

Topics in HIV Medicine™

A publication of the International AIDS Society–USA

Perspectives

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About This Issue

In this issue, 4 *Perspectives* articles are offered, based on presentations at the International AIDS Society–USA – sponsored 9th Annual Ryan White CARE Act Clinical Update in Washington, DC, in August 2006. First, highlights of important issues concerning immunization practices and the HIV-infected population are reviewed by David H. Spach, MD. A second review discusses prioritizing primary care of HIV-infected patients, including comorbid conditions, long-term treatment toxicities, and comorbid behaviors, as presented by Amy C. Justice, MD. In his talk, Derek M. Fine, MD, considered the increase in renal disease amongst the HIV-infected population. Finally, Chloe L. Thio, MD, discussed the care of patients with HIV and hepatitis B virus coinfection.

This issue also announces the new logo of the International AIDS Society–USA. For information on our new look and our expanding Continuing Medical Education (CME) activities, including our new IAS-USA Speaker's Bureau, please turn to page 175.

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Correspondence

Topics in HIV Medicine welcomes editorial correspondence. Address letters to:

Editor, *Topics in HIV Medicine*
International AIDS Society–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120

Phone: (415) 544-9400
Fax: (415) 544-9401

Web site: <http://www.iasusa.org>
E-mail: topics2007@iasusa.org

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Matthew Stenger - Medical Writer

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Perspective

Immunizations for HIV-infected Adults: Indications, Timing, and Response

Vaccines routinely recommended for HIV-infected adults include those for influenza, hepatitis A virus, hepatitis B virus, pneumococcal infection, and tetanus. Responses to vaccination may be affected by CD4+ cell count and viral load. A number of live vaccines are contraindicated in the HIV-infected population. This article summarizes a presentation on immunization in HIV-infected adults made by David H. Spach, MD, at the 9th Annual Ryan White CARE Act Clinical Update in Washington, DC, in August 2006. The original presentation is available as a Webcast at www.iasusa.org.

Issues in immunization for HIV-infected adults include appropriate use of recommended vaccines, variable responses to some vaccines based on the degree of HIV-related immune suppression, and awareness of live vaccines that are contraindicated in this population.

Case 1: Influenza Vaccine

A 31-year-old HIV-infected woman on antiretroviral therapy with a CD4+ cell count of 182/μL presents in late November for a routine follow-up visit. Which of the following would you recommend regarding immunizing her against influenza:

1. Give her influenza (inactivated) vaccine at this visit,
2. Wait and give her influenza (inactivated) vaccine after her CD4+ cell count increases to above 200/μL, or
3. Give her live attenuated influenza vaccine (since it gives better immune responses in patients who have a low CD4+ cell count)?

The risk of mortality due to influenza is increased among HIV-infected patients compared with adults in the general population who do not have HIV infection, even those persons older than 65

years (Figure 1, Lin et al, *Arch Intern Med*, 2001).

Influenza vaccine has a protective benefit for HIV-infected individuals. A placebo-controlled study of 102 HIV-infected patients with CD4+ cell counts of approximately 400/μL reported in 1999 showed that influenza vaccination reduced the incidence of respiratory illness from 49% to 29% ($P = .04$) and that of laboratory-confirmed influenza from 21% to 0% ($P < .001$; Tasker et al, *Ann Intern Med*, 1999), with no observed adverse effect of vaccination on CD4+ cell count or HIV viral load. A study that investigated vaccine efficacy during a 1996 influenza outbreak indicated that among 38 HIV-infected adults, estimated vaccine efficacy was reduced from 65% in those with CD4+ cell counts above 100/μL to 11% in those with lower counts; efficacy was 52% in those

with plasma HIV RNA levels below 30,000 copies/mL and 40% in those with higher viral load (Fine et al, *Clin Infect Dis*, 2001).

The correct answer for the above case, therefore, is to give the patient trivalent inactivated vaccine at the current visit, despite her relatively low CD4+ cell count. Data from the last 30 years show that peaks of influenza activity in the US occur from November to March. Considering this patient was seen in late November, it would not be warranted to wait for her to achieve an increase in CD4+ cell count before giving influenza vaccination, since influenza season would be rapidly approaching. Despite earlier concerns, there is no evidence of long-term adverse effects of administering vaccines to patients with low CD4+ cell counts, and influenza vaccination should not be withheld in patients with CD4+ cell counts under 100/μL despite evidence of reduced efficacy. However, it should not be assumed that such patients are protected, and clinicians need to remain vigilant in diagnosing influenza in patients who were vaccinated at lower CD4+ cell counts and who present with respiratory illness during the flu season.

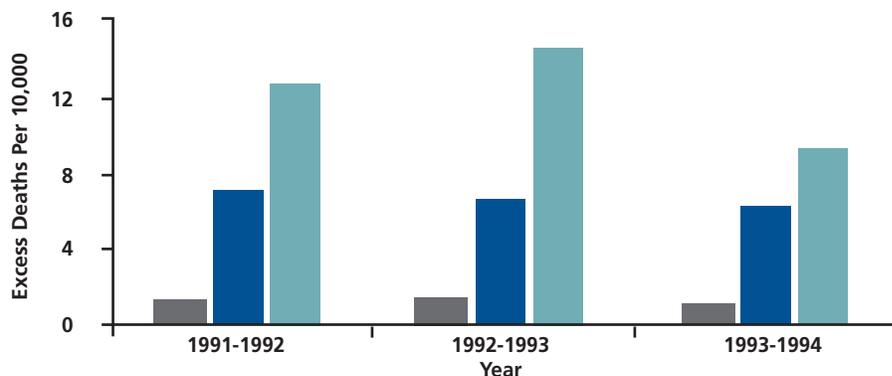


Figure 1. Excess death rate due to influenza or pneumonia during influenza season compared with preinfluenza baseline periods in all adults in the general population aged 13 years or older (gray), adults in the general population aged 65 years or older (dark blue), and in those with HIV-infection aged 13 years or older (light green). Adapted with permission from Lin et al, *Arch Intern Med*, 2001.

Dr Spach is Professor of Medicine, Division of Infectious Diseases, at the University of Washington. He is also the Clinical Director at Northwest AIDS Education and Training Center in Seattle, Washington.

The general recommendations for influenza vaccination in HIV-infected persons are to vaccinate annually with trivalent inactivated vaccine regardless of CD4+ cell count or HIV RNA level (Centers for Disease Control and Prevention [CDC], *MMWR Recomm Rep*, 2006); Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep*, 2006). Live, attenuated, trivalent vaccine is contraindicated in HIV-infected persons.

Case 2: Varicella and Zoster Vaccines

A 42-year-old HIV-infected man on antiretroviral therapy with an undetectable HIV RNA level and a CD4+ cell count of 346/ μ L wants to know if he should get the new "shingles vaccine." Which one of the following would you recommend for him:

1. Do not give this vaccine,
2. Give this vaccine if he has a negative varicella antibody titer, or
3. Give the vaccine if he has a history of chickenpox or zoster?

The herpes zoster vaccine was approved by the US Food and Drug Administration (FDA) in 2006 for use in persons aged 60 years or older, after demonstration that it reduced the incidence of shingles by approximately 50% in this age group and reduced severity of outbreaks.

The vaccine is a live attenuated (high-dose) varicella-zoster virus (VZV) vaccine (VZV titer at least 5-times greater than that in the chickenpox vaccine), and currently is contraindicated for use in all HIV-infected individuals. It absolutely should not be used in any HIV-infected person with negative varicella antibody titer. Whether this vaccine could be safely used in HIV-infected patients with prior exposure and antibody response to VZV should be more extensively examined, since this patient population has a particularly high risk of developing zoster and a reduction in incidence or severity of zoster in such patients would

provide considerable benefit. Thus, based on current recommendations, the correct answer above would be to not give the zoster vaccine.

Prevention of varicella infection infrequently arises as an issue in adult HIV-infected persons. The varicella vaccine is contraindicated in HIV-infected adults. With regard to varicella postexposure prophylaxis, it bears remembering that varicella zoster immune globulin (VZIG) production was discontinued in 2004. One compound produced in Canada known as VariZIG, a purified human immune globulin containing high levels of anti-varicella antibodies and similar to licensed VZIG, became available under an investigational new drug program in 2006 (VariZIG can be obtained through its California distributor FFF Enterprises at 1-800-843-7477). At the time of this writing, the product VariZIG was under review by the US FDA. The requirement of administering the product within 96 hours after exposure reduces the feasibility of this approach in most circumstances. In clinical practice, an individual would typically present 1 or 2 days after a varicella exposure with a concern that they had never had chickenpox or shingles.

Assuming the patient's varicella antibody status had not been previously documented, performing the appropriate varicella antibody test would be required and generally would take at least 24 hours. Moreover, obtaining approval for, then ordering and shipping VariZIG would typically require several additional days. Thus, practically providing postexposure prophylaxis with VariZIG to a susceptible HIV-infected patient within 96 hours would be very difficult.

Given the current barriers that exist for providing VariZIG, clinicians should be aware of other less-established options. In particular, alternatives that have been suggested in cases of exposure in at-risk patients include use of general immune globulin (IVIG), or the prophylactic use of antiviral medications (valacyclovir, famciclovir, or high-dose acyclovir). Although these alternative approaches are reasonable on a

theoretical basis, there are no well-established data to indicate that they are effective in postexposure prophylaxis.

Case 3: Hepatitis Vaccine

A 28-year-old woman with a CD4+ cell count of 522/ μ L received her first 2 doses of hepatitis B vaccine on schedule approximately 1 year ago. She is lost to follow up for 9 months and now returns. What would you recommend regarding her hepatitis B immunization:

1. Start over at the beginning,
2. Give 2 doses 1 month apart, or
3. Give the final dose (pick up where you left off)?

Hepatitis B vaccine is recommended for all HIV-infected patients without evidence of prior hepatitis B virus (HBV) infection. There are 2 formulations of recombinant hepatitis B vaccine and a combined hepatitis A (inactivated)/recombinant hepatitis B vaccine. All are administered on the same schedule: at 0, 1, and 6 months. Antibody testing is recommended at 1 to 6 months after completion of the 3-dose series. Increasing the interval between the first and second doses has little effect on immunogenicity or final antibody titer. The third dose acts as a booster dose and confers optimal longer-term protection. Extended intervals between the last 2 doses (4 to 12 months) actually result in higher final titers of anti-HBV surface antigen antibody (anti-HBsAB). However, a long interval between the second and last dose also leaves the patient at risk for acquiring infection during the interval prior to receiving the third dose. In the case above, the patient should receive her final dose in the series at the current visit (pick up where you left off).

A recent study compared standard and double dosing of hepatitis B vaccine in 210 HBV-seronegative, HIV-infected patients and found that a vaccine series using double dosing resulted in improved seroconversion rates among patients with higher CD4+ cell counts and lower viral loads

(Fonseca et al, *Vaccine*, 2005). Overall, seroconversion (anti-HBsAB titer > 10 mIU/mL) occurred in 47% of patients receiving double doses (40 µg) and 34% of those receiving standard doses of 3 immunizations given at 0, 1, and 6 months. Serconversion rates were 64% with double dosing and 39% with standard dosing in patients with CD4+ cell counts above 350/µL and 24% and 26% in those with lower counts, respectively. Rates were 58% and 37%, respectively, in those with HIV RNA levels less than 10,000 copies/mL and 16% and 17%, respectively, among those with higher HIV RNA levels.

These data, as well as others, have led to the new 2006 Advisory Committee on Immunization Practices (ACIP) recommendation that HIV-infected adults should receive the double dose (40 µg) of hepatitis B vaccine (CDC, *MMWR Recomm Rep*, 2006). Given the recommendation to use double dosing, fixed dose combined hepatitis A and B immunization should not be given because the hepatitis B vaccine dose is too low in these preparations.

Unresolved issues remain regarding management of patients who do not respond to the vaccination series. The recommendation for HIV-infected patients is to obtain a post-vaccination hepatitis B virus titer 1 to 2 months after the last dose; for those individuals who have anti-HBs concentration below 10 mIU/mL, most experts recommend these patients receive 3 additional doses (40 µg) and have a repeat hepatitis B virus titer checked after the second series has been completed. In my experience, intradermal vaccination or other unconventional options are likely to fail in patients who have not responded to 2 courses of hepatitis B immunizations.

Hepatitis A Vaccine

Indications for hepatitis A vaccine include: travel to an endemic region, male-to-male sex, injection drug use, chronic liver disease, and clotting factor disorders. There are 2 formulations of inactivated vaccine that are given in 2 doses at 0 and 6 to 12 months. There is

strong evidence that response to hepatitis A vaccine is dependent on CD4+ cell count. In a placebo-controlled study of 133 hepatitis A virus (HAV)-seronegative, HIV-infected patients, doses of vaccine (1440 enzyme-linked immunosorbent assay [ELISA] units) at 0 and 6 months resulted in seroconversion (anti-HAV titer > 33 mIU/mL) at 7 months post-vaccination in 11%, 53%, and 73% of patients with CD4+ cell counts below 200/µL, 200 to 500/µL, and above 500/µL, respectively; rates at 9 months post-vaccination were 9%, 69%, and 67%, respectively (Kemper et al, *J Infect Dis*, 2003). Vaccination had no effect on CD4+ cell count or viral load.

Another study in 214 HIV-infected persons who received vaccine and were followed up between 1996 and 2003 in Atlanta, Georgia, indicated an overall seroconversion rate of 60%, with a gradation of seroconversion rates by CD4+ cell count (Figure 2; Rimland et al, *AIDS*, 2005). Given the overall response rate and the correlation with CD4+ cell count, it is prudent to check antibody titers after vaccination. It remains unclear whether it is the nadir CD4+ cell count or the cell count at time of vaccination that determines likelihood of response. For patients with low CD4+ cell counts who are expected to have increases in their CD4+ cell count due to initiation or change in antiretroviral therapy, it is reasonable to wait until after CD4+ cell count has increased to administer vaccine. Similarly, vaccine can be readmin-

istered after CD4+ cell count increases in a patient not responding to vaccination at a lower CD4+ cell count.

Pneumococcal Vaccines

Recommendations for pneumococcal vaccine in HIV-infected persons consist of the use of the standard 23-valent vaccine with 1-time revaccination at 5 years after the initial dose. Currently, there are insufficient data to suggest any advantage of using the 7-valent conjugate pneumococcal vaccine over the standard polysaccharide vaccine in HIV-infected adults. Response rates to pneumococcal vaccine are reduced in patients with CD4+ cell counts below 200/µL. It is recommended that vaccination be considered in such patients—with recognition that protection probably is not afforded—and that revaccination occur if the CD4+ cell count increases to 200/µL or greater as a result of antiretroviral therapy (ACIP, *MMWR Morb Mortal Wkly Rep*, 2005; CDC, *MMWR Morb Mortal Wkly Rep*, 2002)

A recent study showed that widespread pediatric use of the conjugate pneumococcal vaccine reduced the risk of invasive pneumococcal disease in HIV-infected adults. Compared with the average rate of invasive disease among HIV-infected adults in the pre-conjugate vaccine years of 1998 to 1999, the overall rate in 2003 was reduced by 19% ($P = .002$). The rate of disease from serotypes included in the

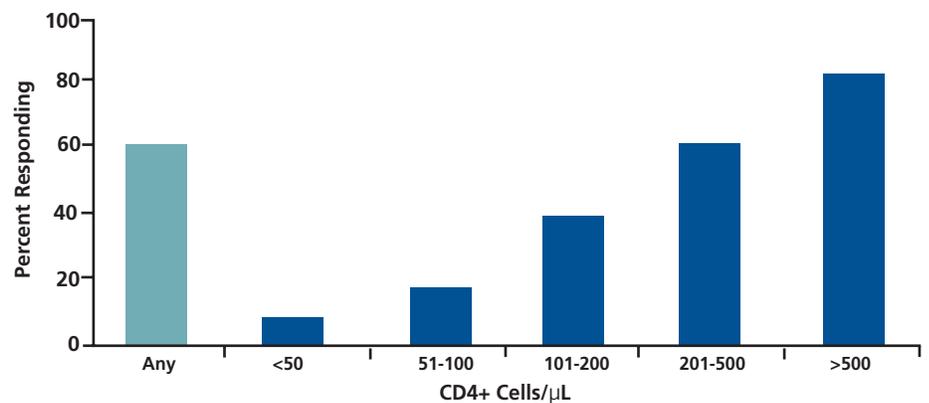


Figure 2. Relationship between CD4+ cells/µL at vaccination and response to hepatitis A vaccine (HAV; anti-HAV IgG titer >20 mIU/mL) in 214 HIV-infected adults. Adapted with permission from Rimland et al, *AIDS*, 2005.

Table 1. General Immunization Recommendations and Contraindicated Live Vaccines in HIV-infected Adults

Recommended Vaccines	
<ul style="list-style-type: none"> • Pneumococcal polysaccharide vaccine. (revaccinate once after 5 years; better responses occur in patients with higher CD4+ cell count) • Tetanus-diphtheria vaccine. (every 10 years; Tdap vaccine for next booster) • Influenza vaccine. (yearly) 	<ul style="list-style-type: none"> • Hepatitis A vaccine. (better responses occur in patients with higher CD4+ cell count) • Hepatitis B vaccine. (better responses occur in patients with higher CD4+ cell count and lower plasma HIV RNA level) • Measles, mumps, and rubella (MMR) vaccine. (contraindicated in severe immunosuppression)
Contraindicated Live Vaccines	
<ul style="list-style-type: none"> • Live attenuated influenza vaccine • Varicella or zoster vaccine • Vaccinia (smallpox) vaccine • Live oral poliovirus vaccine 	<ul style="list-style-type: none"> • Measles vaccine (avoid with severe immunosuppression) • Yellow fever vaccine • Typhoid Ty21a vaccine

Tdap indicates tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

pediatric vaccine was reduced by 62% ($P < .001$), whereas there was a 44% increase ($P < .001$) in disease due to serotypes not included in the vaccine (Flannery et al, *Ann Intern Med*, 2006).

Case 4: Tetanus Vaccines

A 28-year-old HIV-infected man with a CD4+ cell count of 455/μL comes in after cutting his hand on an old table. He received all of his childhood immunizations, but he has not had a tetanus shot for at least 10 years. Which of the following would you recommend:

1. He should not receive tetanus vaccine because of his HIV status,
2. He should receive the standard tetanus-diphtheria toxoids (Td) vaccine, or
3. He should receive the new tetanus, diphtheria, and acellular pertussis (Tdap) vaccine?

According to the 2006 ACIP adult immunization recommendations (CDC, *MMWR Recomm Rep*, 2006) adult patients should receive a tetanus-diphtheria (Td) vaccine booster every 10 years. However, guidelines for adults aged 19 to 64 years, including those with HIV infection, have recently been changed to recommend substituting

the new tetanus, diphtheria, acellular pertussis (Tdap) vaccine for the standard Td vaccine with the next booster dose. The rationale for using Tdap instead of Td is to provide additional protection against pertussis. The Tdap vaccine is not contraindicated in HIV infection and thus in the case above, the patient should receive the Tdap vaccine.

Case 5: Live Vaccines

A 19-year-old woman is newly diagnosed with HIV and she has a CD4+ cell count of 122/μL. Which one of the following vaccines would be considered safe to give to her:

1. Varicella vaccine,
2. Conjugate meningococcal vaccine,
3. Measles, mumps, and rubella (MMR) vaccine, or
4. Oral polio vaccine?

Live virus vaccines contraindicated in HIV-infected persons include: live attenuated influenza vaccine, varicella and zoster vaccines, vaccinia (smallpox) vaccine (except in pandemic or bioterrorism scenarios), live oral polio vaccine, measles vaccine (in those with severe immune suppression), yellow fever vaccine, and typhoid Ty21a vac-

cine. The ACIP has defined severe immune suppression based on the HIV-infected patient's age: CD4+ cell count below 750/μL for those younger than 12 months, CD4+ cell count below 500/μL for ages 1 to 5 years, and CD4+ cell count below 200/μL for those 6 years of age or older. Thus, the correct answer to the question above would be to give the conjugate tetravalent meningococcal vaccine (MCV4) since it is a killed vaccine and it has been deemed safe for use in HIV-infected individuals. The conjugate meningococcal vaccine is now recommended for all adolescents at age 11 or 12 and for those adolescents entering high school who have previously received this vaccine. In addition, the conjugate meningococcal vaccine is recommended for unvaccinated young adults and adolescents who are going to college who will be living in a dormitory setting.

Summary

Vaccines recommended for HIV-infected adults and contraindicated live vaccines are summarized in Table 1.

Presented by Dr. Spach in August 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Spach in November, 2006.

Financial Disclosure: Dr Spach has received honoraria for lectures from Merck and GlaxoSmithKline.

Suggested Reading and Resources

The Advisory Committee on Immunization Practices (HCIP). ACIP Web site. Available at: <http://www.cdc.gov/nip/acip>. Accessed January 5, 2007.

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Top HIV Med. 2006;14(5):154-158

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Correction

Management of Dyslipidemia and Other Cardiovascular Risk Factors in HIV-infected Patients: Case-based Review (Aberg JA, *Topics HIV Med.*

2006;14(4):134-139). On page 136, the last sentence contained an error in wording and should read:

“Examples of drug interactions include: an increase of atorvastatin area-under-the-concentration-time curve (AUC) of 347%, an increase of simvastatin AUC of 3059%, and a decrease in pravastatin (which is minimally metabolized via the cytochrome P450 system) AUC of 50% when each is combined with ritonavir-boosted saquinavir; increases in atorvastatin AUC of 74% and simvastatin AUC of 505% when combined with nelfinavir; and increases in atorvastatin AUC of 588% and in pravastatin AUC of 30% when combined with ritonavir-boosted lopinavir.”^{1,2}

A corrected version of the full article is available at www.iasusa.org.

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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,

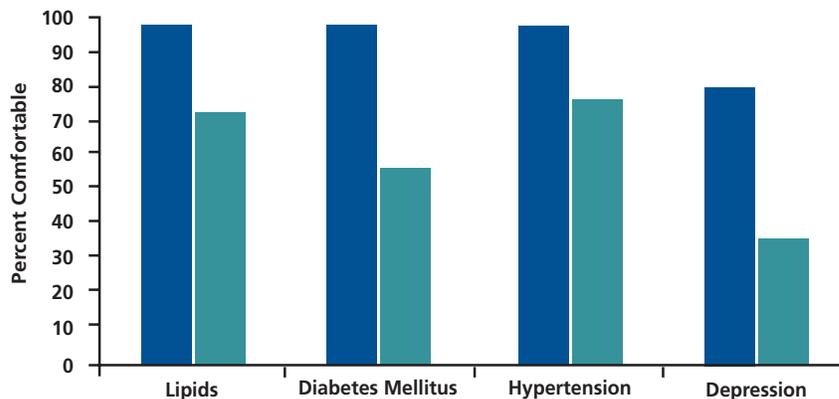


Figure 1. Veterans Aging Cohort Study general medicine provider (blue bars) and HIV provider (green bars) comfort with primary care in terms of treating common conditions. Adapted with permission from Fultz et al, *Clin Infect Dis*, 2005.

Dr Justice is the Section Chief of General Internal Medicine at West Haven Veterans Affairs Healthcare System. She is an Associate Professor of Medicine and Public Health at Yale University School of Medicine in New Haven, Connecticut and the Principal Investigator of the Veterans Aging Cohort Study—a national study of aging veterans with and without HIV infection.

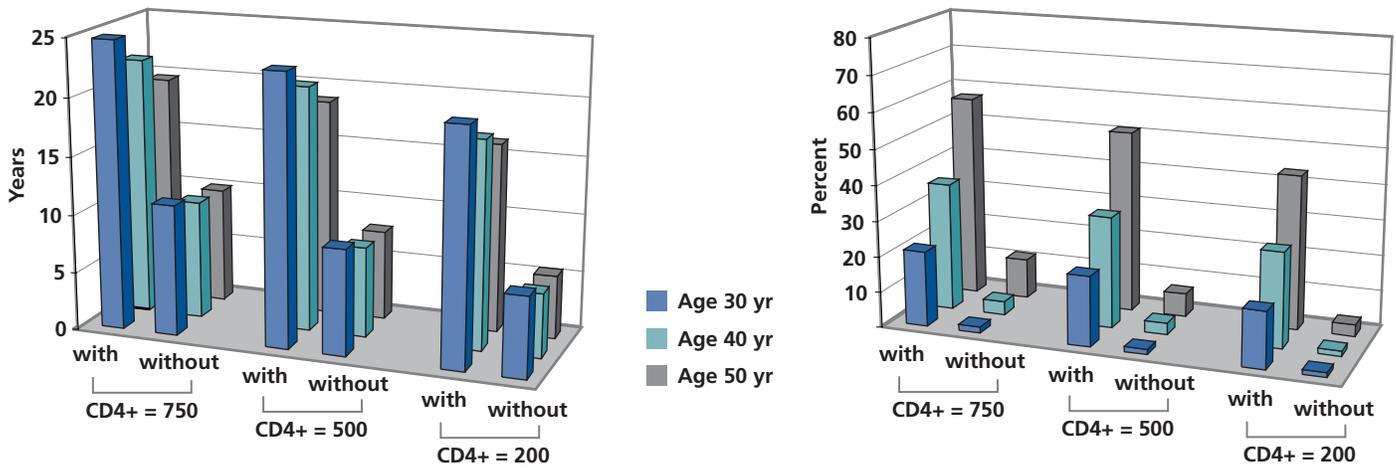


Figure 2. Estimated life-expectancy in HIV-infected persons with or without antiretroviral therapy using the model of Braithwaite et al (left), and predicted proportions of patients dying from non-AIDS related causes (right). Adapted with permission from Braithwaite et al, *Am J Med*, 2005.

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-

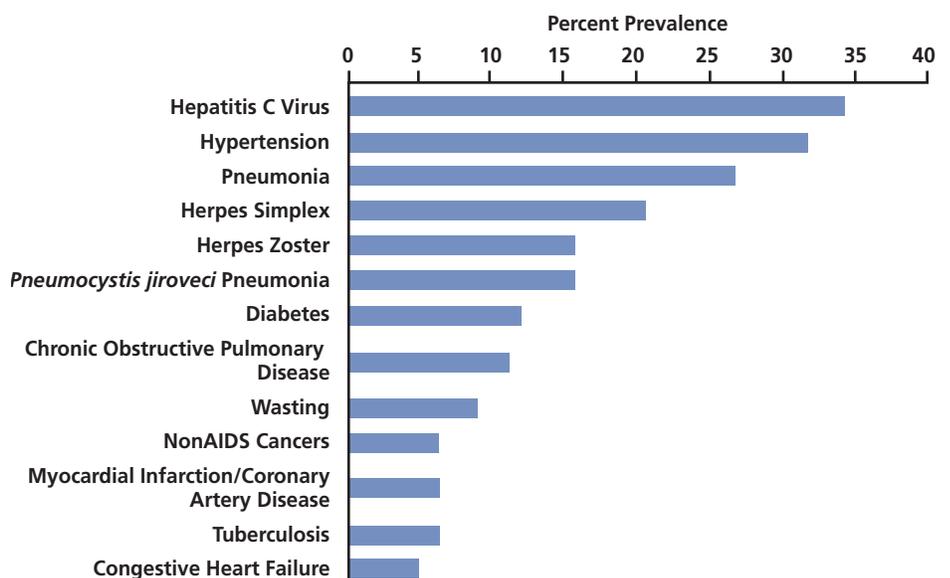


Figure 3. Medical conditions in HIV-infected patients in the Veterans Aging Cohort Study. Adapted with permission from Justice et al, *Med Care*, 2006.

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.

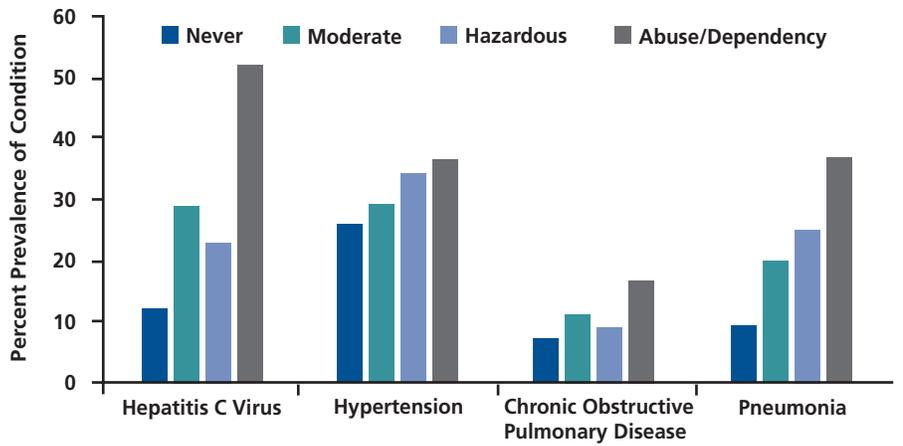


Figure 4. Association of alcohol use and comorbidities in the Veterans Aging Cohort Study. After adjustment for age, CD4+ cell count, viral load, drug use, exercise, and smoking, each step in increase in alcohol use (from never to moderate to hazardous to abuse or dependence) was associated with a statistically 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-

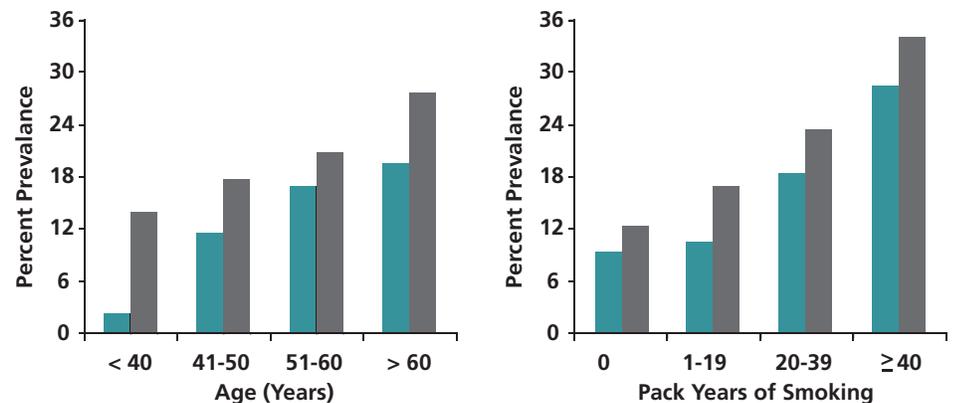


Figure 5. Unadjusted prevalence of chronic obstructive pulmonary disease in HIV-noninfected (green bars) and HIV-infected (gray bars) patients in the Veterans Aging Cohort Study according to age (left) and cigarette pack-years of smoking (right). Adapted with permission from Crothers et al, *Chest*,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

Presented by Dr Justice in August 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Justice in December 2006.

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Suggested Reading

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Perspective

Renal Disease and Toxicities: Issues for HIV Care Providers

The prevalence of renal disease is increasing in the HIV-infected population, likely reflecting increases in renal disease in the general population due to hypertension and diabetes, clustering of HIV cases in black Americans (who have a higher frequency of renal risk factors), and toxicities of antiretroviral and other drugs taken by HIV-infected patients. Screening for renal function and regular follow up are recommended for all HIV-infected individuals starting at the time of HIV diagnosis. Elements of screening include quantitative risk-factor assessment and screening tests, such as urine protein quantitation and estimation of creatinine clearance and glomerular filtration rate. Diagnosis of renal dysfunction includes consideration of causative factors common in the general population as well as HIV-specific factors. This article summarizes a presentation on renal impairment in HIV disease made by Derek M. Fine, MD, at the 9th Annual Ryan White CARE Act Clinical Update in Washington, DC, in August 2006. The original presentation is available as a Webcast at www.iasusa.org.

The prevalence of kidney disease is increasing in the US HIV-infected population, even though the incidence of end stage renal disease (ESRD) attributed to HIV-associated nephropathy (HIVAN) has remained constant since the mid-1990s. Although the incidence of ESRD attributed to AIDS nephropathy—which may or may not represent HIVAN—reached a plateau after 1996, there is little information about the incidence of earlier stages of HIVAN in the potent antiretroviral therapy era. It is currently estimated that renal function is abnormal in up to 30% of HIV-infected patients (Gupta et al, *Clin Infect Dis*, 2005), and abnormal renal function is an independent predictor of mortality in this population (Szczech et al, *Clin Infect Dis*, 2004). Renal dysfunction, unless in advanced stages, is usually asymptomatic. Since it poses serious risks, including risks of drug toxicities, HIV-infected patients should have renal function assessed at the time of HIV diagnosis and at regular intervals thereafter, depending on renal function and risk factors.

Dr Fine is an Assistant Professor of Medicine in the Division of Nephrology at The Johns Hopkins University School of Medicine in Baltimore, Maryland.

Risk Factors

Risk factors for kidney disease in the HIV-infected population include hypertension, diabetes, black race and other genetic factors, family history, and hepatitis C virus infection, which are also risk factors in the general population, as well as HIV-specific factors such as lower CD4+ cell count and higher HIV viral load. There have been marked increases in rates of ESRD due to hypertension and diabetes in the general population over the past 20 years. These causes now account for 70% or more of ESRD, and these increases are likely occurring in the HIV-infected population. Part of the increase in renal disease in the HIV-infected population is also likely associated with clustering of HIV cases in black Americans and the high frequency of

hypertension and diabetes in this racial group. Centers for Disease Control and Prevention (CDC) data from 2003 indicate that 48% of US AIDS cases are in black individuals, who constitute only 13% of the US population. Black Americans are 1.8 times as likely to have diabetes as age-adjusted white Americans, and it has been estimated that more than 30% of black individuals aged 18 years and older have hypertension.

Hypertension, which is estimated to be present in 12% to 21% of the HIV-infected population, is an independent risk factor for mortality in patients beginning antiretroviral therapy. Independent risk factors for mortality include measures of renal function (elevated serum creatinine, proteinuria) and hypertension in HIV-infected women (Table 1; Szczech et al, *Clin Infect Dis*, 2004). Some antiretroviral therapies may increase risk of hypertension, and thus risk of renal dysfunction, in HIV-infected patients (Crane et al, *AIDS*, 2006).

Assessment

The Infectious Diseases Society of America (IDSA) guidelines for screening for renal disease in HIV-infected patients are summarized in Figure 1 (Gupta et al, *Clin Infect Dis*, 2005). Risk-factor assessment and screening should begin at the first provider contact at which HIV infection is documented. History of nephrotoxic-medication use should include ask-

Table 1. Multivariable Independent Predictors of Mortality After Initiation of Antiretroviral Therapy in Women

Variable as Predictor of Death	Hazard Ratio (95% CI)	P-value
Proteinuria (presence vs. absence)	2.21 (1.33–3.67)	.002
History of hypertension	2.25 (1.37–3.68)	.001
CD4+ count (per 100 cells/ μ L decrease)	1.36 (1.15–1.60)	.0003
Hepatitis C virus infection	2.13 (1.34–3.39)	.001
Albumin level (per 1 mg/dL decrease)	2.04 (1.26–3.29)	.004
Prior history of AIDS-defining illness	1.81 (1.09–3.01)	.02

Adapted with permission from Szczech et al, *Clin Infect Dis*, 2004. CI indicates confidence interval.

Kidney Disease Risk: Qualitative Assessment

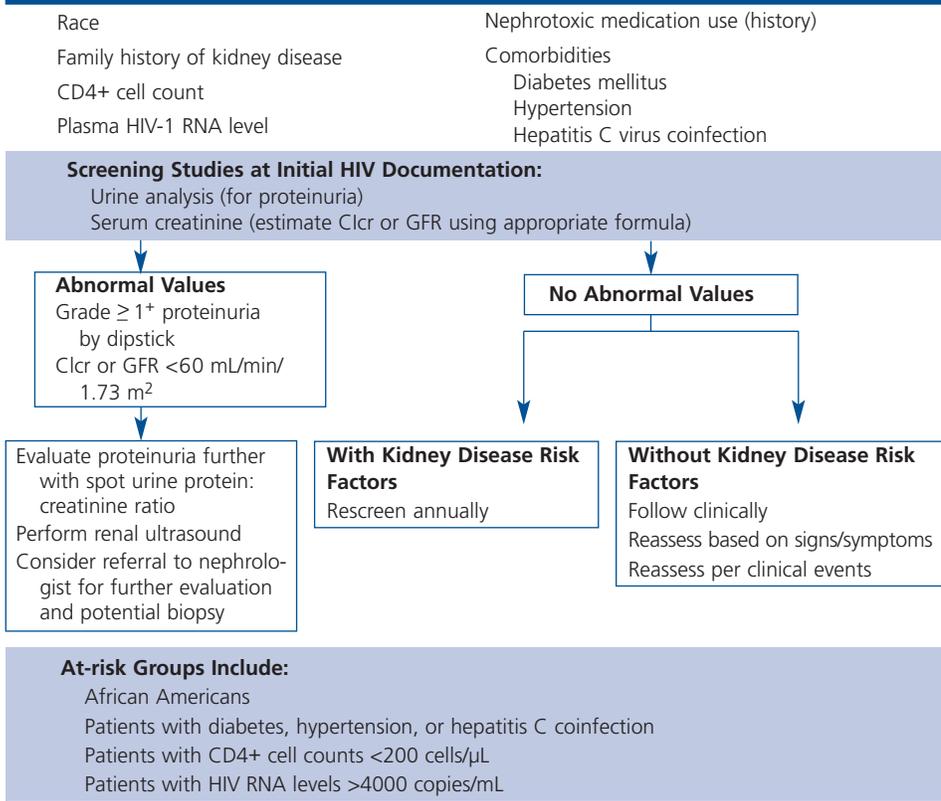


Figure 1. Infectious Diseases Society of America (IDSA) guidelines: Screening Algorithm for HIV-related Renal Diseases. Clcr indicates creatinine clearance; GFR, glomerular filtration rate. Adapted with permission from Gupta et al, *Clin Infect Dis*, 2005.

ing if the patient is using over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs). These are frequently omitted from consideration in terms of risk for renal dysfunction. The IDSA

guidelines recommend screening tests, including urinalysis for proteinuria and serum creatinine level for calculation of creatinine clearance or glomerular filtration rate (GFR)—proteinuria of grade

1+ or higher on dipstick and an estimated GFR below 60 mL/min/ 1.73 m² are the abnormal thresholds that should prompt additional work-up.

Serum creatinine measurement alone does not provide sufficient information on renal function. The left section of Figure 2 shows that a substantial proportion of individuals with abnormal renal function based on measured actual inulin clearance (GFR) has serum creatinine levels that would be considered within the normal range. There is not a good correlation between change in serum creatinine and change in GFR.

The Cockcroft-Gault formula and the Modified Diet in Renal Disease (MDRD) formula are used to calculate GFR from serum creatinine, but it is important to note that neither is perfect. The Cockcroft-Gault formula has the advantage of including body weight as a variable, which accounts for the significant weight changes that can occur in HIV-infected patients and patients with renal disease. The MDRD formula, which does not include body weight, has been widely adopted in the 4-variable form. The middle and right sections of Figure 2 show the correlations between creatinine clearance predicted by the Cockcroft-Gault equation and GFR predicted by the MDRD formula and actual GFR. The correspondence between predicted and actual values is fairly tight at GFR below 60 mL/min/ 1.73 m². Both equations can

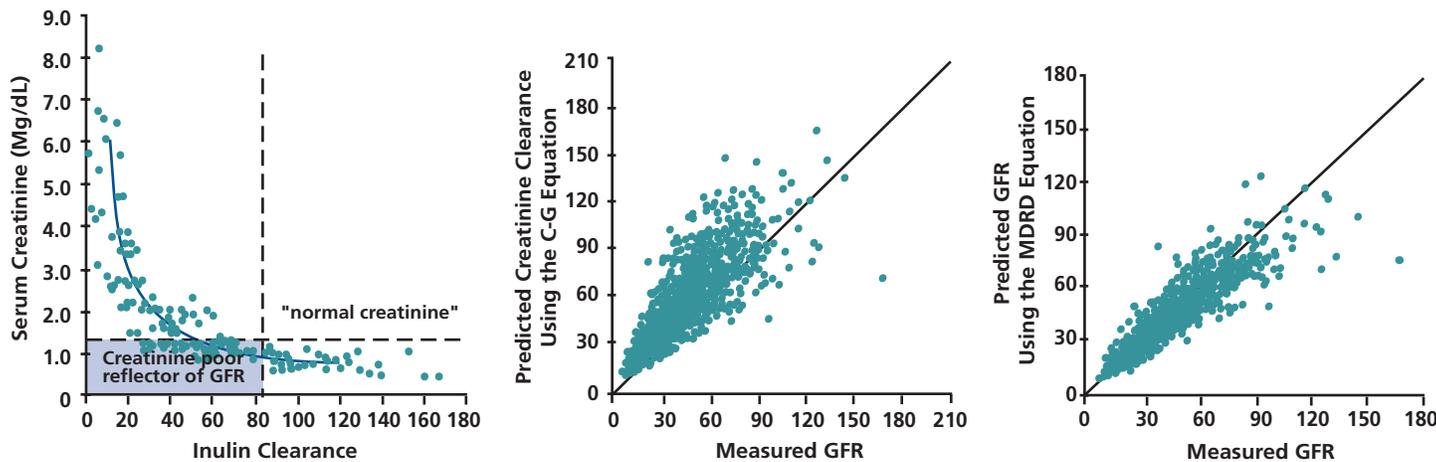


Figure 2. Left: relationship of serum creatinine level and inulin clearance rate (mL/min/ 1.73 m²) estimated by using the Cockcroft-Gault (C-G) equation; middle: correlation of creatinine (cr) clearance rate (mL/min/ 1.73 m²) predicted by C-G equation with measured glomerular filtration rate (GFR; mL/min/ 1.73 m²); and right: correlation of GFR predicted by the 6-variable (cr, blood urea nitrogen, age, race, sex, albumin) Modified Diet in Renal Disease (MDRD) equation with measured GFR. Left section adapted with permission from Johnson et al, *Comprehensive Clinical Nephrology*, 2000. Middle and right sections adapted with permission from Levey et al, *Ann Intern Med*, 1999.

Table 2. Differential Diagnosis of Acute Renal Failure in HIV Disease

HIV-related Causes	Other Causes
HIV-associated nephropathy	Usual causes in general population: pre-renal, etc.
Thrombotic microangiopathy	Acute interstitial nephritis: multiple medication exposures
Membranoproliferative glomerulonephritis (MPGN)	Hepatitis B virus- and hepatitis C virus-related disease
Immune complex glomerulonephritis (MPGN or lupus-like)	Rhabdomyolysis: statins and protease inhibitors
Medication	
Indinavir, tenofovir, sulfadiazine, pentamidine, sulfamethoxazole, and trimethoprim	

be used to provide a “ballpark” estimate of GFR, although the MDRD is considered the more accurate of the two. Neither formula, however, has been validated in the HIV population.

Determination of urine protein via dipstick, as recommended in current guidelines, is unreliable. In 52 HIV-infected patients in The Johns Hopkins HIV Nephrology Clinic with proteinuria of 500 to 1000 mg, dipstick results were “none” or “trace” in 19%, and within each dipstick grade there was a wide variation of amount of protein (unpublished data). The newer automated dipsticks are highly sensitive, resulting in a large proportion of false-positives among grade 1+ results. The 24-hour urine collection is the gold standard for measuring protein but is highly impractical, since a large number of patients will not complete the test. A practical and reliable method for quantitation of urine protein in initial work-up is the random urine protein:creatinine ratio, which divides protein concentration by creatinine concentration in a random urine sample. This method has shown a good correlation with 24-hour protein measurement. Although it may be inconvenient or too expensive to use this method at every contact, it is very useful for providing an initial quantitative assessment that will more accurately reflect whether or not the patient has renal dysfunction and requires further work-up.

Diagnoses

Differential diagnosis of acute renal failure in HIV-infected patients includes HIV-related conditions (eg, HIVAN and drug-related renal failure) and other conditions that may affect HIV-infected

and noninfected individuals (see Table 2). After consideration of non-HIV-related causes, HIVAN should be ruled out first, due to its poor prognosis if untreated. Drug-related problems that have occurred with some frequency in the HIV-infected population include acute tubular necrosis and tubular disorders (eg, with tenofovir), acute interstitial nephritis (eg, with trimethoprim/sulfamethoxazole, indinavir, or a variety of other drugs), and crystalluria or renal stones (eg, with indinavir, acyclovir, sulfadiazine). There should also be heightened suspicion for hepatitis C virus-related membranoproliferative glomerulonephritis and rhabdomyolysis in HIV-infected patients.

HIVAN

HIVAN *must* be diagnosed when present, given its extremely rapid progression to ESRD over the course of weeks

to months. HIVAN occurs almost exclusively in patients of African descent. Patients have a rapidly rising creatinine level, proteinuria that is usually in the nephrotic range (> 3 g), and, almost invariably, a detectable viral load. Definitive diagnosis can be made only by biopsy. Although biopsy carries some risk, the benefit of immediate diagnosis of HIVAN (and ruling out the numerous other diseases that may be present) outweighs such risk.

Antiretroviral therapy can treat and prevent HIVAN, and should be immediately initiated in patients with HIV infection and HIVAN. A 12-year study in a Johns Hopkins HIV clinic cohort showed that rates of presumed HIVAN (based on clinical diagnosis) among HIV-infected patients without AIDS were 0% in those on highly active antiretroviral therapy, 5.0% in those receiving only nucleoside reverse transcriptase inhibitor (nRTI) therapy, and 2.6% in those receiving no antiretroviral treatment. In patients with AIDS, rates were 6.8% in those receiving antiretroviral therapy, 14.4% in those receiving nRTI therapy, and 26.3% in those receiving no antiretroviral treatment ($P < .001$ for trend; Lucas, *AIDS*, 2004). Among 56 patients with HIVAN followed up in The Johns Hopkins HIV Nephrology Clinic, 20 were on dialysis within 1 month of diagnosis; dialysis-free survival was significantly pro-

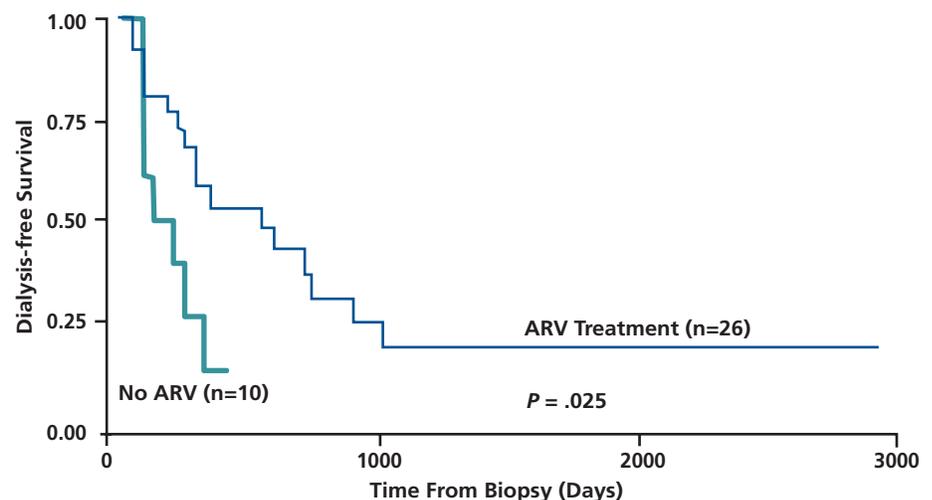


Figure 3. Dialysis-free survival estimate in patients with HIV-associated nephropathy in The Johns Hopkins Nephrology HIV Cohort according to treatment with antiretroviral therapy (ARV). Adapted with permission from Atta et al, *Nephrol Dial Transplant*, 2006.

longed among the remaining 26 who received antiretroviral therapy compared with the 10 who did not (with the 1 patient in the latter group who did not require dialysis disappearing from treatment with a creatinine of 6 mg/dL; see Figure 3; Atta et al, *Nephrol Dial Transplant*, 2006).

Other treatments that may be attempted include glucocorticoids (Eustace et al, *Kidney Int*, 2000; Smith et al, *Am J Med*, 1996) and angiotensin converting enzyme (ACE) inhibitors (Kimmel et al, *Am J Kidney Dis*, 1996; Wei et al, *Kidney Int*, 2003) or angiotensin-II receptor blockers (ARBs), though none of these treatments have been tested in a randomized clinical trial. Due to the aggressive nature of HIVAN, initiation of such potentially useful agents should be considered in all cases if tolerated by the patient.

Tenofovir-associated Renal Dysfunction

Tenofovir is closely related to adefovir, a known nephrotoxic agent that was removed from the HIV treatment market due to its causing acute renal failure and Fanconi syndrome; this toxicity has not been observed with adefovir at currently-used hepatitis B treatment doses. No significant nephrotoxicity with tenofovir was reported in clinical trials of the agent, although a small but statistically significant decline in GFR was observed in patients receiving tenofovir over 48 weeks in an observational cohort (Gallant et al, *Clin Infect Dis*, 2005). In this study, a greater than 50% reduction in creatinine clearance occurred in 4.4% of patients receiving tenofovir compared with 1.9% of those receiving other nRTIs, and a decline of 25% to 50% occurred in 13.4% and 10.8%, respectively. These data suggest that some patients may be experiencing significant renal impairment on tenofovir.

The drug is secreted by the renal tubule but is also filtered freely through the glomerulus. It is likely that renal impairment from other causes (whether pre-existing chronic kidney disease or new acute renal failure) results in reduced clearance of tenofovir, with the elevated tenofovir levels then con-

tributing to renal dysfunction. Table 3 shows independent risk factors for renal impairment from a CDC analysis of 9535 antiretroviral therapy-experienced patients with 17,357 person-years of follow up. Tenofovir use compared with use of other antiretroviral drugs was associated with a statistically significant 1.6-fold greater risk for renal impairment (Heffelfinger, 13th CROI, 2006)

There have been several case reports of renal toxicity, including Fanconi syndrome, associated with tenofovir. Fanconi syndrome is a loss of proximal tubular function that results in failure to reabsorb electrolytes and nutrients (eg, glucose, bicarbonate, phosphates, uric acid, potassium, sodium, amino acids), with subsequent elimination of these compounds in the urine. The syndrome is defined by a hypokalemic, metabolic acidosis with hypophosphatemia and glucosuria, however, the presence of any combination of these features can

occur when the proximal tubule is affected. The underlying risk factors cannot be determined on the basis of these reports; however, in some of these cases, there was an acute event leading to renal failure that did not resolve until tenofovir was discontinued. In a report of 27 cases of tenofovir-associated renal dysfunction, mean baseline creatinine was 0.9 mg/dL, peak creatinine was 3.9 mg/dL ($P < .05$), and post-discontinuation creatinine was 1.2 mg/dL ($P < .05$), with creatinine returning to baseline levels in 22 (81%) of patients. Proteinuria was present in 6 (35%) of 17 patients assessed. Fanconi syndrome was diagnosed in 16 (59%) of the patients, and 2 (7%) required dialysis (Zimmerman, *Clin Infect Dis*, 2006).

A summary of 25 reported cases of Fanconi syndrome in patients receiving tenofovir indicates that patients had a mean age of 45.5-years old (range, 34–60-years old) and mean time to diagnosis from the initiation of teno-

Table 3. Independent Risk Factors for Acute Renal Failure in 9535 Antiretroviral Therapy-experienced Patients with 17,357 Person-years of Follow-up

	Odds Ratio (95% Confidence Interval) for Renal Impairment			
	Any (GFR <90 vs ≥ 90)	Mild (GFR 60-89 vs ≥ 90)	Moderate (GFR 30-59 vs ≥ 90)	Severe (GFR 0-29 vs ≥ 90)
CD4+ Count (Cells/μL): Vs 350 (Referent)				
<50	1.5 (1.3–1.7)	1.3 (1.1–1.5)	3.0 (2.2–4.1)	3.5 (2.1–5.9)
50–199	1.3 (1.2–1.5)	1.3 (1.2–1.4)	1.7 (1.4–2.2)	2.2 (1.4–3.4)
200–349	1.1 (1.1–1.2)	1.1 (1.0–1.2)	1.2 (0.9–1.5)	1.5 (1.0–2.4)
Hemoglobin (Mg/dL): Vs 10.5 (Referent)				
<8.0	4.7 (3.9–5.7)	2.4 (1.9–3.0)	13.8 (10.1–18.8)	75.6 (47.5–120.3)
8.0–10.4	1.7 (1.5–1.9)	1.3 (1.2–1.5)	3.8 (2.9–4.9)	14.6 (9.3–22.9)
Diabetes Yes vs no (referent)	1.3 (1.1–1.5)	1.2 (1.0–1.4)	1.5 (1.1–2.0)	1.9 (1.2–3.0)
Hypertension Yes vs no (referent)	1.5 (1.4–1.7)	1.4 (1.3–1.6)	2.6 (2.1–3.2)	3.6 (2.5–5.0)
Antiretroviral Therapy Prescribed Tenofovir vs other (referent)	1.6 (1.4–1.7)	1.6 (1.4–1.7)	1.5 (1.2–1.9)	1.5 (1.0–2.2)

Glomerular filtration rate (GFR) in mL/min/1.73 m². Adapted with permission from Heffelfinger et al, 13th CROI, 2006.

fovir therapy of 9.6 months (range, 1–25 months). Concurrent antiretroviral drug use included ritonavir in 18 patients (72%), lopinavir in 15 (60%), lamivudine in 11 (44%), and abacavir in 11 (44%). As would be expected in a proximal tubule disorder in which glucose and phosphate are not being reabsorbed and are wasted in the urine, hypophosphatemia was found in 20 (100%) of 20 patients and glycosuria was found in 12 (89%) of 13. Urine protein was 1.7 mg/g creatinine in 14 patients. Two (8%) were diagnosed with diabetes insipidus. Tenofovir levels were elevated in patients in whom such levels were measured. Both the electrolyte abnormalities and glycosuria resolved with discontinuation of tenofovir treatment. Biopsies showed proximal acute tubular necrosis with no glomerular, vascular, or interstitial changes.

It appears likely that most patients experiencing tenofovir nephrotoxicity have some degree of renal impairment to begin with, or experience acute renal failure due to another cause that results in, and is exacerbated by, tenofovir toxicity. Nonetheless, the data indicate that patients receiving tenofovir should be monitored for renal function fairly closely, and the need for initial screening and monitoring of renal function in all patients should be emphasized. The IDSA guidelines suggest biannual monitoring in patients receiving tenofovir.

Acute Interstitial Nephritis

For many years, the model of drug-related interstitial nephritis was that of methicillin-related interstitial nephritis, characterized by eosinophilia, pyuria, hematuria, and extrarenal symptoms including flank pain and rash. Although cases of drug-related interstitial nephritis may include many of these symptoms, it may also be present in the absence of these findings, and patients may have no symptoms other than a high or rising creatinine level. Acute interstitial nephritis should be considered in cases in which creatinine level is increasing after the introduction or reintroduction of any drug treatment in the absence of any other explanation for the renal dysfunction.

Diagnosis, if not apparent by clinical criteria, is made by biopsy, and early diagnosis is crucial for avoiding tubulointerstitial fibrosis and permanent renal insufficiency. The putative culprit medication should be withdrawn immediately. Corticosteroid treatment should be considered if renal function does not improve within 7 to 10 days.

Conclusions

Dr Fine concluded with his personal recommendations regarding screening for renal impairment in HIV-infected patients: (1) Initial screening of patients should include urine protein quantification by spot-urine protein:creatinine ratio, rather than dipstick. The threshold for nephrologist referral on this test should be estimated proteinuria of above 500 mg (although one could consider a lower cut-off at 300 mg, the upper limit of normal). (2) Patients with no abnormal findings at baseline, who are nevertheless at high risk due to other factors (eg, CD4+ cell count below 200/ μ L, plasma HIV RNA level above 4000 copies/mL, diabetes, hepatitis C virus infection), should undergo screening every 6 months rather than annually. (3) Monitoring for renal function and urinary abnormalities should occur every 3 months, rather than every 6 months, in patients receiving tenofovir.

In addition to the recommendation for renal-function screening and follow up in all HIV-infected patients, certain elements of the IDSA guidelines need to be stressed. In patients with evidence of chronic kidney disease, blood pressure should be controlled to 125/75 mmHg. In those with proteinuria, initial use of ACE inhibitors or ARBs is preferred based on evidence of benefit in other proteinuric diseases. Diagnosis of HIVAN is crucial, and patients with HIVAN should have antiretroviral therapy started at confirmed diagnosis. Insufficient improvement with antiretroviral treatment warrants consideration of treatment with ACE inhibitors, ARBs, and prednisone (although, as stated earlier, the aggressive nature of this entity may support early initiation of both these agents). In patients with renal impair-

ment, dose-reduction is warranted for antiretroviral drugs that are primarily renally excreted. Likewise, in hemodialysis patients, attention must be given to providing additional post-dialysis doses of antiretroviral drugs that are readily removed in dialysis.

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Perspective

Hepatitis B Virus Treatment in HIV-infected Patients

Hepatitis B virus (HBV) infection is common in HIV-infected persons and is associated with increased risk of liver-related morbidity and mortality. Agents available to treat HBV infection in coinfecting patients include lamivudine, entecavir, emtricitabine, adefovir, tenofovir, peginterferon alfa, and the recently approved telbivudine. Treatment decisions should take into account a number of factors, including antiretroviral therapy status, HBV genotype, prior experience of lamivudine, and the need to avoid drug resistance in both HIV- and HBV-infected persons. This article summarizes a presentation on treatment and management of HBV infection in HIV-infected patients made by Chloe L. Thio, MD, 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.

It is estimated that 1 to 1.25 million persons in the United States (US) have hepatitis B virus (HBV) infection. The incidence of infection decreased by 67% between 1990 and 2002, reflecting at least in part the use and efficacy of HBV immunization. However, between 1999 and 2002, incidence rates increased by 5% in men aged 20 to 39 years, and by 20% in men and 31% in women aged 40 years or older (age groups that are also at increased risk of HIV infection). Coinfection with HIV is common. It is estimated that approximately 10% of HIV-infected individuals also have chronic HBV infection. Coinfecting patients have increased risks of rapid progression of HBV liver disease, liver-related mortality, antiretroviral therapy-related hepatotoxicity, and hepatic failure as part of an immune reconstitution syndrome. Figure 1 shows the marked increase in liver-related mortality in coinfecting patients in a study of 5293 men with or without HIV or HBV infection (Thio et al, *Lancet*, 2002).

Case 1: Patient With No Prior Antiretroviral Therapy

A 28-year-old white man is referred for elevated liver function tests. He has a history of hypertension and review of

systems shows fatigue and decreased appetite. Physical exam shows no jaundice and no right-upper quadrant tenderness or hepatosplenomegaly. Laboratory tests show alanine aminotransferase (ALT) of 126 IU/mL and total bilirubin of 0.6 mg/dL, and the patient is positive for HBV surface antigen (HBsAg). What test is most helpful in initially characterizing the patient's HBV infection:

1. HBV DNA,
2. Liver biopsy,
3. HBV envelope antigen (HBeAg),
4. 1 and 3, or
5. 1, 2, and 3?

This patient should be tested for both HBV DNA and HBeAg. Acute HBV infection is indicated by an IgM antibody response to HBV core antigen (HBcAg). Chronic infection is indicated by presence of HBV surface antigen (HBsAg) for more than 6 months. Individuals who have responded to HBV vaccine exhibit anti-HBs antibody, and those with past infection exhibit both anti-HBs antibody and anti-HBc antibody. The patient's HBsAg-positive status indicates chronic infection.

Among patients with chronic infection, active infection is indicated by HBeAg-positive status, which is often accompanied by ALT greater than 2 times the upper limit of normal, HBV DNA level greater than 1×10^5 copies/mL ($\sim 2 \times 10^4$ IU/mL), and evidence of disease on liver biopsy. Patients

who are HBeAg-negative also may have active infection, with similar ALT levels and positive liver biopsy but may have lower HBV DNA levels (eg, greater than 10^4 copies/mL [$\sim 2 \times 10^3$ IU/mL]) than HBeAg-positive patients. HBeAg-negative patients without active infection, "healthy carriers," tend to have normal ALT levels and undetectable, or very low, HBV DNA levels and would be unlikely to have significant findings on liver biopsy. Figure 2 provides an idea of how serologic markers, liver function tests, and clinical and immune states are correlated in the natural history of HBV infection. HBV/HIV-coinfecting patients who are HBV-inactive carriers require monitoring for HBV DNA and ALT (eg, every 6-12 months) to promptly detect reactivation of HBV infection.

The patient is found to have HIV infection, with a CD4+ cell count of 500/ μ L. He is HBsAg-positive, HBeAg-positive, and anti-HBe antibody-negative, has HBV DNA of 5×10^6 IU/mL, and stage 1 to 2 fibrosis on liver biopsy. What other tests should be done:

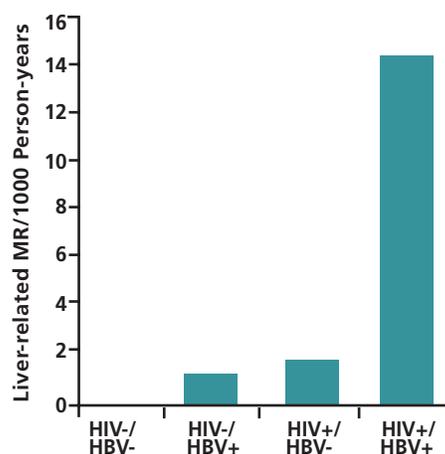


Figure 1. Liver-related mortality rate (MR) per 1000 person-years in 5293 men with (+) or without (-) hepatitis B virus (HBV) or HIV infection. Cohort included 326 men who were HBV surface antigen-positive (HBsAg+). Adapted from Thio et al, *Lancet*, 2002.

Dr Thio is an Associate Professor of Medicine at The Johns Hopkins University in Baltimore, Maryland.

1. Ultrasound or computed tomography (CT) scan and measurement of alpha-fetoprotein,
2. Total hepatitis A virus (HAV) antibody,
3. HBV genotype,
4. 1 and 2, or
5. 1, 2, and 3?

Patients with HBV infection are at increased risk for hepatocellular carcinoma, which should be ruled out by ultrasound or CT scan and testing for alpha-fetoprotein. They are also at increased risk of more fulminant HAV infection; HAV antibody should be assessed, and the patient should receive hepatitis A vaccine if he is antibody-negative.

HBV genotyping is becoming increasingly useful in HBV-disease management, as more is learned about associations of genotype with disease progression (including risk of hepatocellular carcinoma) and response to HBV treatment. For example, in a recent trial comparing peginterferon alfa with peginterferon alfa plus lamivudine in patients without HIV infection, response measured as HBeAg loss occurred in 29% and 44% of patients, respectively, at end of treatment at week 52 ($P = .01$), with the response rate increasing to 36% in the monotherapy group and decreasing to 35% in the combination group at end of follow up at week 78 ($P =$ not statistically significant [NS]; Janssen et al, *Lancet*, 2005). The

study indicated that the addition of lamivudine did not provide benefit and showed that HBV genotype influenced response at end of follow up. Among all patients, response at week 78 was observed in 47% of 90 patients with genotype A, 44% of 23 patients with type B, 28% of 39 patients with type C, and 25% of 103 patients with type D. Types A and D are the most common in the United States, and there was a statistically significant increase in response for type A versus type D (odds ratio, 2.4; 95% confidence interval, 1.3-4.6; $P = .01$) in the study. There currently are no data on association of genotype with response in coinfecting patients.

In addition to the findings already noted, genotyping shows the patient to be infected with HBV genotype A. His plasma HIV RNA level is 12,000 copies/mL. What treatment should he receive:

1. Lamivudine,
2. Entecavir,
3. Tenofovir,
4. Peginterferon alfa, or
5. 2 or 4?

US Food and Drug Administration (FDA)-approved therapies for HBV infection consist of: the L-nucleoside analogues, lamivudine, telbivudine, and entecavir; the nucleotide analogue, adefovir; and peginterferon alfa. Agents with activity

against HBV that are available but not FDA-approved include the nucleoside analogue emtricitabine, and the nucleotide analogue tenofovir. Lamivudine, emtricitabine, and tenofovir have intrinsic anti-HIV activity. Adefovir, a forerunner of tenofovir, also has anti-HIV activity but is given at lower doses in HBV infection than those associated with anti-HIV activity. Adefovir is not used for HIV treatment because doses with anti-HIV activity were associated with severe renal toxicity. Peginterferon alfa has some anti-HIV activity but is not associated with HIV resistance. Given the patient's HIV RNA and CD4+ cell count, he can begin treatment for HBV infection before antiretroviral therapy for HIV is considered. To avoid the emergence of HIV resistance that would arise with suboptimal suppression of viral replication and compromise future treatment, the agents with intrinsic anti-HIV activity should not be used to treat HBV infection. Of the choices listed, one option for the patient is peginterferon alfa; however, it has yet to be assessed in patients with coinfection. Entecavir is also an option since published data do not show evidence of anti-HIV activity. Other options, which are not listed, include initiating antiretroviral therapy early or adefovir.

Case 2: Patient On Antiretroviral Therapy

A 42-year-old HIV-infected man presents with elevated liver enzymes. He has received zidovudine, lamivudine, and efavirenz for the past 3 years and has a CD4+ cell count of 350/μL and plasma HIV RNA level below 50 copies/mL. He is HBsAg-positive and HBeAg-negative, with HBV DNA of 3.6×10^5 IU/mL. What should you do with his medications:

1. Replace zidovudine with tenofovir,
2. Continue current medications,
3. Add entecavir,
4. Replace lamivudine with emtricitabine, or
5. None of the above?

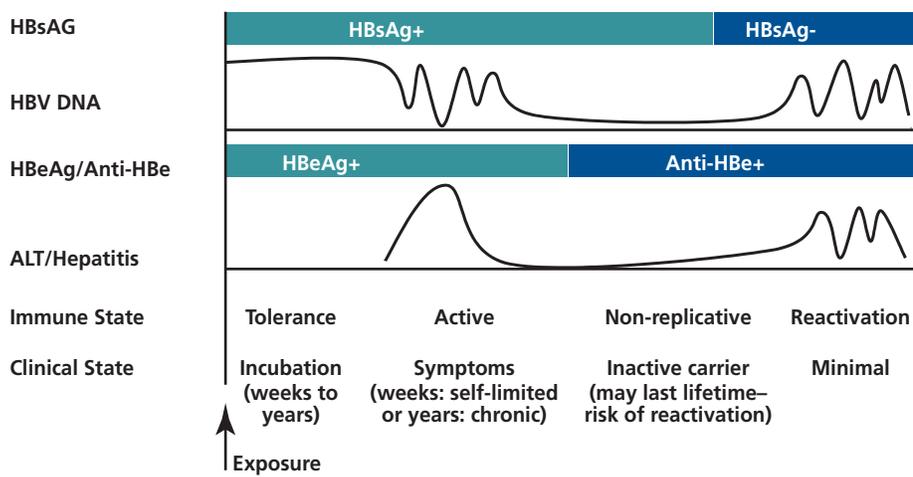


Figure 2. Natural history of hepatitis B virus (HBV) infection. HBsAg indicates HBV surface antigen; HBeAg, HBV envelope antigen; anti-HBe, antibody to HBe; ALT, alanine aminotransferase; +, positive; -, negative.

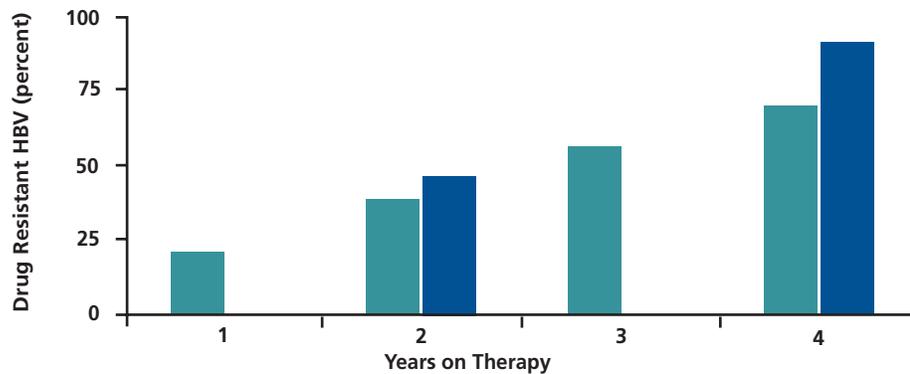


Figure 3. Development of hepatitis B virus (HBV) resistance to lamivudine (LMV) in HBV monoinfection (light green) or HBV/HIV coinfection (dark blue). Adapted from Benhamou et al, *Hepatology*, 1999; Liaw et al, *Gastroenterology*, 2000; Chang et al, *J Gastroenterol Hepatol*, 2004.

The patient has been receiving lamivudine for 3 years as part of a antiretroviral therapy regimen that remains effective in suppressing HIV replication. HBV resistance to lamivudine develops more rapidly in coinfecting patients than in HBV–monoinfected patients (Figure 3), with approximately 90% of coinfecting patients having HBV resistance after 4 years of treatment. The emergence of resistance is clinically evidenced by increases in transaminases. For example, in one study ALT flares (greater than 3 times the upper limit of normal) showed statistically significant increases in patients with lamivudine resistance, as well as statistically significant increases as the duration of presence of lamivudine resistance lengthened. Hepatitis flares occurred in about 20% of patients with no evident lamivudine resistance, about 35% of those with presence of resistance mutations for less than 1 year, and about 75% of those with mutations present for more than 4 years. Hepatic decompensation and liver-related adverse events increased after 4 years of lamivudine resistance (Lok et al, *Gastroenterology*, 2003).

In this patient, the lamivudine is needed for his HIV infection. Although data exist suggesting that continuing lamivudine despite resistance might still benefit the patient in terms of continued reduction in HBV DNA and maintained loss of HBeAg, growing evidence, on hepatitis flares and the association of such flares with worsened liver dis-

ease, argue against continuing lamivudine alone in the setting of resistance.

The patient's medications need to be changed to provide additional anti-HBV activity. Among potential drugs that may be substituted or added are adefovir, tenofovir, and entecavir. Adefovir does not appear to be as effective in treating HBV infection as tenofovir. In a cohort of

35 coinfecting patients with lamivudine-resistant HBV, 48-week outcomes with adefovir treatment (10 mg/d) were relatively poor, including reduction in HBV DNA to below 1000 copies/mL in 6%, HBeAg loss in 8.6%, and ALT normalization in 14%, although responses appeared to improve over longer durations (Figure 4; Benhamou et al, *J Hepatol*, 2006). There is a concern that adefovir treatment might result in HIV that is resistant to tenofovir; no evidence of resistance was found in the above study or in other limited experience with adefovir in this setting. AIDS Clinical Trial Group (ACTG) study 5127 was performed to demonstrate noninferiority of tenofovir 300 mg compared with adefovir 10 mg in reducing HBV DNA in 52 coinfecting patients on stable antiretroviral therapy, who had HBV DNA levels above 100,000 copies/mL and HIV RNA levels below 10,000 copies/mL (Peters et al, *CROI*, 2005 and *Hepatology*, 2006). The time-weighted average reductions in HBV DNA at 48 weeks with tenofovir versus adefovir were 4.03 versus 3.12 log₁₀ on

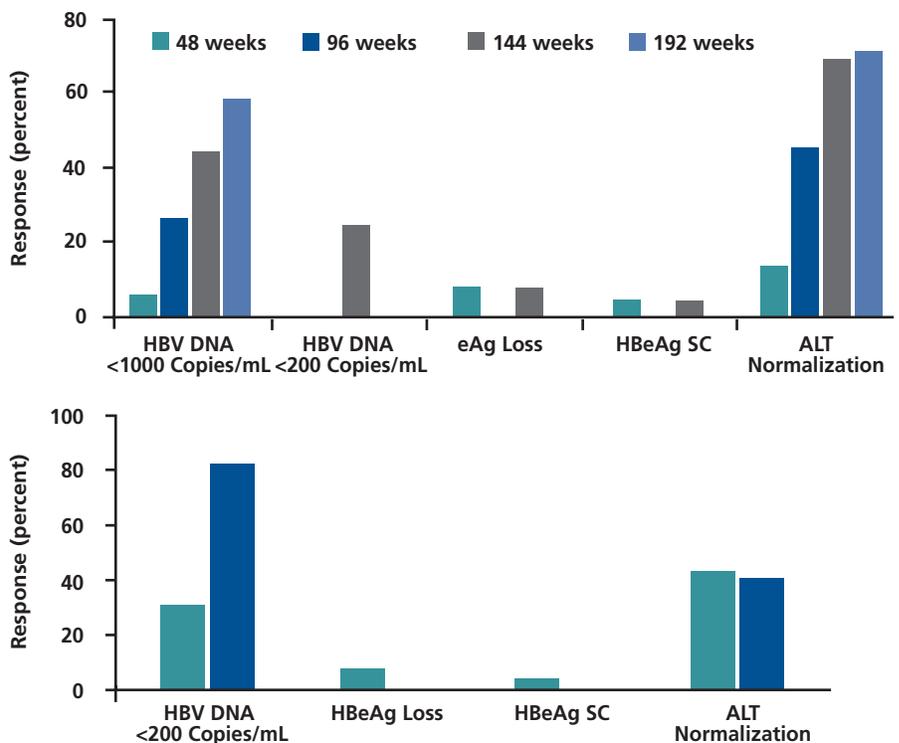


Figure 4. Top: Outcomes of adefovir treatment in observational cohort of 35 patients with lamivudine-resistant hepatitis B virus (HBV); n=31 at 48 weeks and n=29 at 144 weeks. Adapted from Benhamou et al, *J Hepatol*, 2006. Bottom: Outcomes of tenofovir treatment for 12 months in observational cohort of 65 patients with lamivudine-resistant HBV. Adapted with permission from Benhamou et al, *Hepatology*, 2006. SC indicates seroconversion; ALT, alanine aminotransferase; eAg, envelope antigen; HBeAg, HBV envelope antigen; +, positive; -, negative.

Table 1. Outcomes with Tenofovir or Lamivudine or the Combination at 24 Weeks

	Lamivudine-naive			Lamivudine-experienced		
	Tenofovir (n=10)	Lamivudine (n=11)	Tenofovir + Lamivudine (n=6)	Tenofovir (n=12)	Lamivudine (n=9)	Tenofovir + Lamivudine (n=11)
Change in HBV DNA (Log ₁₀ copies/mL)	- 4.66	- 3.31	- 5.03*	- 3.41*	- .82	- 3.93*
HBV DNA <400 Copies/mL (ITT)	40%	36.4%	50%	16.7%	0%	36.4%
ALT Normalization (ITT)	30%	63.6%	50%	25%	0%	36.4%

**P*<.05 compared with lamivudine-alone group. ITT indicates intent-to-treat analysis; HBV, hepatitis B virus; ALT, alanine aminotransferase. Adapted from Nelson et al, CROI, 2006.

intent to treat analysis and 4.76 versus 3.48 log₁₀ on an as-treated analysis, respectively. In a cohort study of tenofovir in coinfecting patients with lamivudine-resistant HBV, 1-year outcomes were better than those reported in the adefovir cohort study, including greater proportions of patients with HBV DNA levels reduced to below 200 copies/mL and greater proportions of patients with ALT normalization (Figure 4; Benhamou et al, *Hepatology*, 2006). In a trial comparing entecavir with continued lamivudine for 24 weeks in 68 coinfecting patients with lamivudine-resistant HBV, mean HBV DNA of 9.13 log₁₀ copies/mL and mean HIV-1 RNA of 2 log₁₀ copies/mL, entecavir (n= 51) reduced HBV DNA to below 300 copies/mL in 6% compared with 0% with lamivudine. The mean decline in HBV DNA was 3.65 log₁₀ copies/mL with entecavir compared with an increase of 0.11 log₁₀ copies/mL with lamivudine (entecavir package insert).

One study evaluated the combination of lamivudine with tenofovir in HBV-monoinfected patients. Patients without prior lamivudine exposure had a significantly greater reduction in HBV DNA with the combination therapy than with lamivudine alone (Table 1; Nelson et al, CROI, 2006). Among lamivudine-experienced patients, both the combination therapy and tenofovir alone significantly reduced HBV DNA compared with lamivudine, with the combination appearing to improve other outcomes as well, despite the prior lamivudine exposure.

There are few data on HBV resistance to adefovir, tenofovir, and entecavir (Borroto-Esoda et al, *J Hepatol*, 2006; Colonno et al, *J Hepatol*, 2005). Data on adefovir indicate rates of resistance of 3% in year 2 of treatment, 11% in year 3, 18% in year 4, and 29% in year 5 among mainly HBeAg-negative patients without HIV infection. Resistance has not been observed in patients continuing lamivudine despite lamivudine resistance and was not observed in any of 29 coinfecting patients over 144 weeks of monitoring. Resistance to entecavir was observed in 9% of patients at 2 years and occurs mainly in the setting of lamivudine-resistant virus. Entecavir resistance is infrequent in the setting of wild-type HBV. Case reports from Australia now confirm several cases of entecavir resistance in lamivudine-naive, monoinfected patients (Colonno et al, *Hepatology*, 2006). Entecavir shares 2 of its 4 identified HBV resistance mutations with lamivudine. Table 2 shows cross-resistance among lamivudine, entecavir, adefovir, telbivudine, and the investigational L-nucleoside analogue, clevudine. Resistance to lamivudine is associated with resistance to other L-nucleoside analogues, raising the issue of losing class activity in the presence of lamivudine resistance. Data such as these indicate that the entecavir dose should be increased from 0.5 mg to 1 mg when lamivudine-resistant virus is present. Adefovir-resistant virus also appears to reduce susceptibility to most of the L-nucleoside analogues.

Given the above considerations, a

likely option for the patient is to replace zidovudine with tenofovir to maintain anti-HIV efficacy and provide anti-HBV activity. The addition of entecavir might also be considered, but the likelihood of lamivudine resistance in the patient suggests risk for entecavir resistance as well.

Treatment Strategies

Treatment of HBV alone

If HBV infection is to be treated without concurrent antiretroviral therapy (eg, in patients who have not yet started antiretroviral therapy), drugs that are not active against HIV should be used to prevent development of drug-resistant HIV. Peginterferon alfa is an option; it may be most useful in patients who are HBeAg-positive, have HBV genotype A, and have elevated ALT. Adefovir is another option. Published data do not show activity of entecavir against HIV, so that is another option.

Treatment of HBV and HIV

In patients receiving antiretroviral therapy, treatment for HBV infection should occur only with maximally suppressive antiretroviral therapy. In lamivudine-naive patients, the first-line therapy consists of tenofovir plus either lamivudine or emtricitabine with preference given to emtricitabine since it is coformulated with tenofovir into 1 pill. Other approaches that may be considered include entecavir with or without tenofovir or peginterferon alfa treatment. In

Table 2. Cross-resistance in Hepatitis B Virus (HBV) by Drug

HBV Strain	Fold-resistance				
	Lamivudine ¹	Adefovir ²	Clevudine ³	Telbivudine ⁴	Entecavir ^{4,5}
Wild-type	1	1	1	1	1
Lamivudine-resistant	1.7	0.5	>120	12	1
	>106	0.7	>120	236	30
Adefovir-resistant	>105	0.2	>120	133	30
	2-6	1-5	NA	NA	NA
Entecavir-resistant	3-8	7-10	4.7	2.4	0.67
	>1000	1.0	NA	>100	>1000
	>1000	2.0	NA	>1000	>1000

¹Adapted from Chin et al, *AAC*, 2001.; ²Angus et al, *Gastroenterology*, 2003.; ³Ono-Nita et al, *AAC*, 2002.; ⁴Levine et al, *AAC*, 2002.; ⁵Tenney et al, *AAC*, 2004. NA indicates not available.

lamivudine-experienced patients, the preferred option is the addition of tenofovir to ongoing lamivudine. If this is not possible, other options might include use of entecavir at the 1-mg dose (to compensate for likelihood of reduced susceptibility due to lamivudine resistance) or, in some instances, the addition of adefovir (if sparing of tenofovir is desired), although there is concern regarding efficacy and toxicity with this option.

Monitoring and Duration of Treatment

In patients starting treatment for HBV infection, HBV DNA and liver function tests should be performed every 3 months for the first year and every 3 to 6 months thereafter, provided resistance is not suspected. Patients who are HBeAg-positive should be monitored for HBeAg status and anti-HBe antibody status on the same schedule. Treatment is lifelong in patients who are HBeAg-positive. Those HBeAg-positive patients who seroconvert to HBeAg-negative and anti-HBe positive should continue treatment for at least 6 months to determine if seroconversion is stable. Duration of treatment with nucleoside or nucleotide analogues in patients who begin therapy with HbsAg-negative status is probably lifelong. The optimal duration of

treatment with peginterferon alfa in HBeAg-negative patients remains unclear. Treatment should continue for more than 12 months since relapse is virtually universal in patients treated for less than 12 months. The recommended duration of treatment in HBeAg-positive patients is 12 months.

Summary

Treatment of HBV infection should be considered in HIV-infected persons. HBV resistance occurs to single-agent therapy, but resistance rates appear to vary; cross-resistance may also occur. The treatment plan should be individualized based on the need for treatment of HIV infection and prior lamivudine therapy, with a primary objective of preventing emergence of drug-resistant HBV and HIV. More potent agents are needed, and combination therapy needs further investigation.

Presented by Dr. Thio in August 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Thio in December 2006.

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Suggested Reading

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The IAS-USA would like to thank Larry Wolheim, Kevin Eddleman, and the staff of Giant Creative Strategy, LLC in San Francisco for donating their time and creative energy to developing the new look. Thank you!

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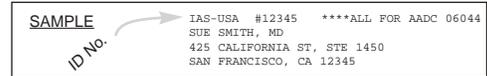
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Contributors

Pedro Cahn, MD, PhD, Hospital Juan Fernandez/University of Buenos Aires
Chinazo Cunningham, MD, Albert Einstein College of Medicine
Carl J. Fichtenbaum, MD, University of Cincinnati
Hillary V. Kunins, MD, Albert Einstein College of Medicine
Jaime C. Robertson, MD, University of Cincinnati
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Myron S. Cohen, MD, The University of North Carolina at Chapel Hill
Raymond T. Chung, MD, Harvard University
Judith S. Currier, MD, University of California Los Angeles
Eric S. Daar, MD, University of California Los Angeles
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Joseph J. Eron, Jr, MD, The University of North Carolina at Chapel Hill
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Charles W. Flexner, MD, The Johns Hopkins University
Stephen E. Follansbee, MD, Kaiser Permanente Medical Center San Francisco
Donna C. Futterman, MD, Albert Einstein College of Medicine
Julie L. Gerberding, MD, Centers for Disease Control and Prevention
Marshall J. Glesby, MD, Cornell University
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Paul E. Klotman, MD, Mount Sinai Medical Center
Margaret J. Koziel, MD, Harvard University
Daniel R. Kuritzkes, MD, Harvard University
Jens D. Lundgren, MD, University of Copenhagen
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Toby A. Maurer, MD, University of California San Francisco
Anthony Mills, MD, University of California Los Angeles

Eugene D. Morse, PharmD, University at Buffalo School of Pharmacy and Pharmaceutical Sciences
 Graeme Moyle, MD, MBBS, Chelsea and Westminster Hospital
 David G. Ostrow, MD, PhD, David Ostrow and Associates
 Marion G. Peters, MD, University of California San Francisco
 Ana M. Puga, MD, Children's Diagnostic and Treatment Center
 Stuart C. Ray, MD, The Johns Hopkins University
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 Jürgen Rockstroh, MD, University of Bonn
 Michael S. Saag, MD, The University of Alabama at Birmingham
 Mauro Schechter, MD, PhD, Universidad Federal do Rio de Janeiro
 Robert T. Schooley, MD, University of California San Diego
 Morris Schambelan, MD, University of California San Francisco
 Kenneth E. Sherman, MD, PhD, University of Cincinnati
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 Donna E. Sweet, MD, University of Kansas
 Chloe L. Thio, MD, The Johns Hopkins University
 Glenn Treisman, MD, PhD, The Johns Hopkins University
 Christina M. Wyatt, MD, Mount Sinai School of Medicine
 Carmen D. Zorrilla, MD, University of Puerto Rico

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The Drug Resistance Mutations Group was convened in 2000 to maintain an ongoing, up-to-date list of HIV drug resistance mutations. Each year, the group issues several updates to its list of mutations, the most recent of which appeared in the August/September 2006 issue of *Topics in HIV Medicine* and can also be found at www.iasusa.org/resistance_mutations.

Victoria A. Johnson, MD (Chair), The University of Alabama at Birmingham and Veterans Affairs Medical Center at Birmingham, Alabama
 Françoise Brun-Vézinet, MD, PhD, Hôpital Bichat-Claude Bernard
 Bonaventura Clotet, MD, PhD, Hospital Universitari Germans Trias I Pujol
 Huldrych F. Günthard, MD, University Hospital of Zürich
 Daniel R. Kuritzkes, MD, Harvard University
 Deenan Pillay, MD, Royal and Free University College Medical School
 Douglas D. Richman, MD, (Vice Chair), University of California San Diego and Veterans Affairs San Diego Healthcare System
 Jonathan M. Schapiro, MD, Sheba Medical Center

Guidelines for Treatment of Adult HIV-Infection Panel

Scott M. Hammer, MD, Columbia University College of Physicians and Surgeons
 Michael S. Saag, MD, The University of Alabama at Birmingham
 Mauro Schechter, MD, PhD, Universidade Federal do Rio de Janeiro
 Julio S.G. Montaner, MD, University of British Columbia
 Robert T. Schooley, MD, University of California San Diego
 Melanie A. Thompson, MD, AIDS Research Consortium of Atlanta
 Charles C.J. Carpenter, MD, Brown University
 Margaret A. Fischl, MD, University of Miami
 Brian G. Gazzard, MD, FRCP, Chelsea & Westminster Hospital
 José M. Gatell, MD, PhD, University of Barcelona
 Martin S. Hirsch, MD, Harvard University
 David A. Katzenstein, MD, Stanford University
 Douglas D. Richman, MD, University of California San Diego and Veterans Affairs San Diego Healthcare System
 Stefano Vella, MD, Istituto Superiore di Sanità
 Patrick G. Yeni, MD, Hôpital Bichat-Claude Bernard
 Paul A. Volberding, MD, San Francisco Veteran Affairs Medical Center and University of California San Francisco

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International AIDS Society–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120

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