Aging and HIV disease:A Symbiosis.

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Overview

- Epidemiology of HIV/AIDS in older adults
- Immune activation and immunosenesence
- Clinical considerations of HIV management in an aging patient
- Age-associated comorbidities in patients with HIV
  - Renal disease
  - Bone disease and vitamin D deficiency
  - Cardiovascular disease (CVD)
  - Neurocognitive abnormalities
  - Non–AIDS-defining malignancies

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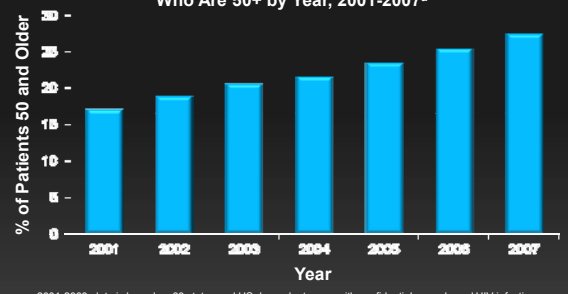
Epidemiology of HIV/AIDS in Older Adults

Growing Older: HIV and Aging

Estimated Percentage of Persons Living with HIV/AIDS Who Are 50+ by Year, 2001-2007[a]



[a]For years 2001-2003, data is based on 33 states and US dependent areas with confidential name-based HIV infection reporting, *CDC HIV/AIDS Surveillance Report, 2005*. For years 2004-2007, data is based on 34 states and 5 US dependent areas with confidential name-based HIV infection reporting, *CDC HIV/AIDS Surveillance Report, 2007*.
Gay Men's Health Crisis. *Growing Older Wth the Epidemic: HIV and Aging*. 2010.

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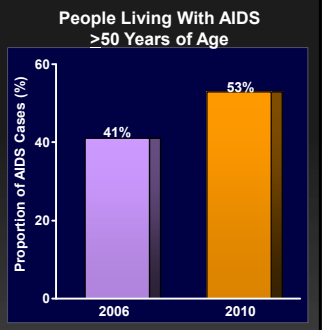
By 2015,

Approximately 50% of People Living With HIV Will Be ≥50 Years of Age

Smith G. Senate Committee on Aging. 2005
Available at: http://aging.senate.gov/events/hr141gs.pdf.

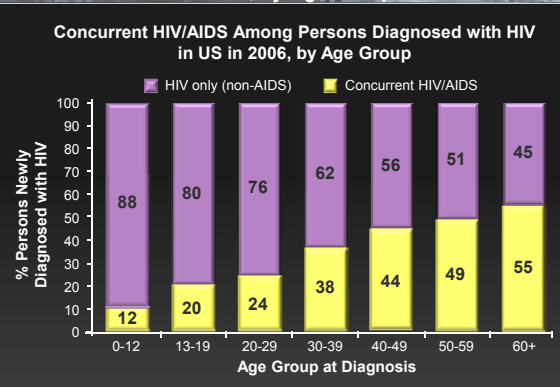
AIDS Cases in San Francisco:Majority ≥50 Years of Age

- Population-based surveillance registry of San Francisco
  - 95% of cases validated
- From 2006 to 2010 (people ≥50 years of age)
  - Newly diagnosed AIDS cases increased from 21% to 27%
  - AIDS-related deaths decreased from 288 to 228
- First time that the majority of people living with AIDS in San Francisco are ≥50 years of age
  - Presents new challenges for research, medical care, and support services



Scheer S, et al. 6th IAS Conference. Rome, 2011. Abstract TuPE131.

Concurrent HIV/AIDS Among Persons Diagnosed With HIV in the US in 2006, by Age Group



Gay Men's Health Crisis. *Growing Older Wth the Epidemic: HIV and Aging.* 2010.

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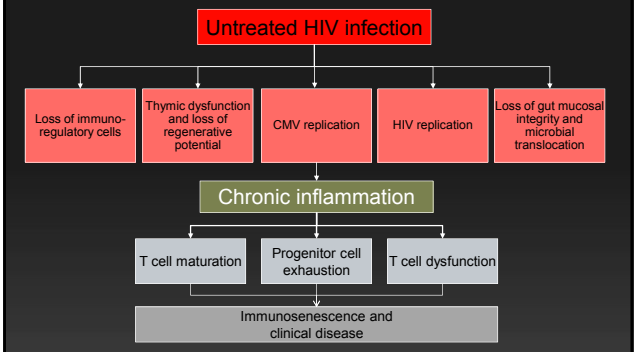
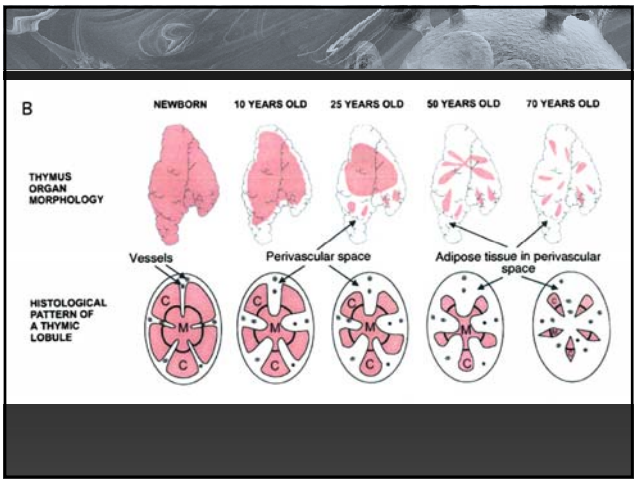
Immune Activation and Immunosenescence

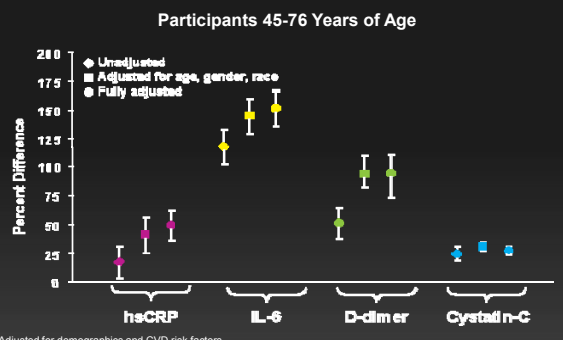
Impact of HIV Infection on Inflammation and Immunosenescene[1,2]



1. Adapted from Deeks SG. *Annu Rev Med.* 2011. 62:141-55. 2. Mascolini M. *Rev Antivir Ther.* 2010;5(suppl):10-36.



Inflammatory Markers* in Treated HIV+ Patients vs HIV- Patients



*Adjusted for demographics and CVD risk factors.

Neuhaus J et al. *J Infect Dis.* 2010; 201(12):1788-1795.

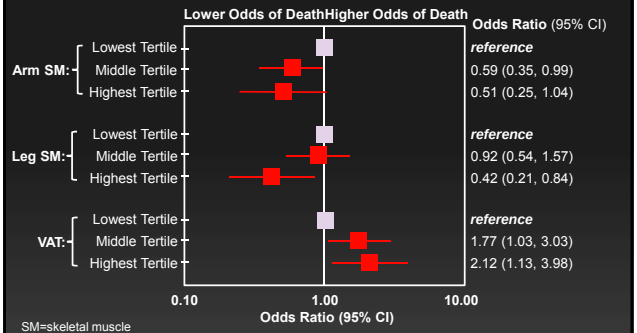
SMART: Baseline Biomarkers and All-cause Mortality

Biomarker	Unadjusted		Adjusted*	
	OR ($4^{th}/1^{st}$ quartile)	*P* value	OR ($4^{th}/1^{st}$ quartile)	*P* value
hs-CRP	2.0	.05	3.1	.02
IL-6	8.3	<.0001	12.4	<.0001
Amyloid A	2.2	.07	3.1	.05
D-dimer	12.4	<.0001	41.2	<.0001

*Adjusted for age, race, ART, HIV RNA level, CD4+ cell count, smoking, BMI, prior CVD, diabetes, antihypertensive and/or lipid-lowering agent use, total/HDL cholesterol, Hepatitis B or C coinfection.

Kuller L et al. *PLoS Med.* 2008;5(10):1496-1508.

FRAM: Sarcopenia and Central Adiposity Associated with 5 Year Mortality

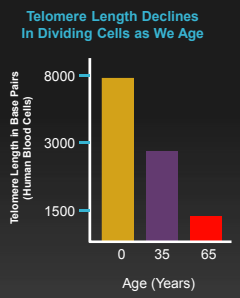


SM=skeletal muscle
VAT=visceral adipose tissue

Scherzer R, et al. CROI 2011, 76.

Telomere Length

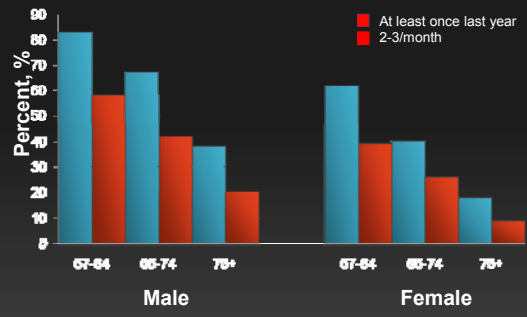
- HIV and aging both associated with early replicative senescence marked by:
  - Low levels of CD28 markers
  - Shortened telomere levels
  - Increased mortality
  - Poor immune response
  - Faster disease progression
  - Increased IL6/TNFα
- May be mitigated by adding telomerase
  - Small molecule telomerase activators (e.g. TAT2)



Effros R, et al. 15th CROI; Boston, MA (2008); Abst. 105.

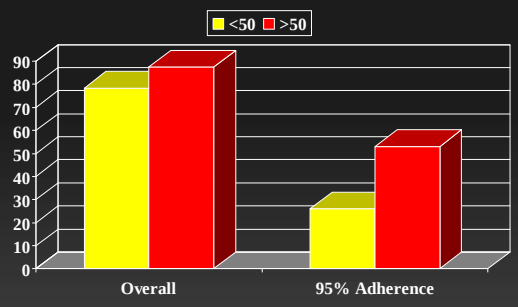
Clinical Considerations of HIV Management in an Aging Patient

Sexual Activity in Older Americans



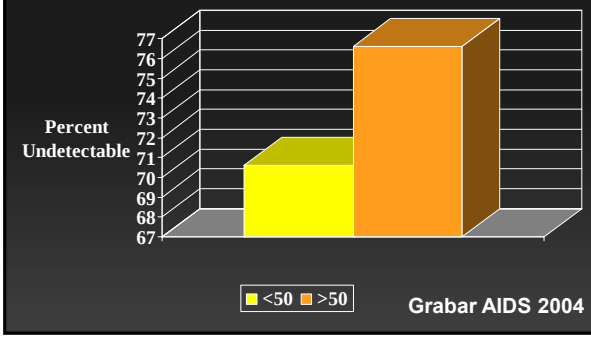
Lindau ST. *N Engl J Med.* 2007;357(8):762-774.

Adherence: Some things do get better with Age



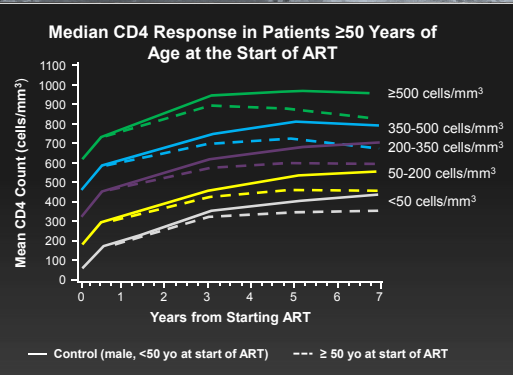
Hinkin AIDS 2004

HIV-1 RNA <500 at 6 months: by Age



Grabar AIDS 2004

ART in Patients >50 Years Old: ATHENA National Cohort



Gras L, et al. *J Acquir Immune Defic Syndr*. 2007;45(2):183-192.

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Clinical Considerations in Aging Adults With HIV

- Older patients more likely than younger patients to present late for HIV diagnosis and care[1]
- Physicians less likely to discuss HIV/AIDS and related risk factors with older patients[2]
- Asymptomatic older HIV-infected individuals are less likely to seek out testing and medical care[3]
- Symptomatic older HIV-infected individuals are more likely to attribute HIV-related symptoms to other illnesses or to the normal aging process[3]

1. Cuzin L. *Clin Infect Dis*. 2007;45(5):654-657.
2. Skiest DJ. *Arch Fam Med*. 1997;6(3):289-294.
3. Siegel K. *AIDS Care*. 1999;11(5):525-535.

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HIV Risk in Older Adults:Unprotected Sexual Activity

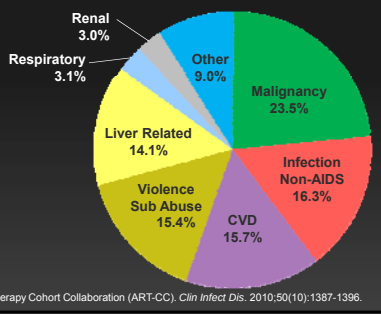
- Use of erectile dysfunction drugs contributes to increased rates of sexual activity
- Menopause
  - No risk for pregnancy=no need for condom
- Vaginal dryness due to estrogen depletion leads to greater likelihood of trauma and increased risk of HIV acquisition

Luther VP, et al. *Clin Geriatr Med*. 2007;23:567-583.
Illa L, et al. *AIDS Behav*. 2008;12:935-942.

Age-Associated Comorbidities in Patients with HIV

Causes of Death In HIV+ Persons Treated With ART (1996-2006)

- Assessed deaths in 13 HIV-1 cohorts comprised of 39,727 persons
- Of 1876 deaths, definitive cause in 85%
- Non-AIDS related deaths in 50.5%:



Antiretroviral Therapy Cohort Collaboration (ART-CC). *Clin Infect Dis*. 2010;50(10):1387-1396.

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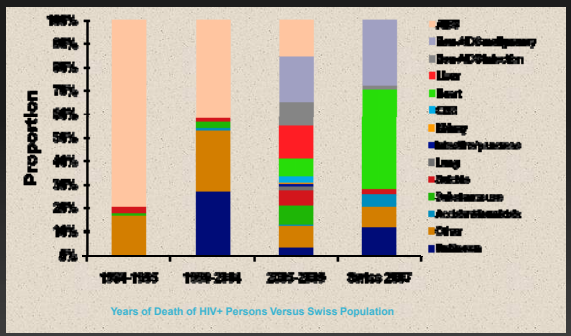
- SHCS is a prospective observational cohort
- Characteristics of participants that died from 2005-2009
- 459 deaths/9,053 participants (5.1%)

Changing Patterns of the Causes of Death in a Swiss Cohort (SHCS)



Years of Death of HIV+ Persons Versus Swiss Population

Ruppik M, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 789.

Look to the Long-Term, in Money and in HIV

Focus on Non–AIDS-Defining Illnesses

- Renal disease
- Bone disease
- Cardiovascular disease (CVD)
- Non–AIDS-defining malignancies
- Neuropsychologic abnormalities

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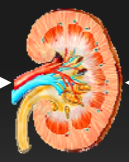
Risk Factors Contributing to Development of Kidney Disease

- Modifiable risk factors
  - Diabetes mellitus
  - High blood pressure
  - Kidney stones
  - Inflammation (eg, glomerulonephritis)
  - Allergic reactions to medications (eg, antibiotics)
  - Medications
    - eg, NSAIDs
  - Drug abuse
  - Use of creatine, testosterone, hGH



- Nonmodifiable risk factors
  - Age
  - Family history of kidney disease
  - Trauma or accident
  - Presence of other diseases
    - HIV/AIDS, hepatitis C, lupus, sickle cell anemia, cancer, congestive heart failure

Adapted from KDOQI CKD Guidelines. http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p7_risk_g13.htm. Accessed July 5, 2010.

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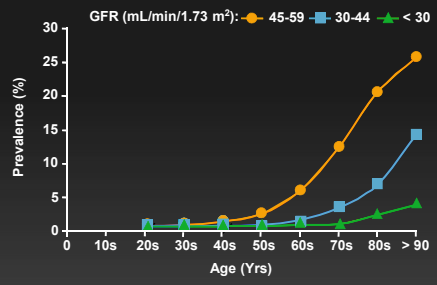
Renal Disease Increases With Age in the General Population



Hallan SI, et al. Br Med J. 2006; 333:1047.

Renal Function Evaluation: Complementary Ways to Monitor Kidney Function

- Serum creatinine
- Creatinine clearance (calculated by Cockcroft-Gault [CG])
- GFR (calculated by MDRD)
- 24-hour urine test
- Urinalysis
  - Dipstick to screen for albuminuria or proteinuria
- Microalbuminuria
  - 24-hour urine for albumin
  - Microalbuminuria/creatinine ratio in a spot specimen
- Proteinuria
  - 24-hour urine test for protein
  - Protein/creatinine ratio in a spot specimen

GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.
KDOQI CKD Guidelines. http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm Accessed June 24, 2010.

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Estimating GFR: Similar Serum Creatinine Levels Do Not Mean Similar GFRs

Plasma Creatinine: 1.4 mg/dL

Estimated GFR*

	White Male, 25, 210 lb	Black Female, 86, 115 lb
CG	108	52
MDRD	66	46
CKD-EPI	69	39

CKD-EPI, chronic kidney disease epidemiology collaboration.
*GFR measured in mL/min/1.73 m².

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Focus on Non—AIDS-Defining Illnesses

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Many Potential Contributors to Decreased BMD in Patients With HIV

- Liver disease
- Premature menopause
- Hypogonadism
- Smoking
- HIV infection

- Decreased bone acquisition
- Fat deposition in marrow
- Decreased physical activity
- Decreased muscle mass
- Decreased fat mass
- Malnutrition
- Vitamin D deficiency

Decreased bone mineral density

- Alcohol use
- Medications
  - Corticosteroids
  - Anticonvulsants
  - Nucleoside analogues/ mitochondrial dysfunction
  - Protease inhibitors

- Family history
- Female sex
- Increasing age

Adapted from Glesby M et al. *CID.* 2003; 37(Suppl 2):S91-S95.

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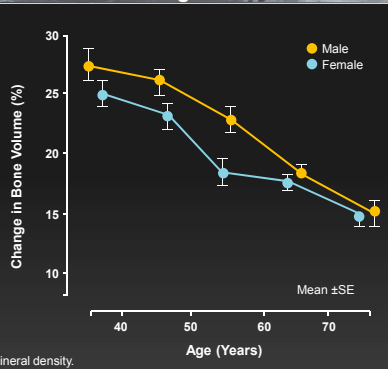
BMD Decreases With Age



BMD, bone mineral density.

Orwoll ES et al. *Endocr Rev*. 1995;16(1):87-116.

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BMD in HIV+ Persons

- Multiple studies have found increased prevalence of osteoporosis and osteopenia in HIV-infected persons compared with uninfected persons
- Meta-analysis of studies
  - 67% HIV infected persons had reduced BMD (OR 6.4)
  - 15% HIV+ had osteoporosis (OR 3.7)

Brown et al. *AIDS*. 2006;20:2165-2174.

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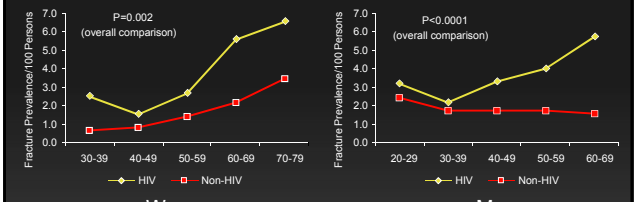
Fracture Prevalence in HIV-infected and Non-HIV-infected Persons in MGH/Partners Healthcare System: 1996-2008



8,525 HIV-infected
2,208,792 non HIV-infected patients

Triant. JCEM, 2008

2008 US National Osteoporosis Foundation (NOF) Guidelines for DXA Screening

- Those with a history of fragility fracture
- Women ≥65 years, Men ≥70
- Postmenopausal women and men 50-70 years, if there is concern based on risk factor profile

Screening in HIV-infected Patients:

All post-menopausal women
Men ≥50 years

2008 US NOF Guidelines: Who to Treat

- Those with hip or vertebral fractures
- Those with BMD T-scores ≤-2.5 at the femoral neck, total hip, or spine by DXA
- Those with T-score between -1 and -2.5 (osteopenia) at above sites AND 10-year hip fracture probability ≥3% or 10-year all major osteoporosis-related fracture ≥20% based on FRAX model

*Applies to post-menopausal women and men ≥50 years

http://www.shef.ac.uk/FRAX

Management Options

- General recommendations
  - Calcium/vitamin D supplementation
  - Smoking cessation, alcohol reduction
- Rx options
  - Bisphosphonates

Focus on Non—AIDS-Defining Illnesses

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- Non—AIDS-defining malignancies
- Neuropsychologic abnormalities

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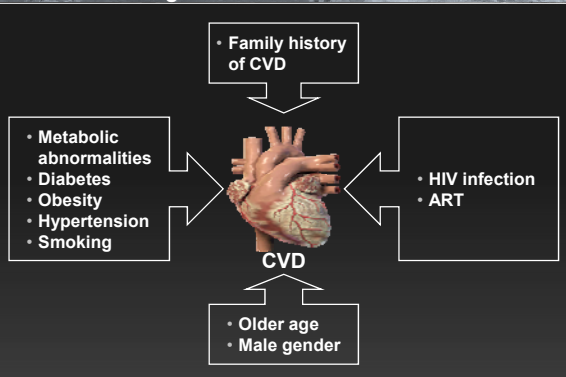
Factors Affecting Risk for CVD in Patients with HIV



Adapted from Grinspoon S et al. *N Engl J Med.* 2005;352:48-62.

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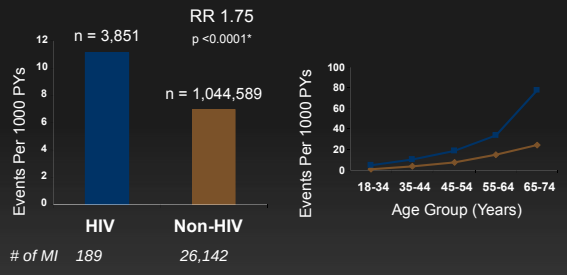
Coronary Aging in HIV-Infected Patients

- **Method**: Cross-sectional study, 400 patients (mean age 48) had cardiac CT for coronary artery calcium (CAC)
- **Results**: 162 patients (40%) had increased vascular age with average of 15 years over chronological age

Guaraldi G, et al. CID 2009;49:1756

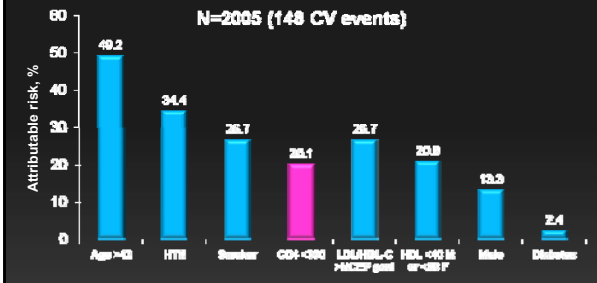
Risk of MI in Patients Presenting at Least Twice to Either of Two Boston Hospitals By HIV Status



* Adjusted for age, gender, race, hypertension, diabetes and dyslipidaemia. Proportion of patients with hypertension, diabetes and dyslipidaemia significantly higher in HIV-positive vs HIV-negative cohort

Triant et al., JCEM, 2007

HOPS: Attributable Risk for CVD[1]



- HOPS finding corroborated by the FIRST[2] study
  - Patients with higher on-treatment CD4 cell count had lower risk of non-AIDS events, including CVD[2]

[1]Lichtenstein KA, et al. *Clin Infect Dis*. 2010;51(4):435-447. [2]Baker JV. *AIDS*. 2008;22:841-848.

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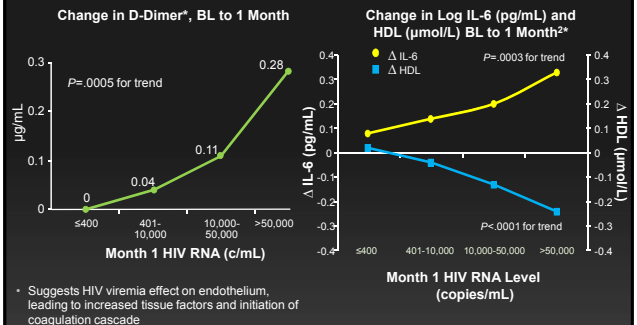
SMART: Changes in D-Dimer and IL-6 Levels



- Suggests HIV viremia effect on endothelium, leading to increased tissue factors and initiation of coagulation cascade

*DC patients on ART at baseline with HIV RNA ≤400 copies/mL

[1]Kuller L, et al. *PLoS Med*. 2008;5(10):1496-1508. [2]Duprez DA, et al. *Atherosclerosis*. 2009;207(2):524-529.

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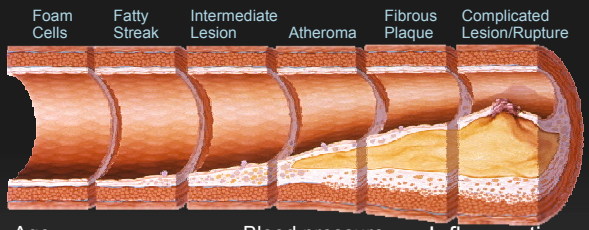
Atherosclerosis, CVD

HIV



Age
Gender
Hypertension
Lipid profile: LDL, HDL, Trig
T2D
Smoking

Blood pressure
LDL
Glucose

Inflammation

Focus on Non–AIDS-Defining Illnesses

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- Non–AIDS-defining malignancies

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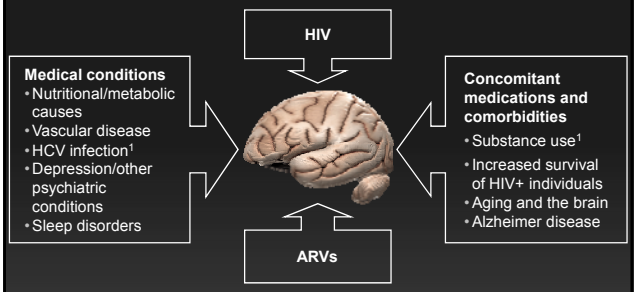
Multifactorial Etiology of HIV-Associated Neurocognitive Conditions



Adapted from Valcour VG, et al. *J Acquir Immune Defic Syndr.* 2006;43(4):405-10.
[1]Gonzalez R, Cherner M. *Int Rev Psychiatr.* 2008;20(1): 49-60.

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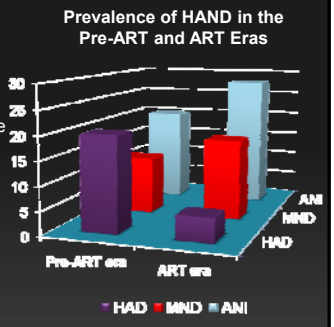
HIV Infection and Aging Independently Affect Brain Function by Functional MRI

- **Method**
  - fMRI in age matched persons with HIV (n=25) and without HIV (n-26)
  - Goal – changes in visual cortex due to impact of aging
  - HIV patients – med CD4 486, 60% HAART
- **Results**
  - **HIV infection added 21 years to brain age**

Ances BM. JID 2010;201:336

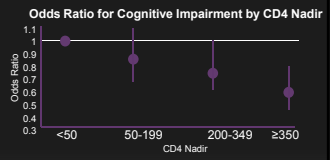
HIV-associated Neurocognitive Complications

- Chronic HIV infection may result in progressive neurodegenerative disease
  - Initially termed NeuroAIDS
  - More recently reclassified as HIV-associated neurocognitive disorders (HAND)
- HAND severity:
  - Asymptomatic neurocognitive impairment (ANI)
  - Mild neurocognitive disorder (MND)
  - HIV-associated dementia (HAD)



Neurocognitive Disorders Associated with Nadir CD4 Counts

- Multicenter cohort study (CHARTER) of 1526 pts evaluating HIV-associated Neurocognitive Disorders (HAND)
- Complex testing consistent with defined criteria used to determine HAND
  - 603 had HAND (without a substantial confounder); 726 not impaired
  - Most with hand (n=428) were asymptomatic and only a few (n=27) had frank dementia
- Multivariate analysis: Higher CD4 nadir associated with lower risk of HAND



Odds Ratios for NP Impairment

	N	Impaired	Unimpaired	OR (95% CI)
All	1525	799	726	
Nadir CD4 <50	387	222	165	1.00 (reference)
Nadir CD4 50-199	481	258	223	0.86 [0.66, 1.13]
Nadir CD4 200-349	370	189	181	0.78 [0.58, 1.03]
Nadir CD4 ≥350	287	130	157	0.62 [0.45, 0.84]
On ART, Plasma VL <50c/ml	589	320	269	
Nadir CD4 <50	185	112	73	1.00 (reference)
Nadir CD4 50-199	214	118	96	0.80 [0.54, 1.19]
Nadir CD4 200-349	133	64	69	0.60 [0.39, 0.95]
Nadir CD4 ≥350	57	26	31	0.55 [0.30, 0.99]

Ellis R, et al. 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 429.

Focus on Non—AIDS-Defining Illnesses

- Renal disease
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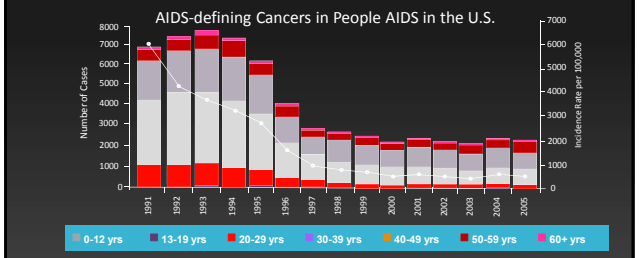
- Neuropsychologic abnormalities
- Non–AIDS-defining malignancies

Cancer Pathogenesis

- The roots of the genesis of cancer lie in multiple mutations in proliferating cells, predominantly involving regulatory genes that affect cell cycling.
- These mutations may be provoked by chronic activation of the tissue response and here lies the potential contribution of chronic inflammation

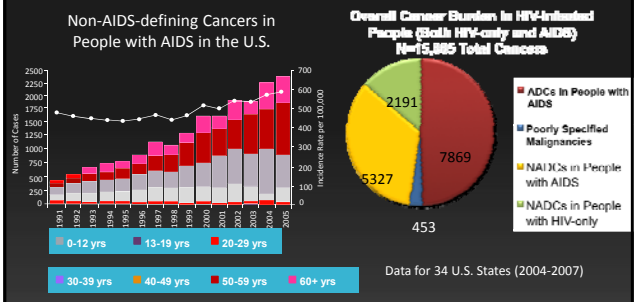
Burden of Cancer Among HIV-infected Persons in the US Population

- Estimate of the total number of cancers (cancer burden) in patients with AIDS as well as in HIV(+) patients without AIDS in the US
- CDC collects HIV data from US states
  - AIDS from entire country from 1991-2005
  - HIV only from 34 states 2004-2007
- NCI HIV/AIDS cancer match study



Shiels M, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. WEAB0101.

The Burden of Cancer Among HIV-infected Persons in The US Population



Shiels M, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. WEAB0101.

Incidence of Non-AIDS Defining Cancers Increasing in HIV+ Patients

- Incidence of cancers was increased significantly in ASD/HOPS cohort (HIV+) vs general population (HIV-):

Cancer Type	SRR (95% CI)*
Anal	42.9 (34.1-53.3)
Vaginal	21.0 (11.2-35.9)
Hodgkin lymphoma	14.7 (11.6-18.2)
Liver	7.7 (5.7-10.1)
Lung	3.3 (2.8-3.9)
Melanoma	2.6 (1.9-3.6)
Oropharyngeal	2.6 (1.9-3.4)
Leukemia	2.5 (1.6-3.8)
Colorectal	2.3 (1.8-2.9)
Renal	1.8 (1.1-2.7)

*Standardized ratio rate: observed ASD/HOPS (HIV+) rate to standardized rate (SEER, HIV-).

Patel P. *Ann Intern Med.* 2008;148(10):728-736.

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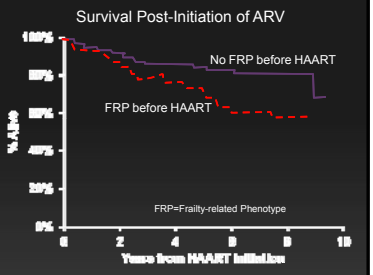
Functional Issues with Aging and HIV

- Frailty phenotype (presence of >3 of the following)
  - Exhaustion, slowed walking speed, low activity level, weakness, and weight loss
  - Associated with poorer health outcomes
- MACS
  - A 55-year-old HIV-infected person has similar frailty as a 65-year-old HIV-negative person
- Proposed mechanisms
  - Mitochondrial dysfunction and increased number of free radicals and cytokines activate inflammatory pathways, ultimately leading to frailty

Gebo KA, et al. Curr Infect Dis Rep. 2009;11:246-254.
Desquilbet L, et al. J Gerontol A Biol Sci Med Sci. 2007;62:1279-1286
Oursler KK, et al. AIDS Res Hum Retroviruses. 2006;22:1113-1121

Frailty May Influence Survival Post-ARV Initiation

- Retrospective comparison of time to death and AIDS diagnoses in HIV-infected men with known date of HIV diagnosis and frailty phenotype measured within 6 months of starting ARV (n=596)
- Results unchanged when analysis restricted to ARV responders



Desquilbet L, et al. J Gerontol A Biol Scie Med Sci 2011;66A:1030-8.

HIV Treatment May Be Complicated by Polypharmacy

- Overlapping toxicities
- Drug-drug interactions
  - Increase or decrease in drug plasma levels
  - Inadequate levels of ARVs may lead to incomplete viral suppression and development of resistance
- ART-induced organ toxicities may exacerbate pre-existing age-related conditions
- Close monitoring is required to detect any emerging problems

Simone MJ. Geriatrics. 2008;63(12):6-12.

Screening in HIV Patients

1. Start ART earlier because older patients have slower CD4 recovery and more comorbidities
   - Any CD4 count.
2. Monitor and aggressively manage CVD risk factors
   - Smoking cessation; cocaine use; BP; lipids; BS and insulin resistance; weight gain; exercise; diet; stress; depression
   - Should we measure hsCRP; D-dimer; fibrinogen levels?
   - Should HIV be a part of the Framingham equation?

Screening in HIV Patients (cont'd)

3. DXA scans and vitamin D levels
   - Should all patients with HIV over 40, over 50, have a dexascan? Most favor >50 years
   - What if there is at least 1 additional risk factor such as smoking, low BMI, white race, hypogonadism, steroid use , HCV, etc? Many favor DXA at any age in this group
   - What is the optimal vitamin D level? >30 ng/mL? >60 ng/mL? Most docs are replacing at <30 ng/mL and winging it
4. Monitor Serum Creatinine/GFR
   - UA dip for protein and glucose/spot Urine Pr/Cr ratio
   - Are these sufficient?

Screening in HIV Patients (cont'd)

5. Neurocognitive mini screens/Depression scores
   - Memory/Attention/Psychomotor speed/Construction
   - Need to eliminate the stigma of the Dx of HIV in the elderly
   - Work, retirement, remaining engaged with family and friends
6. Cancer Screening
   - All usual including vaginal PAP, breast exam and mammography, colonoscopy, DRE + PSA
   - Anal PAP ± HRA should be part of SOC
   - Cancer screening in HIV infected patients should be considered at an earlier age than in the general population

Conclusions

- Toxicity from HAART is substantial and may be exacerbated in older patients
- Drug-drug interactions are common
- Unclear what the "ideal" HIV regimen is for older patients
- High rates of comorbidities in older HIV patients
- General routine health maintenance and screening is important
- Future research is essential for developing accurate treatment recommendations in older patients

Thank You!

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