

Perspective

Prioritizing Primary Care in HIV: Comorbidity, Toxicity, and Demography

Mortality among HIV-infected patients after the first year of antiretroviral therapy has not improved in recent years. Future improvement in survival may come partly through earlier diagnosis and institution of treatment and by maximizing treatment adherence. However, outcomes in HIV disease are also influenced today by long-term treatment toxicities, non-HIV-specific comorbid conditions, and comorbid behaviors. Primary care efforts to improve outcomes should be focused on health behaviors (eg, adherence, elimination of substance abuse, diet, and exercise) and effective management of conditions such as hypertension and depression, since successful intervention in these areas reduces risk of a variety of conditions associated with mortality in HIV disease. Issues in prioritizing primary care in HIV disease were discussed by Amy C. Justice, MD, PhD, at the 9th Annual Ryan White CARE Act Clinical Update in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org.

With the advent of potent antiretroviral therapy, mortality from HIV disease decreased from 29 deaths per 100 person-years to 9 deaths per 100 person-years between 1995 and 1998; between 1997 and 2000, there was a further reduction to 2 to 4 deaths per 100 person-years (Palella et al, *N Engl J Med*, 1998). However, survival after the first year of potent antiretroviral therapy did not change between 1998 and 2003 (May et al, *Lancet*, 2006). In part, this finding is likely due to a trend toward patients presenting with HIV disease at lower CD4+ cell counts. To improve survival in terms of HIV-specific factors most readily, clinicians can work on earlier diagnosis and institution of treatment.

Other factors affecting outcome that can be improved include promoting and optimizing adherence to antiretroviral regimens and managing antiretroviral toxicity. However, outcomes for HIV-infected individuals in the antiretroviral-therapy era are not solely affected

by HIV status and antiretroviral treatment. Aging, comorbid conditions, non-antiretroviral drug toxicity, and risk of comorbid behaviors are all factors in determining outcome, and the role of primary care in addressing and managing these factors has become increasingly important and increasingly complicated. For example, it is frequently difficult to distinguish between comorbidities in HIV disease and long-term toxicities of antiretroviral therapy. Further, comorbidities may interact with effects of antiretrovirals, as in the case of interaction of alcohol or diabetes with antiretroviral-related liver toxicity. Figure 1 shows that the difficulty inherent in managing common medical conditions in the HIV-infected individu-

al translates into decreased practitioner comfort with the conditions, compared with practitioners encountering these conditions in the non-HIV population (Fultz et al, *Clin Infect Dis*, 2005).

Practitioner discomfort partly derives from the attempt to follow, or interpret, general population-management guidelines in patients with all the medical complications that HIV infections bring. In order to focus care in the HIV-infected population on interventions that are likely to improve outcome, it would be beneficial to examine the degree to which recommendations for the general population are applicable to the HIV-infected population. Questions to consider in this regard include: (1) will the patient live long enough to benefit (prognosis)?; (2) is the condition prevalent and harmful (impact)?; and (3) can we decrease harm through intervention (benefit)?

Life-expectancy on Antiretroviral Therapy

Braithwaite and colleagues have developed a model that estimates life-expectancy in HIV-infected patients (Braithwaite et al, *Am J Med*, 2005). The model mimics heterogeneity in clinical populations and yields risk for death based on age, CD4+ cell count,

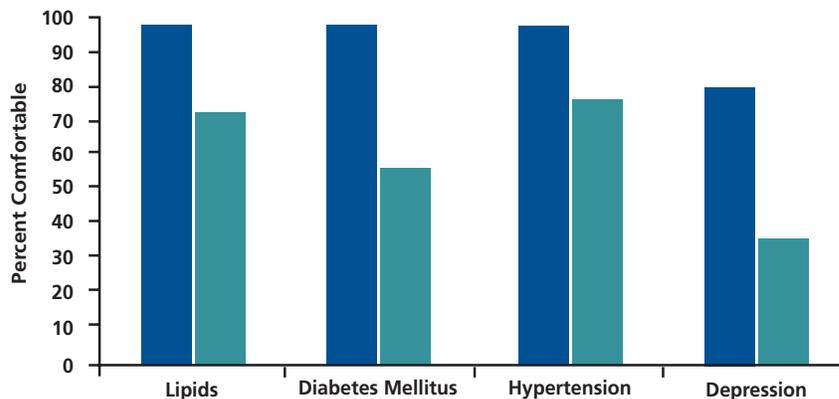


Figure 1. Veterans Aging Cohort Study general medicine provider (blue bars) and HIV provider (green bars) comfort with primary care in terms of treating common conditions. Adapted with permission from Fultz et al, *Clin Infect Dis*, 2005.

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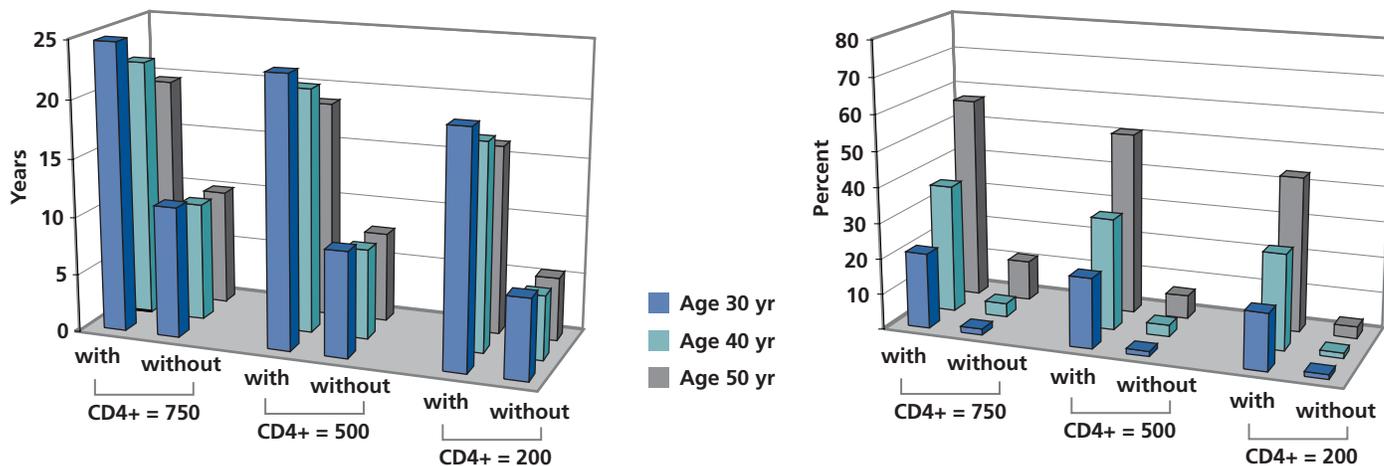


Figure 2. Estimated life-expectancy in HIV-infected persons with or without antiretroviral therapy using the model of Braithwaite et al (left), and predicted proportions of patients dying from non-AIDS related causes (right). Adapted with permission from Braithwaite et al, *Am J Med*, 2005.

and HIV viral load. It incorporates information on mutations in HIV and nonadherence to antiretroviral therapy in arriving at these estimates, and has been calibrated and validated using clinical data. Figure 2 shows the model’s estimates of life-expectancy, according to age 30, 40, or 50 years, and CD4+ cell count at diagnosis in patients receiving or not receiving antiretroviral therapy, and the predicted proportions of patients dying from non-AIDS causes. The mean age at HIV diagnosis currently is 38 years, with additional life-expectancy—as suggested by the model—of approximately 20 years at this age; the average total life-expectancy is on the order of 58 years. The model indicates that nearly half of patients above the age of 40 years will die from non-AIDS causes. These estimates strongly suggest that comorbidities play an important part in outcome and that it is crucial for HIV care to include care of comorbidities. The issue to address is, which comorbidities are to be focused on with the hopes of prolonging and improving remaining life?

Prevalent Comorbidities and Comorbid Behaviors

Hepatitis C virus (HCV) infection, hypertension, diabetes, and obstructive lung disease are the most common non HIV-specific comorbidities in HIV-infected individuals. Figure 3

shows comorbidities in the Veterans Aging Cohort Study (Justice et al, *Med Care*, 2006). The Veterans Aging Cohort Study is currently conducting analyses that will directly compare the prevalence and incidence of comorbid medical disease, psychiatric disease, and substance use disorders among veterans with HIV infection and age-, race-, ethnicity-, and sex-matched controls. For the present, direct comparisons of the prevalence and incidence of comorbid disease among HIV-infected individuals and demographically similar controls are not available. Table 1 shows comorbidities in women with HIV disease, represent-

ing subjects from the Women’s Interagency HIV Study (WIHS); approximately 80% were women of color, and most lived below the poverty line. Most of the women enrolled in the WIHS study reported intravenous drug use. The prevalence of hepatitis C virus might be lower in another sample of women with HIV infection.

Additionally, patient behaviors contribute substantially to risk of comorbid diseases such as heart disease. Three studies have shown current or past cigarette smoking in 19% to 58% of HIV-infected patients, and overweight or obesity in 5% to 22% (Data Collection on Adverse Events of Anti-

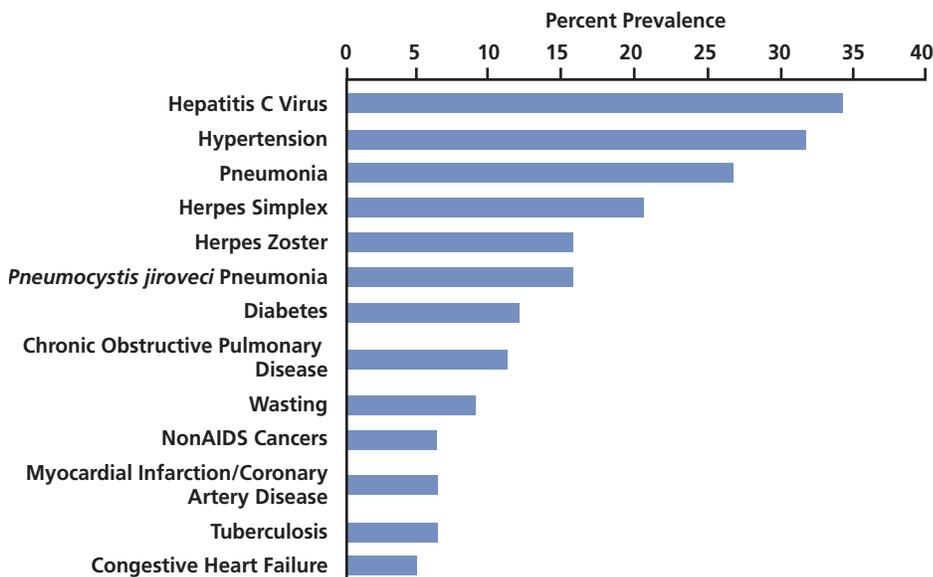


Figure 3. Medical conditions in HIV-infected patients in the Veterans Aging Cohort Study. Adapted with permission from Justice et al, *Med Care*, 2006.

Table 1. Causes of Morbidity in HIV-Infected and Noninfected Women

Condition	Infected (n=2058)	Noninfected (n=568)
Hepatitis C virus	41%	--
Hypertension	18%	14%
Cancer	7%	5%
Diabetes	4%	4%
Lupus	9%	5%
Depressive symptoms	58%	55%
Below poverty line	59%	60%

Approximately 80% are women of color, median age is 35 years. Data from the Women's Interagency HIV Study Web site.

HIV Drugs [DAD] Study Group, *N Engl J Med*, 2003; Klein et al, *J Acquir Immune Defic Syndr*, 2002; Saves et al, *Clin Infect Dis*, 2003).

Indeed, data from a variety of sources indicate that among HIV-infected individuals, 60% to 75% are active alcohol users, 40% to 50% are active smokers, and approximately 30% are active users of other drugs. Associated comorbidities and other adverse consequences of these behaviors are shown in Table 2. It is important to note that an individual patient's profile of comorbid disease is not only determined by their HIV status, but by their demographics (eg, race, ethnicity, sex, age, and economic status) and their behaviors (eg, substance use). Such statistics reemphasize that patients with HIV infection are a special population to which general population guidelines for treating, managing, or preventing common medical conditions do not necessarily directly apply. Currently, HIV-infected patients are more likely to drink or drink heavily, smoke, have viral hepatitis and possibly mental illness, and to be people of color with limited socioeconomic resources. In the Veterans Aging Cohort Study, the level of alcohol use was significantly correlated with likelihood of HCV infection, hypertension, chronic obstructive pulmonary

disease (COPD), and pneumonia (Figure 4; Justice et al, *Med Care*, 2006).

Other data from this cohort showed that unadjusted prevalence of COPD is higher in HIV-infected than in noninfected individuals according to age and according to pack-years of smoking (Figure 5; Crothers et al, *Chest*, 2006). Overall, the prevalence of COPD was 19% in HIV-infected individuals and 15% in noninfected individuals. After adjustment for age, cigarette-pack years, injection-drug use, alcohol use, and race or ethnicity, the odds ratio for COPD in HIV-infected individuals was 1.5 (95% confidence interval, 1.12-2.00), suggesting that smoking has accelerated effects in causing COPD in the HIV-infected population. One limitation of this study is that it did not control for marijuana use, which is also associated with COPD. Other data from this cohort showed that mortality in HIV-infected patients was significantly associated with smoking status, with mortality rates per 100 person-years of: 2.5 in those who never smoked; 4.6 in past smokers; and 5.4 in current smokers ($P < .001$ for trend). After adjustment for age, race or ethnicity, CD4+ cell count, HIV viral load, hemoglobin, and drug and alcohol use, the hazard ratio for death for current smokers was 2 ($P = .04$; Crothers et al, *J Gen Intern Med*, 2005).

Demographics also play an important role. In the general population,

age-related mortality from such conditions as liver disease, coronary disease, cancer, and diabetes are highest in black men and higher in black women than in white women. For conditions such as coronary disease and cancer, risk of mortality is not linear with age, but exhibits a marked acceleration in rate at older ages. There are a number of conditions in which HIV infection accelerates or appears to accelerate disease processes, and it has been considered that HIV disease might actually accelerate aging in terms of hastening morbidity and mortality from chronic conditions. These accelerated effects need to be taken into consideration when deciding what interventions are needed and when they may not make sense in managing HIV-infected patients.

Adapting Primary Care Guidelines for HIV

Numerous preventive guidelines are recommended for application in the general medical population. We must carefully consider which are most appropriate for our patients with HIV infection. Specifically, these recommendations are based on the frequency and impact of the condition and the degree to which outcome associated with that condition can be modified by timely medical intervention. Because many of these preventative guidelines

Table 2. Substance Use Behaviors in HIV-Infected Individuals

Alcohol (60% to 75% active)	
<ul style="list-style-type: none"> • Exacerbation of hepatitis C virus infection • Harder to treat hepatitis C virus infection • Mitochondrial injury • Liver disease • Liver cancer • Hypertension 	<ul style="list-style-type: none"> • Pneumonia • Anemia • Dementia • Risky sex • Poor adherence
Tobacco (40% to 50% active)	
<ul style="list-style-type: none"> • Obstructive lung disease • Pneumonia 	<ul style="list-style-type: none"> • Vascular disease (heart and brain) • Lung cancer
Other drug use (approximately 30% active)	
<ul style="list-style-type: none"> • Obstructive lung disease (marijuana) • Lung disease (talc - heroin) • Heart disease (cocaine) 	<ul style="list-style-type: none"> • Risky sex • Poor adherence

Data from the Women's Interagency HIV Study Web site; Frii-Moller, *N Engl J Med*, 2003.

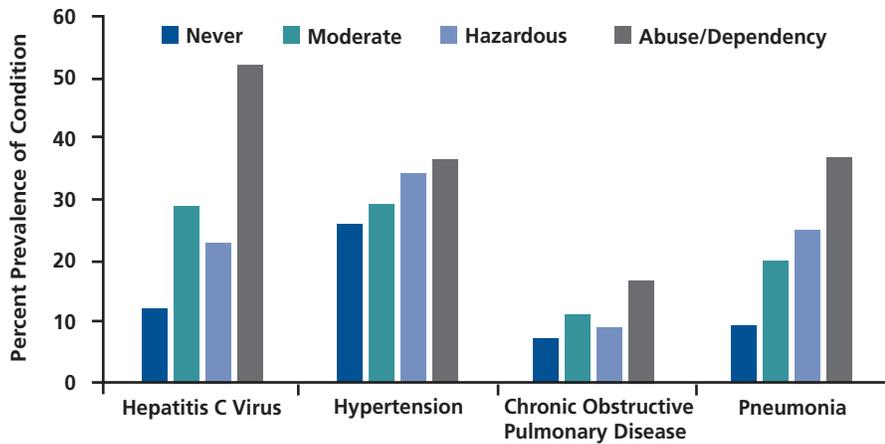


Figure 4. Association of alcohol use and comorbidities in the Veterans Aging Cohort Study. After adjustment for age, CD4+ cell count, viral load, drug use, exercise, and smoking, each step in increase in alcohol use (from never to moderate to hazardous to abuse or dependence) was associated with a statistically significant increase in odds ratio for hepatitis C virus infection (1.4; $P=.001$), hypertension (1.3; $P=.002$), chronic obstructive pulmonary disease (1.3; $P=.03$), and pneumonia (1.5; $P < .001$). Adapted with permission from Justice et al, *Med Care*, 2006.

involve some small immediate risk of harm (complications or pain from the procedure, expense, the possibility of false-positive test results), many are also based upon an assumed remaining life expectancy. Simply put, an individual needs to be reasonably sure of living a sufficient time before they will benefit from a screening procedure. The time needed depends on the up-front risk involved and the potential benefit from screening.

Consider the case of colonoscopy for cancer screening in a 50-year-old HIV-infected man. The advisability of the screening depends on the life-expectancy of the individual given his or her comorbid disease—that is, if the patient is likely to die before the potential benefit from screening exceeds the harms or risks, the screening should not be performed. In this case, the long-term benefit is reduced risk from colon cancer; the short-term risks are anxiety, discomfort, and risk of perforation.

For the general population guidelines, a time requirement is often suggested by the specification of a particular age limit for the guideline's application. For patients with HIV infection, this might most appropriately be determined by their most salient prognostic factors including their response to treatment, their current CD4+ cell

count, their age, and their burden of comorbid disease.

Conclusion

The current likely killers of our “typical” HIV patient today (eg, 38-year-old black man)—are liver disease (associated with alcohol, HCV disease, drug toxicity), related to AIDS (wasting, pneumonia, sepsis), non-AIDS cancers (lung, rectal, liver), and violence (homicide, suicide, accident). If these patients survive 12 additional years,

the likely killers will be liver disease (due to HCV, hepatitis B virus, alcohol, antiretroviral toxicity), vascular disease (due to smoking, alcohol, antiretrovirals), AIDS-related conditions (due to nonadherence or intolerance of antiretroviral regimens), lung disease (due to smoking and alcohol), cancer (due to smoking, alcohol, HCV, possibly antiretrovirals), and violence (associated with alcohol and drug use).

Given these risk profiles, what should primary care focus on in improving patient survival? With regard to liver disease, major efforts should be devoted to decreasing alcohol use for some, and complete abstinence for those most at risk, with attention also given to lifestyle modification that will reduce likelihood of ‘nonalcoholic’ liver disease—eg, treatment or prevention of diabetes including weight reduction and vigilant management of potential liver toxicities of antiretrovirals and other drugs. Although the benefits of drug treatment for viral hepatitis among HIV-infected patients may be limited, there is substantial evidence to support the immediate benefit of these behavioral modifications. At a minimum these should be emphasized along with a trial of treatment for viral hepatitis.

As a general approach, attention is best focused on instituting and maintaining health behaviors, including promoting adherence to antiretroviral and other drug regimens, promoting exer-

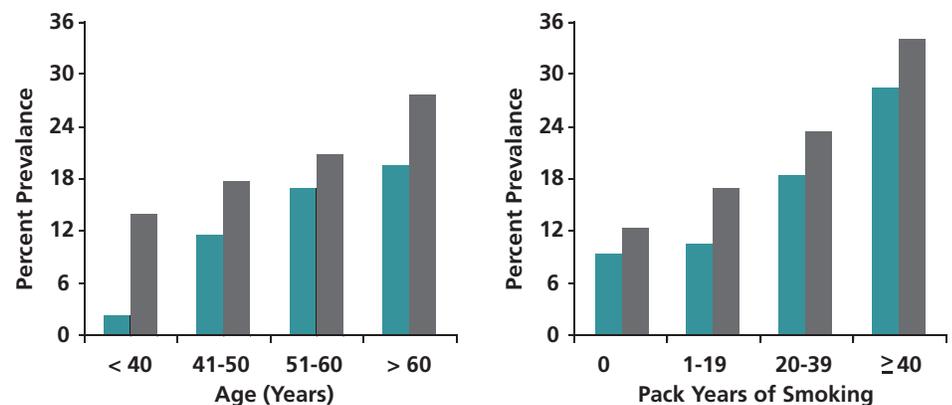


Figure 5. Unadjusted prevalence of chronic obstructive pulmonary disease in HIV-noninfected (green bars) and HIV-infected (gray bars) patients in the Veterans Aging Cohort Study according to age (left) and cigarette pack-years of smoking (right). Adapted with permission from Crothers et al, *Chest*, 2006.

cise and diet, and eliminating substance use (alcohol, tobacco, illicit drugs). Benefits from these measures will reduce risk of many non-AIDS conditions that pose heightened risk of mortality. Hypertension is associated with a number of conditions that increase risk of mortality and therefore should be aggressively diagnosed and treated. Finally, depression should be carefully considered, both because it has a direct effect on the patient's quality of life and because it has combined effects on the patient's ability to adhere to medication, diet and exercise recommendations, and to avoid substance use and abuse.

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Suggested Reading

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