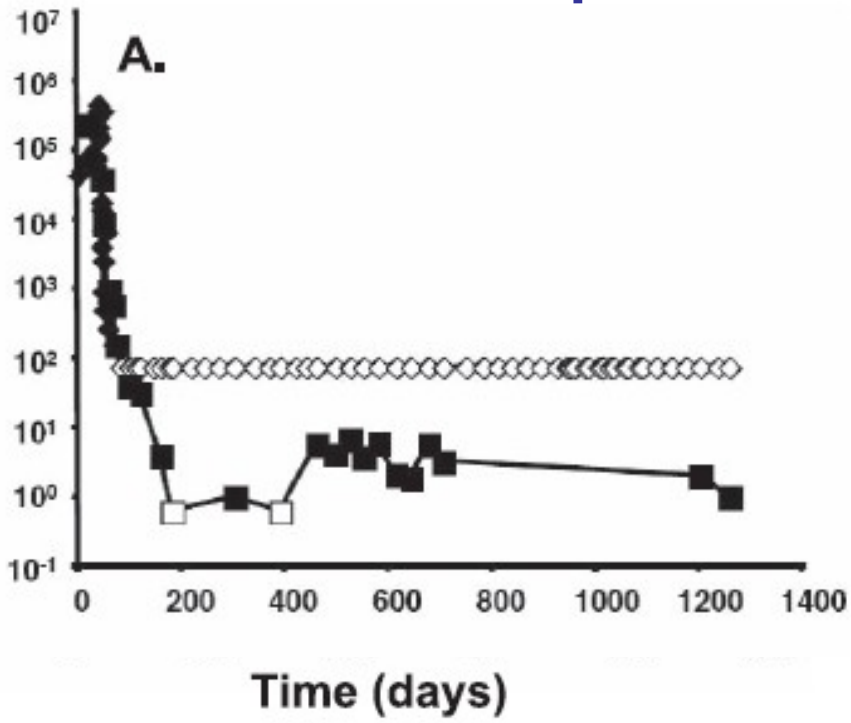
Low-level Viremia <75 copies/ml is Common During Apparent Viral Suppression on HAART

N=130

80% Patients had detectable viremia

Median 3.1 copies/ml

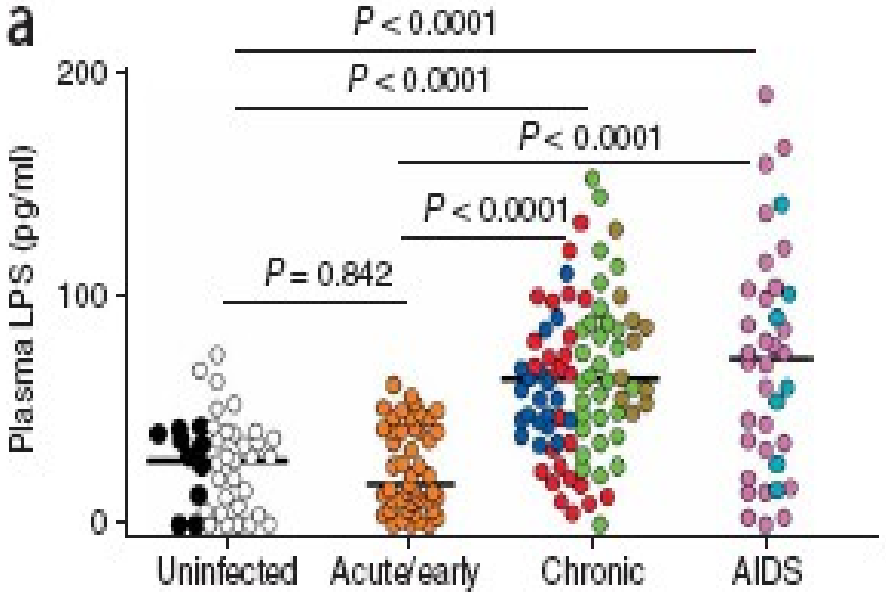


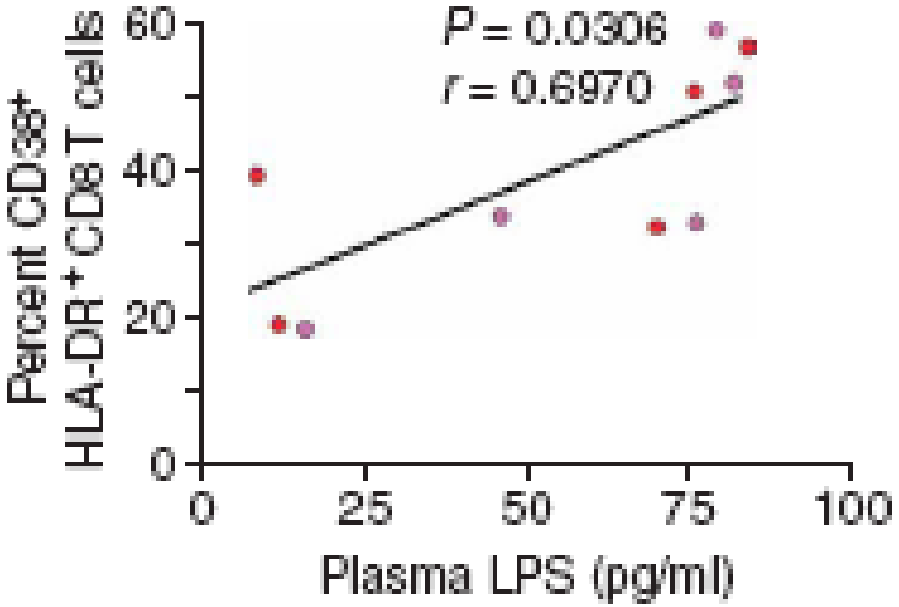


Maldarelli F. et al., PLOS Path, 2007; Palmer S. et al, PNAS, 2008.

Mucosal Translocation of Bacterial Products

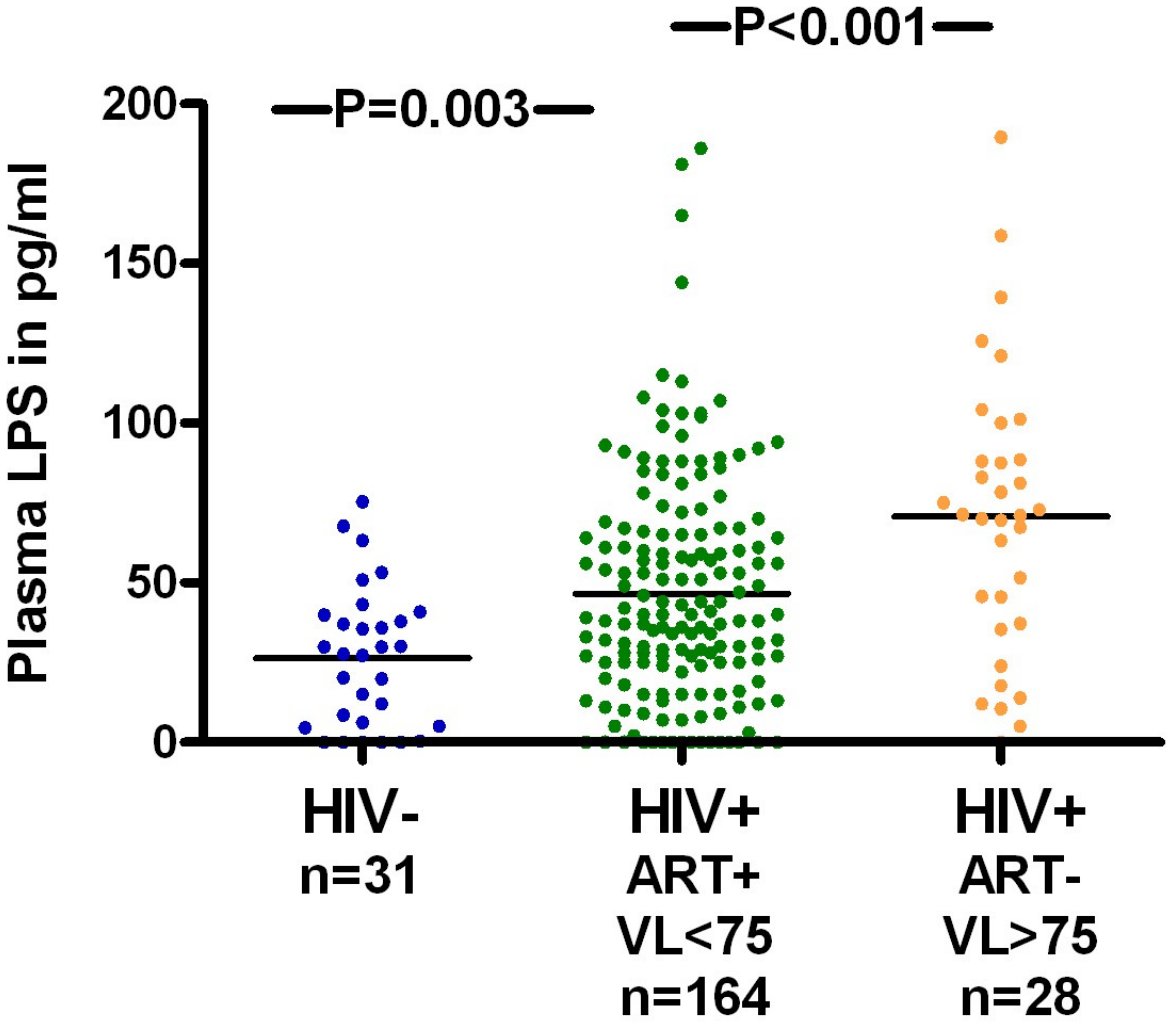
A potential cause of T cell activation in HIV





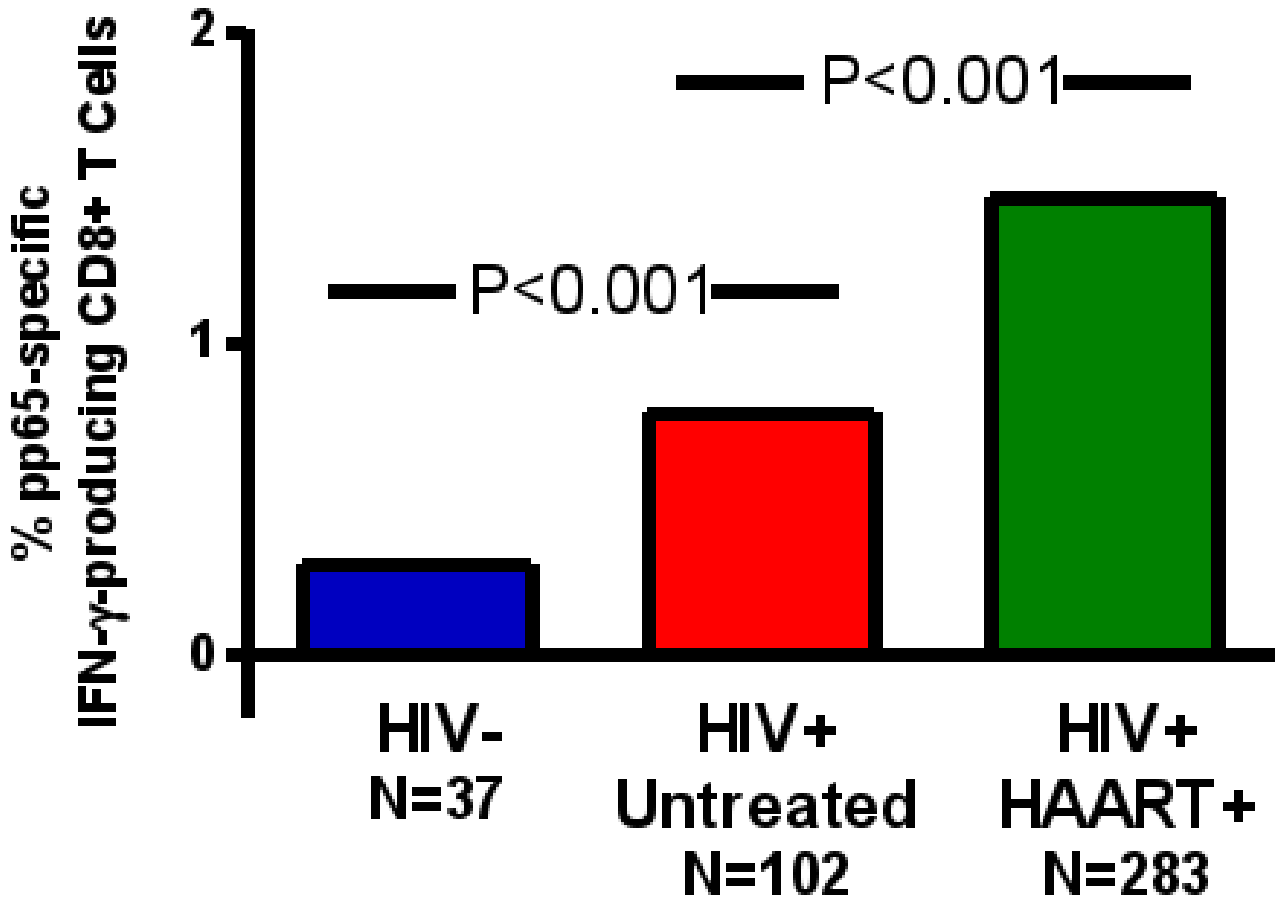
Brenchley et al, Nat Med, 2006

Microbial Translocation Decreases with cART but Persists for Years



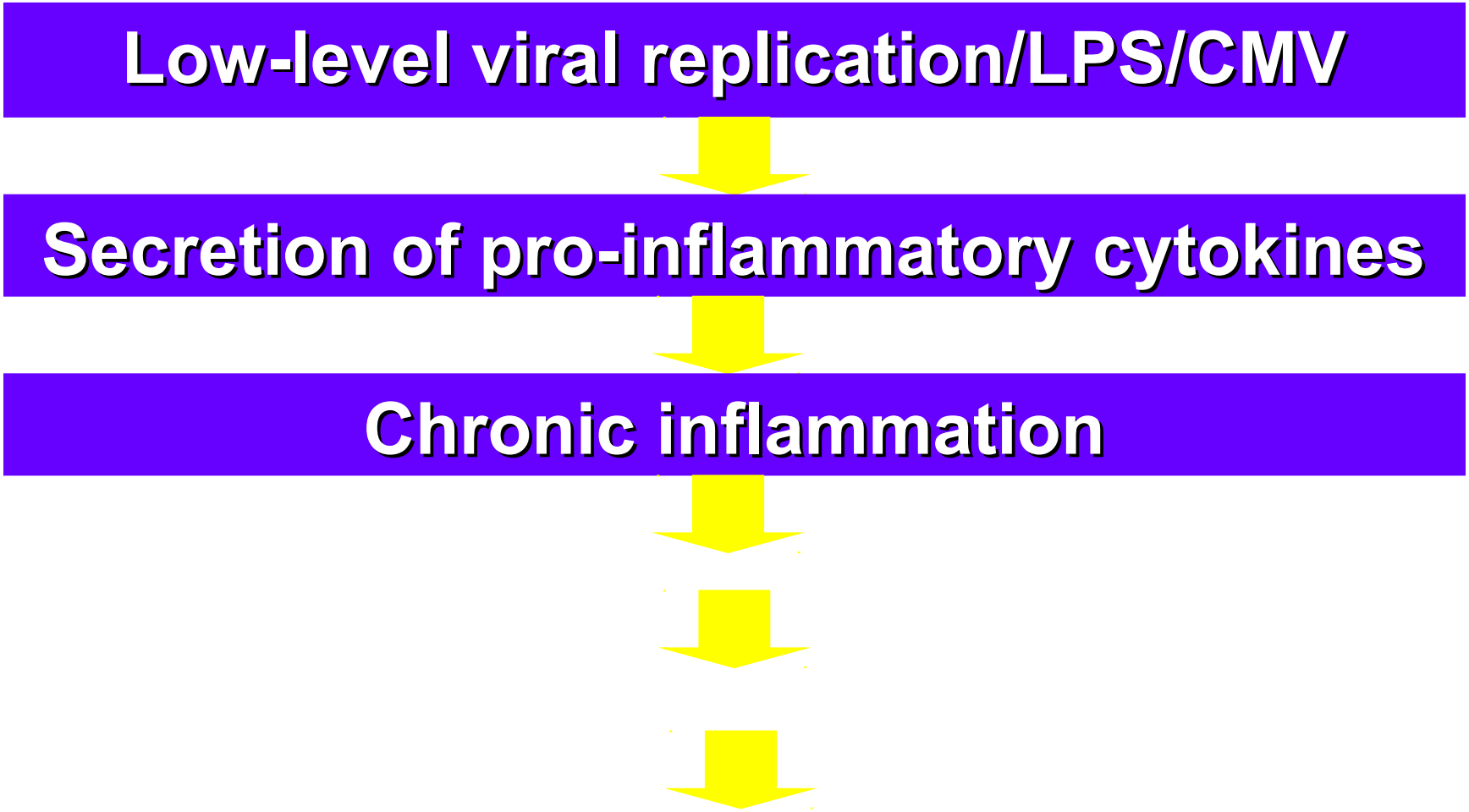
Jiang et al, JID, 2009. Marchetti, AIDS, 2008

CMV-specific T Cell Responses are Higher in HIV-infected Patients



Naeger et al, PLoS One 2010

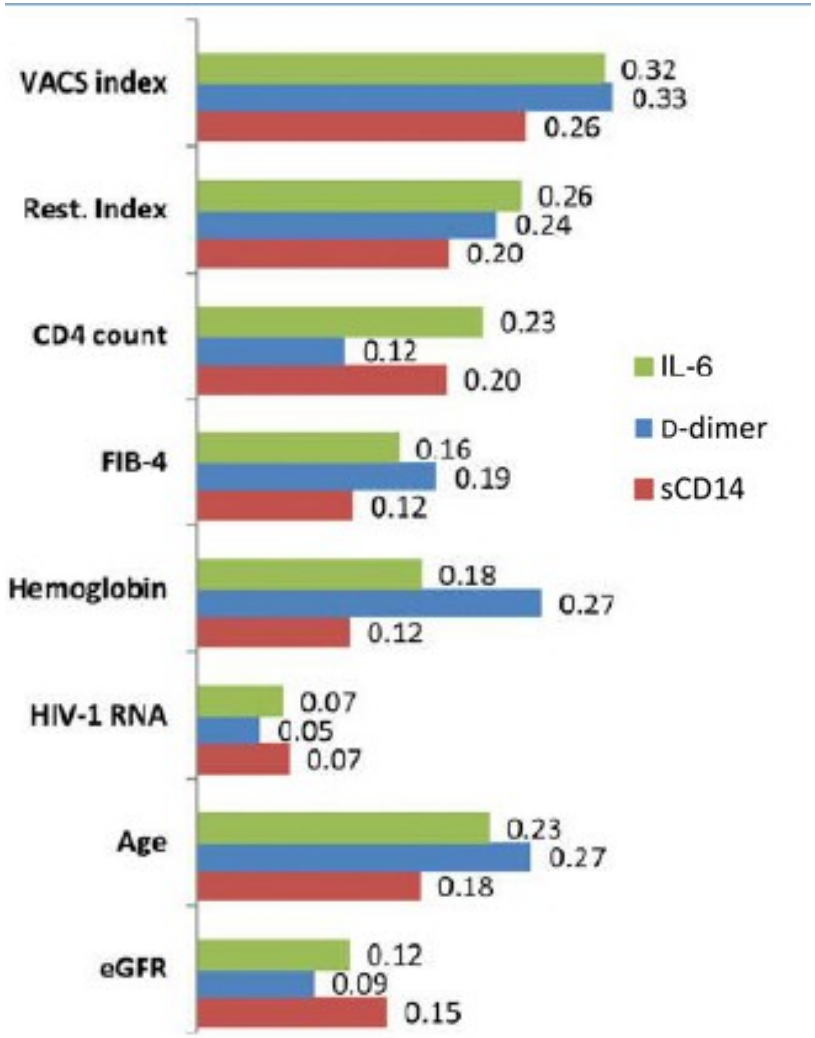
Cascade of events due to chronic inflammation and immune activation




Steatosis
NASH
Cardiov
ri

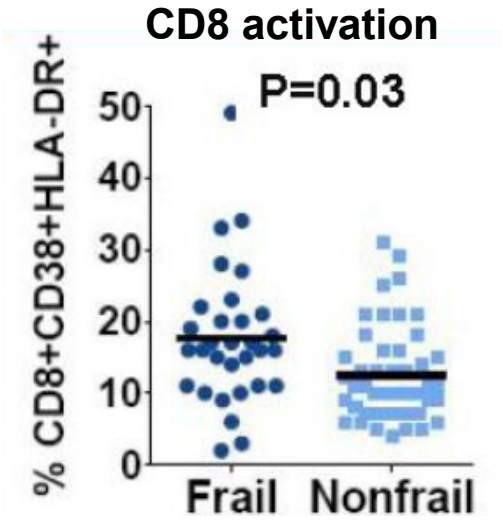
Inflammation correlated with VACS index and end-organ function in HIV

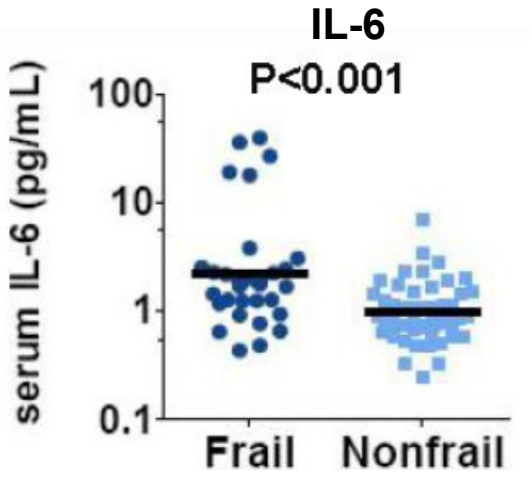
- VACS index combines
  - ✓ HIV-associated factors (CD4, VL)
  - ✓ End-organ function
    - Liver (FIB-4)
    - Anemia (HgB)
    - Renal (eGFR)
    - Age
- VACS index predicts death more strongly than age/CD4/VL alone
- VACS index and components associated with inflammation

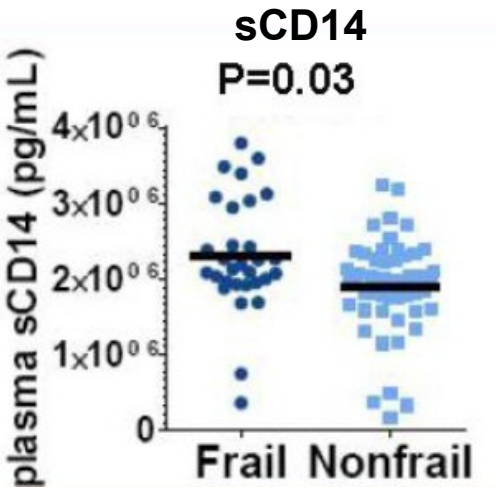


Justice. CID, 2012.

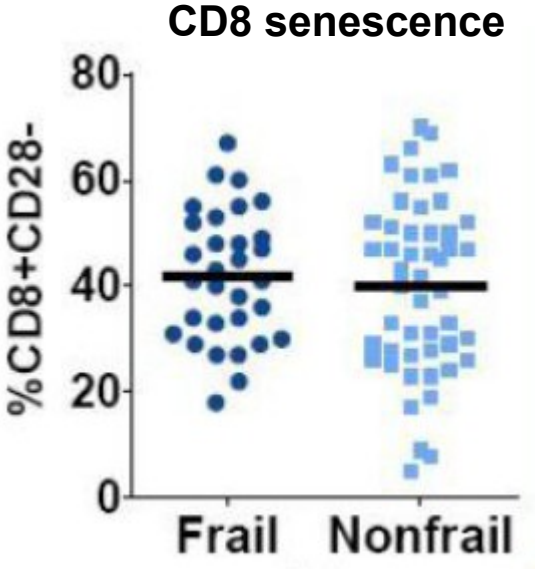
Inflammation associated with frailty during suppressive ART

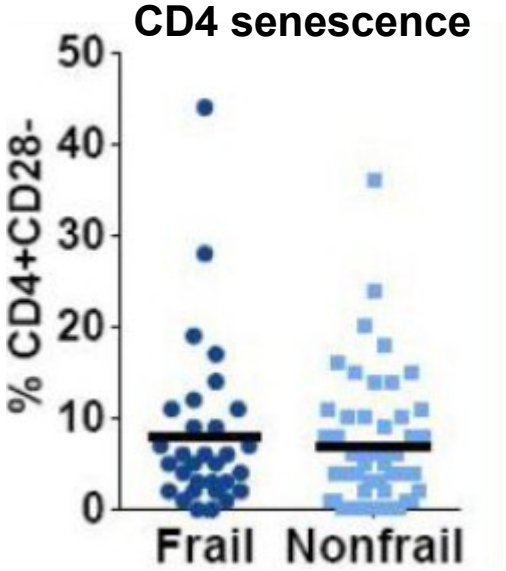






But T-cell senescence not associated with frailty



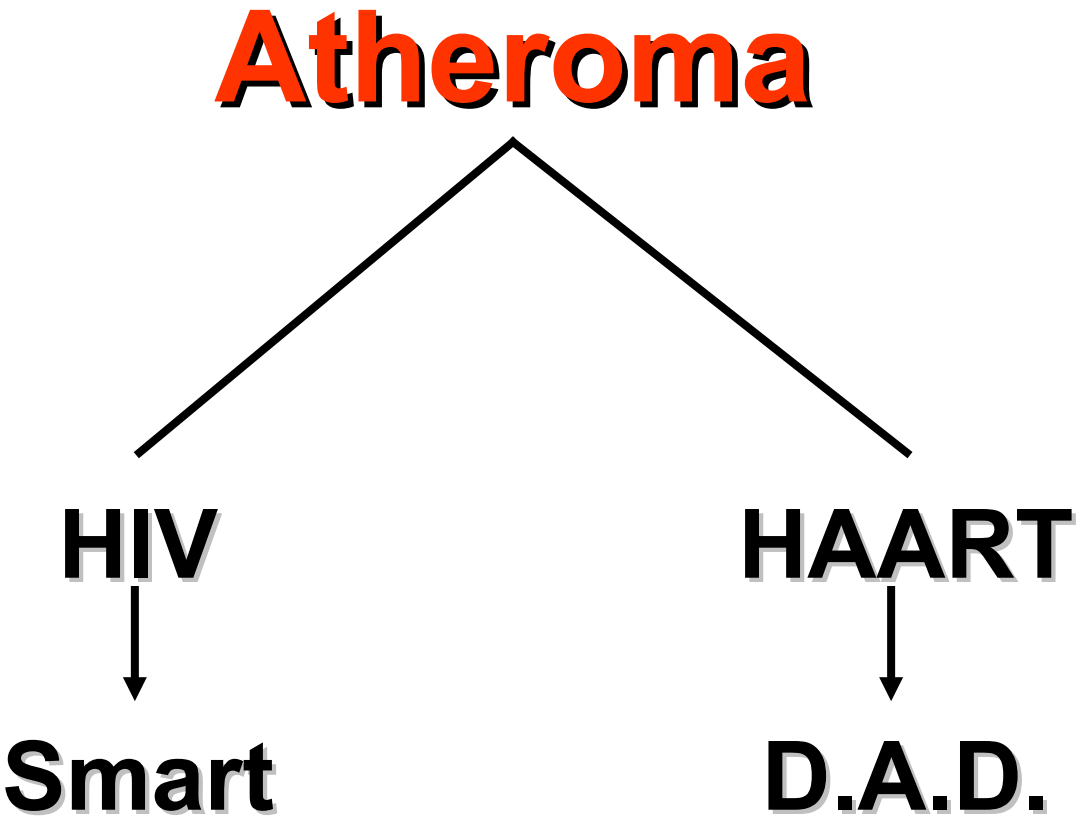


Erlandson. IAS 2011.

The Conundrum of Using cART

- Allow persons to get older
  - Demasking chronic disease processes associated with HIV not perceived as an issue prior to the introduction of cART (eg. HBV, HCV)
  - Allow the normal aging process to manifest itself clinically
  - Exacerbate adverse effects of cART that interacts with the normal aging process

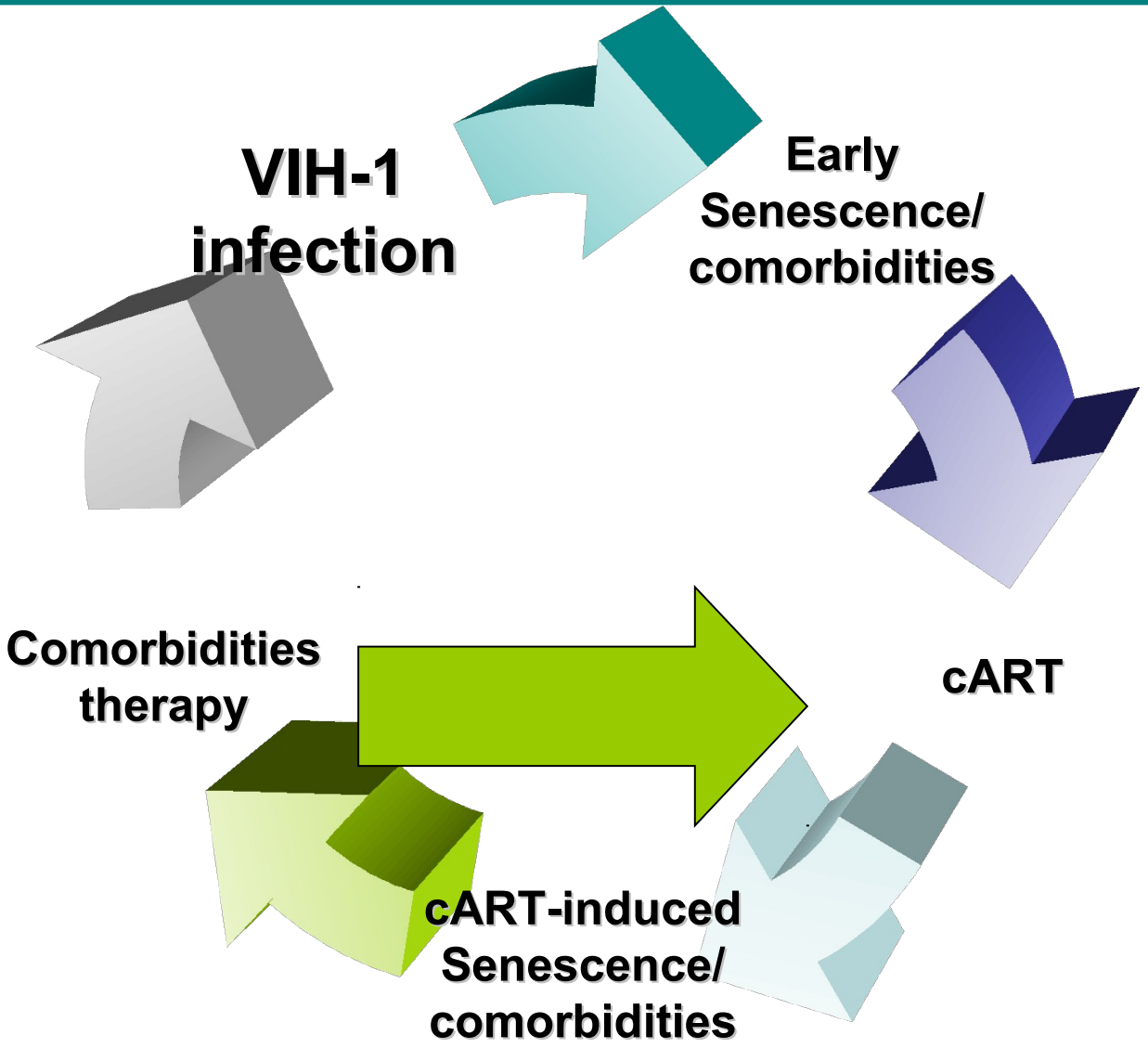
Atherosclerosis, HIV and ART



The geriatric giants

- Atheroma
- Neoplasia
- Dementia

The vicious circle



Summary

- Clinical evidence suggest that age-associated comorbidities are prevalent in HIV-infected patients
- Pathophysiological mechanisms present in HIV-infected patients have been implicated in senescence
- Premature senescence in HIV-infected patients may be HIV- or ART-dependent

“Old age is not so bad when you consider the alternatives”

Maurice Chevalier (1888–1972)