Top 10 Things to Know About the Older Patient With HIV Infection

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Learning Objectives

After attending this presentation, learners will be able to:

- Identify epidemiologic characteristics of the older HIV-infected patient
- Define the impact of HIV infection on the normal aging process and the development of comorbidities
- Describe specific HIV comorbidities with focus on coronary artery disease, its predisposing conditions, and premature bone loss
- Explain changing mortality patterns in the modern era of antiretroviral therapy

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Which of the following statements about HIV-infected patients over 50 years of age is false?

1. They present at an earlier stage of disease.
2. They constitute 45% of HIV-infected patients.
3. They are at increased risk of neurocognitive impairment compared to general population.
4. They develop certain malignancies earlier than the general population.
5. They are more adherent to medical therapy.

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HIV Epidemiology in Older Adult

- Since the 1980s, the percentage of HIV-infected patients over the age of 50 has gradually increased
- In 2015, 17% of newly diagnosed cases of HIV infection were in adults ≥ 50 years old with many having AIDS
- African Americans accounted for 43% of cases, whites for 36% of cases, and Hispanics/Latinos for 17% of cases
- In 2014, approximately 45% of HIV-infected persons in the US were ≥ 50 years old, 27% were ≥ 55 years old, and 6% were ≥ 65 years old
- MSM is the most common mode of transmission in older men, and heterosexual contact is the most common mode in older women

http://www.cdc.gov/hiv/group/age/olderamericans/index.html

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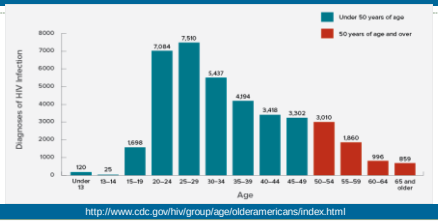
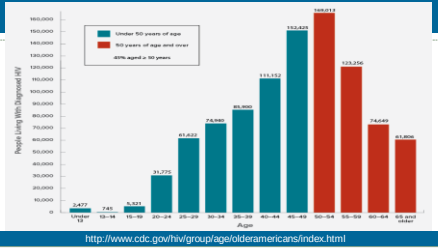
New HIV Diagnoses by Age United States, 2015



Slide 6 of 45 http://www.cdc.gov/hiv/group/age/olderamericans/index.html

People Living with HIV by Age United States, 2014



Slide 7 of 45 http://www.cdc.gov/hiv/group/age/olderamericans/index.html

Issue 1

HIV infection, even when controlled, is associated with chronic immune activation that is superimposed upon immunologic senescence in the older adult

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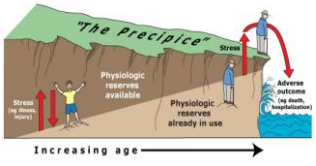
The Effect of Normal Aging on Health



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Taffet GE. Normal Aging. UpToDate. *Wolters Kluwer Health*, 2014.

Issue 2

Older persons may be diagnosed later and have more advanced HIV infection at presentation

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Issue 3

There is a less robust immunologic response to antiretroviral therapy in this population

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Immunologic Response to ART

- Among 12,196 treatment-naive patients in NA-ACCORD who initiated ART (observational cohort), immunologic response after 24 months of therapy decreased with increasing age starting at 40, but there was no effect on viral suppression
- A prospective study that evaluated treatment outcomes in 3,015 patients (401 of whom were over age 50) found that, despite better virologic control, clinical progression to an AIDS-defining diagnosis was higher (HR 1.52; 95% CI 1.2-2.0)

Althoff KN, Justice AC, Gange SJ et al. AIDS 2010;24:2469.
Grabar S, Kousignian I, Sobel A et al. AIDS 2004;18:2029.

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Issue 4

In general, older HIV-infected patients have better medication adherence but an increased risk of drug toxicity

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Medication Adherence

- Literature has reported up to 95% adherence in older HIV-infected patients
- In a recent meta-analysis, older age reduced the risk for non-adherence by 27% (RR 0.72; CI 0.64-0.82)
- Those studies assessing short-term and long-term non-adherence showed a significant reduction in both groups (RR 0.75; CI 0.64-0.87 and RR 0.65; CI 0.50-0.85, respectively)

Ghidei L, Simone MJ, Salow MJ et al. Drugs Aging 2013;30:809.

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Drug Toxicity

- A higher rate of adverse events (64% vs. 35%) on protease inhibitors was reported in patients older than 60 compared to those under 40
- Another study of 508 treatment-naïve patients found that regimen changes due to toxicity were associated with increasing age
- May be from age-related decrease in renal and hepatic function, decrease in serum albumin level, and changes in cytochrome p450 enzyme system

Knobel H, Guelar A, Valldecillo G et al. AIDS 2001;15:1591.
Lodwick RK, Smith CJ, Youle M et al. AIDS 2008;22:1039.

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Issue 5

HIV-infected patients accumulate "age-related" diseases at a younger chronological age

Hypothesis is that increased immune activation and long-term chronic inflammation contribute to premature aging in this population

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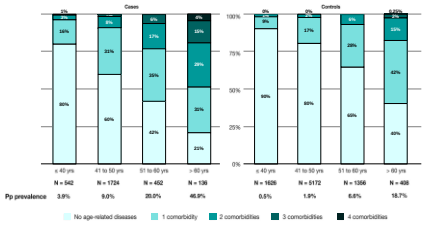
Chronic Complications by Age and HIV Status



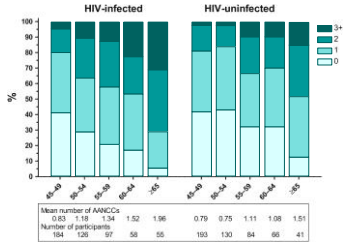
Guaraldi G, Orlando G, Zona G et al. Clin Infect Dis 2011;53:1120.

Chronic Complications by Age and HIV Status

- Retrospective analysis of HIV-infected outpatients compared to seronegative persons (case-control study) from 2002 through 2009
- Examined cardiovascular disease, hypertension, diabetes mellitus, bone fractures, and renal failure
- Independent predictors of polypathology ($p < 0.001$) included older age (OR 1.11), male gender (OR 1.77), CD4 nadir below 200 (OR 4.46), and duration of antiretroviral therapy (OR 1.01)

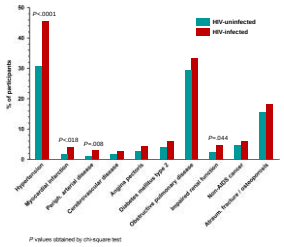
Guaraldi G, Orlando G, Zona G et al. Clin Infect Dis 2011;53:1120.

Distribution of the Number of Age-associated Noncommunicable Comorbidities Stratified by Age Across Both Study Groups



Schouten J, Wit FW, Stolte IG et al. Clin Infect Dis 2014;59:1787.

Prevalences of Each of the Different Age-associated Noncommunicable Comorbidities Over the Two Study Groups



P values obtained by chi-square test

Slide 20 of 45 Schouten J, Wit FW, Stolte IG et al. Clin Infect Dis 2014;59:1787.

Issue 6

Incidence of CAD is higher than that in HIV-negative patients matched for age and gender

CAD risk calculator results need to be interpreted in context of increased risk in the HIV-infected population

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HIV infection has been associated with the following increased percentage risk of acute myocardial infarction beyond that explained by recognized risk factors:

1. 10 percent
2. 20 percent
3. 30 percent
4. 40 percent
5. 50 percent or more

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HIV Infection and Coronary Artery Disease (1)

- Incidence of CAD is higher than that in HIV-negative patients matched for age and gender
- Studies have demonstrated an increase in subclinical atherosclerosis (eg, CMI thickness) and clinical endpoints (eg, acute MI)
- HIV infection is associated with increased soluble and cellular markers of inflammation, endothelial dysfunction, and altered coagulation, all of which have been shown to contribute to cardiovascular disease

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HIV Infection and Coronary Artery Disease (2)

- Degree to which HIV infection itself, antiretroviral therapy, and other risks contribute to increased risk in this population is unknown
- High prevalence of traditional risk factors in this population
- Protease inhibitor class appears to be associated with higher risk of CAD; some data suggesting abacavir and efavirenz may also increase risk
- Discontinuation of ART is associated with higher risk of CAD

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The Risk of Coronary Artery Disease in HIV-infected Patients

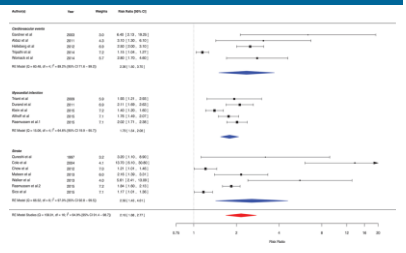
Table 2. Rates of AMI by HIV Status and Age Group[a]

Status	Age Group, y							
	<30	30-39	40-49	50-59	60-69	70-79	80-89	>89
Uninfected								
No. of participants	1175	6753	21 866	19 805	4209	1120	148	3
No. of AMI events	0	10	164	216	66	36	14	0
AMI rates per 1000 person-years (95% CI)	...	0.3 (0.2-0.6)	1.5 (1.3-1.7)	2.2 (1.9-2.5)	3.3 (2.8-4.2)	6.7 (4.8-9.2)	21.5 (12.7-36.4)	...
HIV infected								
No. of participants	725	3845	10 575	9342	2065	557	56	0
No. of AMI events	0	13	105	171	46	25	3	0
AMI rates per 1000 person-years (95% CI)	...	0.7 (0.4-1.2)	2.0 (1.6-2.4)	3.9 (3.3-4.5)	5.0 (3.9-6.7)	10.0 (6.7-14.7)	13.5 (4.3-42.0)	...
Incidence rate ratio (95% CI)	...	2.19 (0.89-5.58)	1.34 (1.04-1.72)	1.80 (1.47-1.21)	1.53 (1.09-2.26)	1.50 (0.86-2.57)	0.63 (0.12-2.25)	...

Abbreviations: AMI, acute myocardial infarction; HIV, human immunodeficiency virus.
[a]An ellipsis indicates that a rate was not calculated because there were 0 events.

Slide 25 of 45 Freiberg MS, Chang CC, Kuller LH et al. JAMA Intern Med 2013;173:614.

Pooled Risk Ratio for Cardiovascular Disease in HIV-infected Persons



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Shah ASV, Stelzle D, Lee KK et al. Circulation 2018;138:1100.

ACC/AHA CV Risk Calculator

Uses data primarily from non-Hispanic whites and African Americans in the United States. Concerns about accuracy of results have been made (statin recommendations, DM yes vs. no categorization, FMH of premature CAD not included).

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Traditional Risk Factors for Atherosclerosis (1)

- **Hypertension:** Use of ambulatory BP monitoring for diagnosis; new definition of hypertension and treatment target (ACC/AHA Hypertension Guideline: J Am Coll Cardiol 2017); no important drug interactions
- **Diabetes Mellitus:** Increased risk of DM in HIV-infected patients, HgbA1c may underestimate glycemia, and DM/HIV detrimental effect on renal function (BMJ Open Diabetes Res Care 2016, Diabetes Care 2009, and Acquir Immune Defic Syndr 2012); metformin AUC increased when given with dolutegravir

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Traditional Risk Factors for Atherosclerosis (2)

- **Hyperlipidemia:** Simvastatin and lovastatin are contraindicated with protease inhibitors and cobicistat; atorvastatin, rosuvastatin, and pitavastatin can be used as alternatives; in this setting, it is prudent to start with low dose of drug and monitor for toxicity
- **Cigarette Smoking:** HIV-infected patients are more likely to smoke and less likely to quit compared to the general population (Ann Intern Med 2015); HIV-infected smokers lose more life-years to smoking than to HIV-related conditions (Clin Infect Dis 2013); no important drug interactions

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Issue 7

HIV infection and its treatment and comorbidities have been associated with premature bone loss

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Premature Bone Loss (1)

- Osteopenia, osteoporosis, and pathological fractures have been described
- Osteopenia is generally asymptomatic, although patients with lower T scores (-1.0 to -2.5) may be at increased risk for fracture
- Osteoporosis may present with fractures of vertebrae, forearms, or hips
- HIV infection itself, TDF, protease inhibitors, alterations in vitamin D metabolism, and lactic acidemia related to older NRTI drugs may be contributing factors to premature bone loss

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Premature Bone Loss (2)

- Immobility, cigarette smoking, excessive alcohol use, chronic renal disease, hypogonadism, hyperparathyroidism, hyperthyroidism, and steroid use accentuate bone loss
- Optimal use of bone densitometry as screening test in this population is uncertain; HIVMA advises baseline in postmenopausal women and men ≥ 50 years of age
- Calcium and vitamin D should be given in high-risk patients; regular exercise and smoking cessation should be advised

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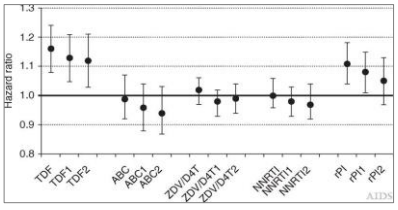
Antiretroviral Exposure and Risk of Osteoporotic Fractures



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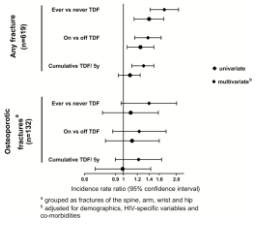
Bedino R, Maalouf NM, Zhang S et al. AIDS 2012;26:825.

Effect of TDF Exposure on Risk of Any Fracture and Osteoporotic Fractures



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Borges AH, Hoy J, Florence E et al. Clin Infect Dis 2017;64:1413.

Issue 8

Increasing age may be a risk factor for HIV-associated neurocognitive dysfunction, although studies examining this issue are limited

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Neurocognitive Dysfunction

- Longitudinal study comparing 106 HIV-infected patients over 50 years of age to 96 patients between 20-39 years of age showed a three-fold higher risk of dementia on multivariate analysis
- Study adjusted for race, education, depression, substance abuse, ART, CD4 count, and viral load
- Depression appears to be more common in older HIV-infected persons compared to seronegative age-matched controls

Valcour V, Shikuma C, Shiramizu B et al. Neurology 2004;63:822.

Applebaum AB, Brennan M. Mental Health and Depression, in *Older Adults with HIV: An In-Depth Examination of an Emerging Population*. New York: Nova Publishers, 2009.

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Issue 9

Lung, hepatic, and anal cancers occur at a younger age in HIV-infected adults compared to seronegative persons

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Malignancies

- Observational studies suggest that lung, hepatic, and anal cancers occur at younger age in HIV-infected adults compared to seronegative persons
- Using 15 HIV and cancer registry databases in the US, including 212,055 persons with AIDS, the age of diagnosis of non-AIDS-defining cancers was examined
- Only lung and anal cancers were seen in AIDS patients at younger age (median 50 years old vs. 54; $p < 0.001$) than expected

Shiels MS, Pfeiffer RM, Engels EA. Ann Intern Med 2010;153:452.

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Which of the following statements regarding mortality in the modern era of ART is false?

1. The overall mortality rate in HIV-infected adults has declined over the past two decades.
2. An increasing percentage of causes of death are related to non-AIDS-defining conditions.
3. The highest percentage of deaths in HIV-infected adults is in the 25-34 age group.
4. Life expectancy of a 20-year-old person recently diagnosed with HIV infection has been modeled to be similar to that of the general population.

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Issue 10

Mortality in HIV-infected persons has fallen substantially over past two decades with non-AIDS-related conditions now accounting for the majority of deaths

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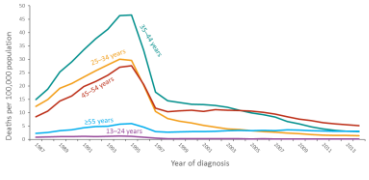
Trends in Annual Rates of Death due to HIV Infection by Age Group, 1987–2014—United States



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Mortality Trends

- In the D:A:D study, 3,909 deaths occurred among 49,731 subjects followed from 1999 through 2011
- Crude mortality rate of 12.7 per 1000 person-years
- AIDS-related causes were responsible for 29% of deaths, non-AIDS-related cancers for 15%, liver disease for 13%, and cardiovascular disease for 11%
- Deaths attributable to AIDS-related events decreased from 34% to 22%
- Proportion attributable to non-AIDS-defining malignancies increased from 9% to 23%

Smith CJ, Ryom L, Weber R et al. Lancet 2014;384:241.

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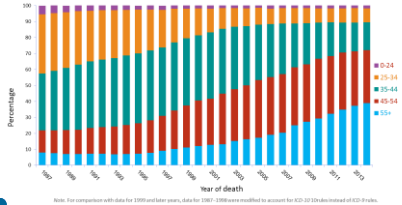
Trends in the Percentage Distribution of Deaths due to HIV Infection by Age Group, United States, 1987-2014



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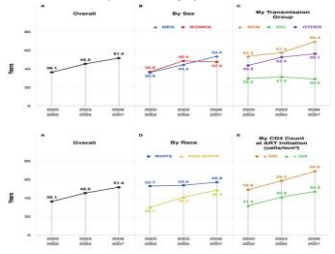
Mid-point Life Expectancy Estimates at Age 20 Years in Three Calendar Periods, Overall and by Sociodemographic Characteristics, 2000–2007



Samji H, Cescon A, Hogg RS et al. 2013; PLOS ONE. https://doi.org/10.1371/journal.pone.0081355

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Question-and-Answer

Top 10 Things to Know About the Older Patient With HIV Infection
Howard Libman, MD

SUGGESTED READINGS

Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;58(1):e1-34.

Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS.* 2012;26:825-831.

Borges AH, Hoy J, Florence E, et al. Antiretrovirals, fractures, and osteonecrosis in a large international HIV cohort. *Clin Infect Dis.* 2017;64(10):1413-1421.

Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173(8):614-622.

Institute of Medicine of the National Academies. HIV screening and access to care: exploring the impact of policies on access to and provision of HIV care. http://iom.edu/Reports/2011/HIV-Screening-and-Access-to-Care-Exploring-the-Impact-of-Policies-on-Access-to-and-Provision-of-HIV-Care.aspx. Accessed on June 10, 2013.

Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis.* 2014;59(12):1787-1797.

Shah ASV, Stelzle D, Lee KK, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV. *Circulation.* 2018;138(11):1100-1112.

Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. *Ann Intern Med.* 2010;153(7):452-460.

Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet.* 2014;384(9939):241-248.

The National Academies of Sciences EaM. *HIV Screening and Access to Care: Exploring the Impact of Policies on Access to and Provision of HIV Care*. The National Academies Press, 2011.