Perspective

Selected Primary-Care Issues in HIV Disease

Primary care for HIV-infected patients includes ensuring that eligible patients receive hepatitis B and A virus vaccinations, all women undergo appropriate screening and follow-up for cervical cytologic abnormalities, and all patients undergo routine screening for renal function abnormalities. Current guidelines in these specific areas of HIV primary care are reviewed. This article summarizes a presentation on issues in primary care for HIV-infected patients by David H. Spach, MD, at the 8th Annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005.

Hepatitis B and A Virus Vaccinations

Current data indicate that most HIV-infected patients eligible for hepatitis B virus (HBV) and hepatitis A virus (HAV) vaccines are not receiving appropriate immunization. In a recent retrospective study of 1071 ambulatory HIV-infected patients at 9 HIV Outpatient Study clinics, 82% of patients were screened for eligibility for HBV vaccine (no prior receipt of HBV vaccine, seronegative for HB surface antibody [anti-HBs], seronegative for HB core antibody [anti-HBc], and seronegative for HB surface antigen [HBsAg]) and 57% were screened for HAV vaccine eligibility (had risk factor for acquiring HAV, no prior receipt of HAV vaccine, and HAV antibody-seronegative status; Tedalid, *Clin Infect Dis*, 2004). Among the 57% of patients eligible for HBV vaccine, only 32% received at least 1 dose and only 17% received the recommended vaccination series. Among the 67% of patients eligible for HAV vaccine, only 23% received at least 1 dose and only 13% received the recommended series. Health care providers in the study cited the following reasons for not vaccinating patients: (1) the patient did not regularly attend the clinic; (2) the patient was not considered to be at high risk for infection; (3) the patient's CD4+ cell count was too low; and (4) insurance did not cover the immunization.

The 2004-2005 Advisory Committee on Immunization Practices (ACIP) guidelines recommend that HBV vaccination be provided for all HIV-infected patients who do not have evidence of prior HBV infection. Thus, assessment of risk of acquisition of HBV infection should not enter into the decision whether to provide vaccination. Similarly, although vaccination is less likely to generate an adequate antibody response in patients with lower CD4+ cell counts, low CD4+ cell count is not a contraindication to vaccination. The schedules for each of the 3 approved products (Energix-B, Recombivax HB, and the combined HBV/HAV vaccine Twinrix) consist of 3 doses, with the second and third doses given at 1 and 6 months after the first (Table 1). Postvaccination testing should be performed at 1 to 6 months after the series is completed to assess whether the antibody to the HBV surface antigen (anti-HBs) has achieved the presumed protective titer of at least 10 IU/L.

An issue in determining eligibility for HBV vaccine arises in the frequently encountered situation in which serologic testing shows a patient is seropositive for anti-HBc but seronegative for anti-HBs and HBsAg. Such a finding has been thought to indicate a history of prior infection and presence of immunity, with waning of anti-HBs over time to undetectable levels. One recent study assessed whether patients with isolated anti-HBc on serologic testing exhibited an anamnestic response to HBV vaccine (Gandhi et al, *J Infect Dis*, 2005). Patients with some existing immunity to HBV typically exhibit a large increase in anti-HBs titer within

Table **1.** Recommended Dose, Route, and Schedule for Hepatitis A and B Vaccines in HIV-Infected Persons.

Vaccine	Dose and Route	No. Doses	Schedule
Hepatitis B Vaccines			
Engerix-B	20 µg (1 mL IM)	3	0, 1, 6 months
Recombivax HB	10 µg (1 mL IM)	3	0, 1, 6 months
Hepatitis A Vaccines			
Havrix	1440 EL U (1 mL IM)	2	0, 6-12 months
Vaqta	50 U (1 mL IM)	2	0, 6-12 months
Combined Hepatitis A and B Vaccine			
Twinrix	Havrix 720 EL U plus Engerix 20 µg (1 mL IM)	3	0, 1, 6 months

EL U indicates enzyme-linked immunosorbent assay units; IM, intramuscular.

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1 to 4 weeks of the first dose of vaccine (anamnestic response), whereas patients who are naive to HBV infection exhibit stepwise increases in antibody with each dose of vaccine (normal vaccine response). Among 69 HIV-infected, anti-HBs–seronegative and HBsAg-seronegative adults evaluated in the study, 29 (42%) were anti-HBc-seropositive. The finding of isolated anti-HBc was significantly associated with hepatitis C virus infection.

Anamnestic response, defined as an increase in anti-HBs titer to greater than 10 IU/L within 4 weeks of HBV vaccination, occurred in 10% of anti-HBc–seronegative patients and in 24% of anti-HBc–seropositive patients. Approximately half of the anti-HBc–seropositive patients also were seropositive for the antibody to hepatitis Be antigen (anti-HBe). Anamnestic response was observed in 43% of anti-HBe–seropositive patients, compared with only 7% of anti-HBe–seronegative patients (Figure 1). Overall, these findings suggest that most patients in the study who had a positive anti-HBe test and a positive anamnestic response probably had prior HBV infection, with anti-HBs titers that gradually diminished over time. On the contrary, most patients who had a negative anti-HBe test and a negative anamnestic response probably did not have prior HBV infection and their positive anti-HBc test may actually represent a false-positive result. It is also possible that some patients with isolated anti-HBc have ongoing occult HBV infection, although prior work would suggest this appears to occur very infrequently. Unfortunately, the optimal approach to patients with isolated anti-HBc remains unclear and further work is needed to determine whether some or all of patients with isolated anti-HBc should undergo HBV vaccination. Ideally, future studies would identify an appropriate subset of patients with isolated anti-HBc who would most likely benefit from the HBV vaccine series.

Another recent study has suggested that doubling the HBV vaccine dose may improve response in HIV-infected patients, at least in those with higher CD4+ cell counts (Fonseca et al, *Vaccine*, 2005). Among 210 HBV antibody-seronegative patients, administration of 3 doses (at 0, 1, and 6 months) of Energix-B vaccine resulted in seroconversion (anti-HBs titer >10 IU/L) in 34% of those receiving the standard 20-µg dose versus 47% of those receiving a 40-µg dose. This improvement was confined to patients with CD4+ cell counts greater than 350/µL; seroconversion occurred in 64% of such patients at the 40-µg dose and in 39% of such patients at the standard dose, compared with rates of 24% at the 40-µg dose and 26% at the standard dose among patients with CD4+ cell counts below 350/µL (Fonseca et al, *Vaccine*, 2005). At this time, however, there are no formal recommendations to use double-dose HBV vaccine in HIV-infected persons.

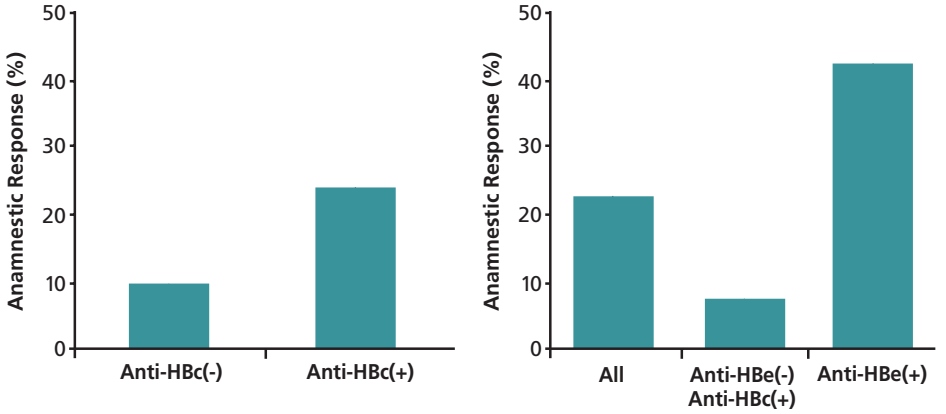

Figure **1.** Anamnestic response to hepatitis B virus vaccine in 69 HIV-infected patients testing seronegative for hepatitis B virus surface antibody (anti-HBs) and hepatitis B virus surface antigen. Left figure shows response according to whether patients were seronegative or seropositive for hepatitis B virus core antibody (anti-HBc). Right figure shows response among anti-HBc–seropositive patients according to hepatitis Be virus antibody (anti-HBe) status. Anamnestic response was defined as an anti-HBs titer above 10 IU/L within 4 weeks of vaccination. Adapted from Gandhi et al, *J Infect Dis*, 2005.

The current ACIP guidelines recommend giving HAV vaccination for those persons who have 1 or more of the following risk factors: travel to an HAV-endemic region, male-to-male sex, injection drug use, chronic liver disease, or a clotting factor disorder. The currently approved Havrix and Vaqta HAV vaccines are given in 2 doses, with the second given at 6 to 12 months after the first; the combined Twinrix vaccine (Havrix and Energix-B) is given in the 3-dose series as noted in Table 1. Protective antibody titers have been poorly characterized, but titers that have been used in studies to date differ between the products.

Rates of antibody response to HAV vaccine have varied. In a study in 133 HAV-seronegative patients, rates of seroconversion (HAV antibody >33 IU/L) following 2 doses of the Havrix vaccine were much lower in patients with CD4+ cell counts below 200/µL (approximately 10% at 9 months) than in patients with higher CD4+ cell counts (approximately 60% at 9 months in those with CD4+ cell counts greater than 200/µL; Kemper, *J Infect Dis*, 2003). This study, however, was conducted predominantly in an era prior to the widespread use of potent antiretroviral therapy. In a recent study comparing responses in 90 HIV-infected adults and 90 adults without HIV infection, seroconversion (antibody titer >10 IU/L) occurred by 28 weeks after Vaqta vaccination in 94% of the HIV-infected persons and in 100% of HIV-seronegative persons. Among the HIV-infected, stratification of responses based on CD4+ cell count showed 100% response rates in those patients with a CD4+ cell count of 300/µL or higher, compared with a

response rate of 87% among patients with a CD4+ cell count below 300/µL (Wallace, *Clin Infect Dis*, 2004). The response rates among HIV-infected persons in this study were far better than response rates in prior studies, presumably because more patients in the recent study had received potent antiretroviral therapy and had better immunologic function. In addition, it is unclear whether the use of different vaccine preparations in these studies, or the use of different antibody titer cut-offs to define a vaccine response, may have contributed to the differences in outcome in these studies. In patients who have a CD4+ cell count less than 200/µL and are eligible to receive either hepatitis B or hepatitis A vaccine, many experts would recommend deferring vaccination for at least 6 to 12 months if the patient is starting (or resuming) antiretroviral therapy and will likely have a significant improvement in CD4+ cell count.

Table **2.** Follow-Up Recommendations for Abnormal Cervical Cytology

Pap Test Result	Recommendation
ASCUS (with severe inflammation)	Evaluate for infection; if found, treat and recheck Pap test in 2 to 3 months
ASCUS	Follow-up Pap test every 4 to 6 months for 2 years (until 3 consecutive PAP tests are negative) If another ASCUS, consider colposcopy
ASCUS (neoplastic process suspected)	Follow-up Pap test every 4 to 6 months; OR colposcopy and biopsy if LSIL persists; OR immediate colposcopy
LSIL	Follow-up Pap test every 4 to 6 months; OR colposcopy and biopsy if LSIL persists; OR immediate colposcopy
HSIL (cervical intraepithelial neoplasia 2 or 3, carcinoma in situ) OR Squamous cell carcinoma	Colposcopy and biopsy of abnormal area

Data from *2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infection in Persons with Human Immonudeficiency Virus*. Pap indicates Papanicolaou test; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Screening for Cervical Abnormalities

The US Public Health Service (USPHS)/Infectious Diseases Society of America (IDSA) 2001 opportunistic infection prevention guidelines recommend that HIV-infected women undergo Papanicolaou (Pap) testing for cervical abnormalities twice in the first year after the diagnosis of HIV infection and once annually if Pap tests continue to be normal. In the case of abnormal findings, follow-up approaches differ according to the presence of atypical squamous cells of undetermined significance (ASCUS), the finding of a low-grade squamous intraepithelial lesion (LSIL), or the finding of high-grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma (Table 2). In addition, for patients with ASCUS, the approach varies based on the presence or absence of inflammation and whether a neoplastic process is suspected from the Pap test results. The Health Resources and Services Administration–HIV/AIDS Bureau publication, *A Guide to the Clinical Care of Women With HIV/AIDS*, provides similar screening recommendations as the USPHS/IDSA guidelines, but also recommends routine twice-yearly screening in women with symptomatic HIV infection and CD4+ cell counts less than 200/µL, owing to increased risk of invasive cervical cancer in such patients.

Very promising results have been obtained thus far in studies of human papilloma virus (HPV) vaccines in the prevention of HPV disease and cervical dysplasia and cancer. In a randomized, double-blind trial of a vaccine directed against HPV-16, the strain accounting for 50% to 60% of cases of cervical cancer, 2392 women aged 16 to 23 years received 3 doses of vaccine or placebo (at 0, 2, and 6 months) and were followed up for a median of 17.4 months (Koutsky et al, *N Engl J Med*, 2002). Rates of persistent HPV-16 infection were 0 and 3.8 cases per 100 person-years of observation ($P<.001$) in the vaccine group and the placebo group, respectively. Nine cases of cervical intraepithelial neoplasia occurred in the placebo group and none occurred in the vaccine group. In a randomized, double-blind trial of a vaccine directed against both HPV-16 and HPV-18, the latter being the second most common HPV strain in cervical cancer, 1113 women aged 15 to 25 years received 3 doses of vaccine or placebo (each at 0, 1, and 6 months) and were followed up for up to 27 months (Harper et al, *Lancet*, 2004). Persistent HPV-16 and HPV-18 infections occurred in 0% of patients in the vaccine group and in 2.6% of placebo patients on per-protocol analysis ($P<.001$) and in 0.5% versus 4% on intent-to-treat analysis ($P<.001$).

Renal Disease

Recommendations on screening for renal disease have recently been published by the HIV Medicine Association (HIVMA) of the IDSA (Figure 2; Gupta et al, *Clin Infect Dis*, 2005). Initial evaluation should include urinalysis for proteinuria and a calculation of serum creatinine to estimate creatinine clearance or glomerular filtration rate (GFR). Findings of dipstick proteinuria of grade 1 or higher or creatinine clearance or GFR less than 60

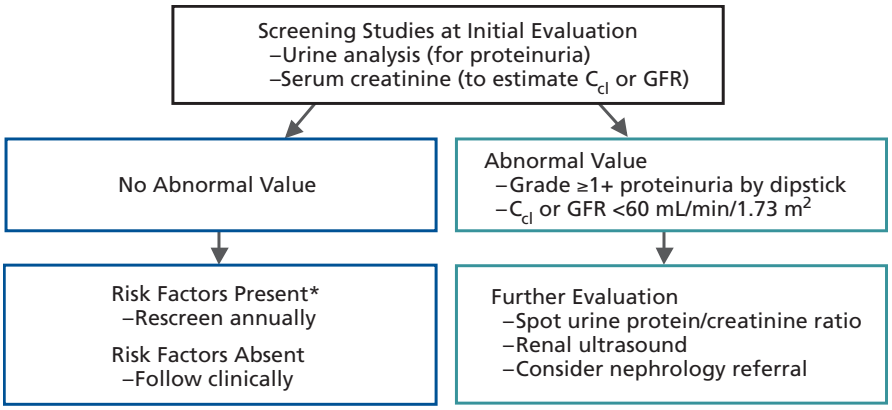

Figure **2.** HIV Medicine Association of the Infectious Diseases Society of America recommendations for screening for renal disease. C_{cl} indicates creatinine clearance; GFR, glomerular filtration rate. *Risk factors for developing proteinuric renal disease: African-American race, CD4+ cell count below 200/µL, plasma HIV RNA level greater than 4000 copies/mL, diabetes, hypertension, or chronic hepatitis C virus infection. Adapted from Gupta et al, *Clin Infect Dis*, 2005.

mL/min/1.73 m^2 should prompt further evaluation, including determination of spot urine protein/creatinine ratio, renal ultrasound, nephrology referral, and possibly renal biopsy. Screening should be repeated annually in patients with no abnormalities but with such risk factors as African-American race, CD4+ cell count below 200/µL, plasma HIV RNA level greater than 4000 copies/mL, diabetes, hypertension, or hepatitis C virus infection. Those with no risk factors should be followed up clinically. Recommendations for management of nephropathy are summarized in Table 3. These include control of blood pressure (preferably with angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors), institution of antiretroviral therapy to treat HIV-associated nephropathy at the time of diagnosis, and use of corticosteroids in nephropathy refractory to antiretroviral therapy.

Table **3.** Key Recommendations From the HIV Medicine Association of the Infectious Diseases Society of America Guidelines for Management of Nephropathy in HIV Infection

- Control blood pressure to at or below 125/75 mm Hg
  - Preferential use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers if proteinuria
  - Avoid calcium channel blockers if patient taking protease inhibitor(s)
- Treat HIV-associated nephropathy with antiretroviral therapy at diagnosis
- Use additional therapies for HIV-associated nephropathy refractory to antiretroviral therapy
  - ACE inhibitors, angiotensin II receptor blockers, corticosteroids
- Perform dialysis if indicated
- Consider renal transplant for end-stage renal disease

Data from Gupta et al, *Clin Infect Dis*, 2005.

Conclusion

The primary care of HIV-infected individuals includes a wide range of prevention and treatment services. All HIV-infected patients who do not have immunity to HBV should receive the complete hepatitis B vaccine series. Further work is needed to define the optimal approach to patients with isolated anti-HBc. Patients with selected risk factors should receive hepatitis A vaccine; the response rates to this vaccine are good, particularly in patients who have a CD4+ cell count greater than 300/µL. Screening HIV-infected women for cervical abnormalities should consist of Pap tests twice in the first year after diagnosis, followed by once-yearly tests as long as the test remains normal. Abnormal Pap tests demand further evaluation, but the evaluation varies based on the specific abnormality. All HIV-infected patients should be screened for renal abnormalities with urinalysis to detect proteinuria and a calculation of serum creatinine to estimate creatinine clearance or glomerular filtration rate.

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Suggested Reading

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