

## 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](http://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.

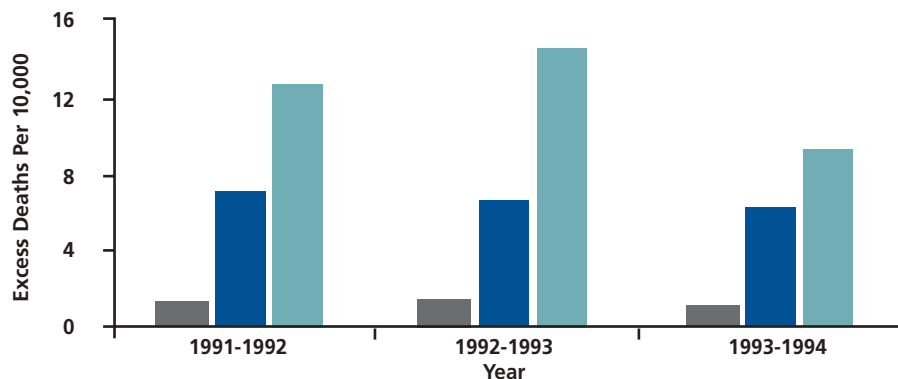


Figure 1. Excess death rate due to influenza or pneumonia during influenza season compared with preinfluenza baseline periods in all adults in the general population aged 13 years or older (gray), adults in the general population aged 65 years or older (dark blue), and in those with HIV-infection aged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

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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/ $\mu$ 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/ $\mu$ 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

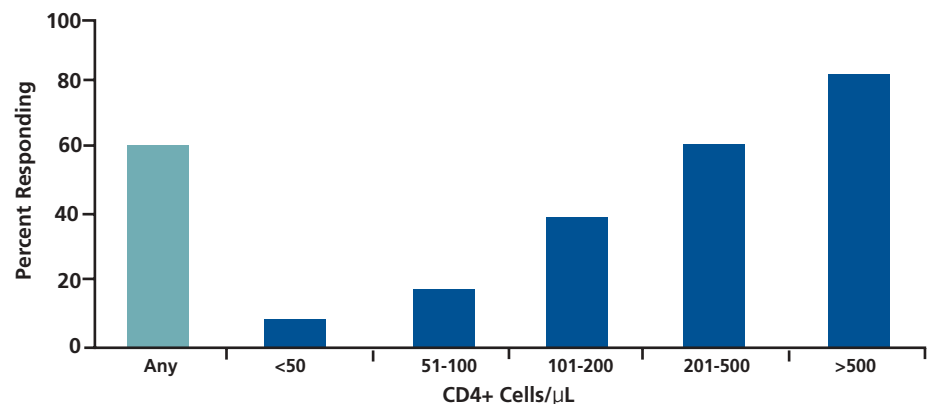


Figure 2. Relationship between CD4+ cells/µL at vaccination and response to hepatitis A vaccine (HAV; anti-HAV IgG titer >20 mIU/mL) in 214 HIV-infected adults. Adapted with permission from Rimland et al, *AIDS*, 2005.

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

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

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.*

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### 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.”<sup>1,2</sup>

A corrected version of the full article is available at [www.iasusa.org](http://www.iasusa.org).

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