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Vaccination in HIV-Infected Adults

Nancy F. Crum-Cianflone, MD, MPH,[1,2] and Mark R. Wallace, MD[3]

Abstract

Vaccines are critical components for protecting HIV-infected adults from an increasing number of preventable diseases. However, missed opportunities for vaccination among HIV-infected persons persist, likely due to concerns regarding the safety and efficacy of vaccines, as well as the changing nature of vaccine guidelines. In addition, the optimal timing of vaccination among HIV-infected adults in regards to HIV stage and receipt of antiretroviral therapy remain important questions. This article provides a review of the current recommendations regarding vaccines among HIV-infected adults and a comprehensive summary of the evidence-based literature of the benefits and risks of vaccines among this vulnerable population.

Importance of Vaccinations for HIV Patients

Vaccinations are particularly important for HIV-infected adults. Due to impaired host defenses, HIV-infected persons have both an increased risk and severity of vaccine-preventable infections. For example, HIV-infected persons have a markedly higher risk of invasive pneumococcal disease despite the advent of combination antiretroviral therapy (CART).[1] Similarly, infection with the hepatitis B virus (HBV) is more likely to progress to cirrhosis and hepatocellular cancer among HIV-infected persons compared with HIV-uninfected persons.[2] In addition to immunologic reasons, HIV-infected persons are at higher risk due to frequent contact with the medical environment and shared routes of transmission with infectious pathogens such as HBV and human papillomavirus (HPV).

Challenges in Achieving Vaccine Coverage

Despite their increased risk for infections and the widespread availability of vaccines, coverage rates among HIV patients are reportedly low.[3–5] A large cohort study of HIV patients found only one-third had received at least one dose of the HBV vaccine, with an even lower percentage for the hepatitis A virus (HAV) vaccine.[3] Another study regarding influenza vaccinations among HIV-infected persons in the US found that only 42% were vaccinated.[5] The low vaccine coverage rates among HIV patients are likely multifactorial including the lack of knowledge regarding currently recommended vaccinations. In addition, HIV specialists may lack the infrastructure within their clinics to provide the necessary vaccines, or be prevented by insurers from giving vaccines reserved for the patient's primary care provider. Recent guidelines[6] highlight the importance of both specialists and primary care providers working together to ensure the timely administration of recommended vaccinations to HIV-infected persons.

Concerns regarding vaccine safety may also encumber vaccination. However, evidence suggests that inactivated vaccines have similar safety profiles among HIV-infected and HIV-uninfected persons. Although studies have not been powered to detect rare adverse events among HIV patients, no post-marketing trends have suggested any special concerns for these vaccines among HIV-infected persons. In addition, modern post CART era studies have not shown vaccines to be important triggers of HIV spikes or progression, thus vaccines should not be withheld for these reasons.[6–8] HIV patients who are not receiving CART may experience transient increases in HIV RNA levels and modest reductions in CD4 counts, but these usually normalize 2–6 weeks post-vaccination and are not typically seen among those receiving effective CART. A large study of over 30,000 HIV patients evaluating influenza immunizations found no long-term negative effects on CD4 counts, HIV RNA levels, or progression to AIDS or death.[9] Overall, there are no substantive data to support the notion that vaccines adversely affect the overall health of HIV patients or accelerate disease progression; hence, the benefits of vaccinations continue to outweigh existing theoretical risks.[6–8]

Another potential concern is the efficacy of vaccinations among HIV patients. Early after HIV infection, immune responses are typically similar to those of HIV-negative

[1]Infectious Disease Clinic, Naval Medical Center San Diego, San Diego, California.
[2]Department of Infectious Disease, Scripps Mercy Hospital, San Diego, California.
[3]Orlando Regional Medical Center, Orlando, Florida.

persons.[10] As HIV infection advances, the same immune deficits that place HIV-infected adults at an increased risk for infections may impair vaccine responses. These deficits include both cell-mediated and B-cell immune abnormalities, which may reduce the magnitude, breath, and durability of vaccinations. Despite these concerns, studies have clearly demonstrated the protective benefit of vaccinations including influenza[11,12] and *Streptococcus pneumoniae*[13,14] even among more advanced patients. Although efficacy data are sparse for other types of vaccines, studies using surrogate endpoints (most commonly post-vaccination antibody levels) have shown that most HIV patients generate antibody responses post-vaccination. Some questions remain, including whether the protective effect of a specific antibody level is the same as for immunocompetent hosts, or whether underlying immune deficiencies alter the protection offered. It is known that if an HIV patient fails to produce a pre-specified antibody level (e.g., anti-HBs <10 mIU/mL), they likely remain at least partially susceptible to infection. Overall, vaccines should be administered to HIV patients, ideally early in the course of infection, and educational counselling should be provided in addition to vaccination for optimizing the prevention of vaccine-preventable infections (e.g., safe sex for reducing HBV infections, and hand hygiene for influenza).

Recommended Vaccines for HIV-Infected Adults

Vaccine recommendations have recently been published for all US adults[8] and for immunocompromised patients, including those with HIV.[6,7,15] Guidelines categorize HIV-infected persons into those with high versus low-level immunosuppression defined as a current CD4 count of <200 or ≥ 200 cells/mm^3, respectively.[6] Recommendations for the HIV patient are summarized in Table 1.

Vaccines should be administered at or shortly after the time of HIV infection since they are most effective before the onset of significant immunosuppression (i.e., shortly after HIV diagnosis among early-diagnosed patients), and ideally given before potential exposures. Vaccines recommended include influenza, pneumococcal, HBV, and tetanus-diphtheria-pertussis (Tdap). HAV, meningococcal, and HPV vaccines are advocated among HIV patients who have additional risk factors or within specific age groups. Live viral vaccines, including measles-mumps-rubella (MMR), varicella, and zoster, can be considered for at-risk HIV patients who are clinically stable and have low level immunosuppression (CD4 ≥ 200 cells/mm^3). The measles-mumps-rubella-varicella (MMRV) vaccine should not be administered since it has not been evaluated in HIV patients and contains seven times more varicella antigens than the monovalent vaccine, hence may pose a safety concern. Current guidelines no longer recommend *Haemophilus influenzae* b vaccine (Hib) for adults with HIV infection. Although HIV-infected persons with advanced disease have a higher risk of infection,[16,17] the overall incidence is low, and most *H. influenzae* cases are due to nontypable strains for which the vaccine is not protective.

Inactivated (Non-Live) Vaccines

Influenza

HIV-infected adults have an elevated risk of morbidity and mortality from influenza infection[18–22] and should be advised to receive annual vaccination with the inactivated influenza vaccine (IIV). The live attenuated influenza vaccine (LAIV) is avoided among HIV patients, largely due to the lack of data among this group and the theoretical risk of prolonged shedding in the setting of underlying immunosuppression. A study of 57 HIV-infected adults vaccinated with LAIV found no adverse safety concerns and did not demonstrate prolonged viral shedding;[23] similar findings were seen in studies of HIV-infected children.[24,25] However, since data on LAIV have been limited, guidelines continue to recommend against its use. HIV patients with mild egg allergies (only hives without other allergic symptoms) may receive IIV per the guidelines, and a vaccine is now available for those with more severe forms of egg allergy (RIV3, Flublok).[26]

The efficacy of the influenza vaccine is dependent on the season (i.e., the match between vaccine and circulating strains) and the immunocompetence of the host, with an overall estimated effectiveness of 27–78% among HIV-infected persons.[27] One prospective study on vaccine efficacy randomized 102 HIV-infected adults to influenza vaccine ($n=55$) or saline placebo ($n=47$), and found a protective efficacy of 100% [95% confidence interval (CI), 73–100%].[11] A second prospective study of 262 HIV-infected adults examined receipt of trivalent influenza vaccine versus no vaccine ($n=66$), and found that vaccination reduced influenza infection by 71% (95% CI, 45–86%).[12] A recent meta-analysis incorporating findings from several studies confirmed that vaccination among HIV patients reduces both influenza-like illness and lab-confirmed influenza.[28]

Although HIV patients clearly benefit from influenza vaccination, antibody responses after seasonal influenza vaccination are typically poorer than among HIV-uninfected persons.[28] Regarding immune responses to the 2009 H1N1 influenza strain, a study found that HIV-infected compared with HIV-uninfected persons were significantly less likely to develop a protective antibody response (56% vs. 80%, odds ratio, 0.20, $p=0.003$) despite studying a well-controlled HIV cohort (median CD4 count of 581 cells/mm^3 with 82% receiving CART).[29] Other studies have also noted suboptimal responses after H1N1 vaccination among HIV patients.[30,31]

Given these data, improving the immune responses to influenza vaccination among immunocompromised persons is of great clinical interest. A second dose of influenza vaccine (administered one month after initial vaccination) was investigated in studies during the pre-CART era, but failed to enhance antibody responses.[32,33] More recently, a study found that a second dose of the H1N1 influenza vaccine significantly increased seroprotective responses (from 68% to 92% after the second dose); however, the study utilized an adjuvant plus vaccine.[34] Another potential strategy is to use vaccines with higher doses of antigen. The high-dose Fluzone vaccine (which contains 60 mcg of antigen per strain vs. 15 mcg) was evaluated among 190 HIV-infected adults; seroprotection rates were greater in the high-dose group for the H1N1 (96% vs. 87%, $p=0.03$), H3N2 (96% vs. 92%, $p=0.30$), and influenza B (91% vs. 80%, $p=0.03$) strains.[35] This study did not evaluate the effectiveness of the vaccine in preventing clinical influenza, and there were only a small number of participants with CD4 counts <200 cells/mm^3. Overall, the use of high-dose influenza vaccines in HIV patients appears to be a promising strategy, but further data are needed to inform vaccine recommendations.

Another question regarding influenza vaccination is the durability of immune responses. Guidelines recommend that influenza vaccines be administered as soon as they become available. Some providers have pondered if HIV patients should be preferentially vaccinated later in season due to concerns regarding waning antibody responses. Delaying vaccination is not currently recommended since influenza can occur early in the season, and a delay may lead to missed opportunities for vaccination. Among normal hosts, vaccine durability is expected to last the entire season (October–April in the Northern hemisphere), although few data exist in HIV-infected persons. A study of 2009 H1N1 vaccine responses found that only 28% of HIV patients had a seroprotective antibody level at 6 months post-vaccination, significantly less than among HIV-uninfected persons (adjusted odds ratio 0.19, $p = 0.005$).[36] These data demonstrate the need for more immunogenic influenza vaccines among HIV-infected persons providing both improved initial and durable antibody responses.

Pneumococcal

In addition to administration of the influenza vaccine, which prevents both viral and bacterial pneumonia,[37] vaccination against *Streptococcus pneumoniae* is recommended. HIV-infected persons have a high burden of invasive pneumococcal disease despite the use of CART.[1] There are currently two types of pneumococcal vaccination—the polysaccharide pneumococcal vaccine containing 23 serotypes (PPV23) available since 1983, and the conjugate pneumococcal vaccine (PCV) containing 13 serotypes available since 2010. Most studies in the US have shown that PPV23 reduces pneumococcal bacteremia and mortality among HIV-infected adults.[13,14] A single study in Uganda found a higher rate of pneumonia,[38] but lower rates of all-cause mortality post-vaccination.[39]

Current recommendations advise administration of the pneumococcal conjugate vaccine (i.e., Prevnar-13) at the time of HIV diagnosis, followed by PPV23 given ≥ 8 weeks later. PCV is an excellent priming vaccine, ideally administered as the first pneumococcal vaccine among immunosuppressed persons.[40–42] Revaccination with PPV23 is administered at 5 years after the initial PPV23, and then again at age ≥ 65 years (5 or more years should separate each PPV23 dose). If an HIV patient has already received PPV23, a single dose of PCV should be administered assuring that ≥ 1 year has elapsed since the last PPV23 vaccination, with repeat PPV23 5 years later.[6–8] The added value of giving PCV after an initial PPV23 has not been found in all studies,[43] but the data are sufficiently strong that current guidelines endorse the practice.

PCV vaccination should not be delayed due a low CD4 counts. A randomized, double-blind, placebo-controlled trial of PCV (using the 7-valent vaccine) among HIV-infected adults in Malawi demonstrated a 74% efficacy against vaccine-type invasive pneumococcal disease, with clear evidence of efficacy even among those with CD4 counts < 200 cells/mm^3.[44] Hence, HIV patients should be vaccinated with PCV regardless of the CD4 count. Immune responses to polysaccharide vaccination (i.e., PPV23) are greatest when the CD4 count is ≥ 200 cells/mm^3. Current recommendations state that patients with CD4 counts ≥ 200 cells/mm^3 should receive a dose of 23-valent PPV (PPV23) ≥ 8 weeks after the PCV. HIV-infected patients with CD4 counts < 200 cells/mm^3 may defer vaccination until the CD4 count is ≥ 200 cells/mm^3 if CART will be initiated in the near future.[7]

Hepatitis B virus

HBV vaccine has been available since 1982, and is recommended among HIV-infected persons, given the viruses' similar routes of transmission. Additionally, HIV patients have a higher risk of chronic infection after exposure, and experience faster progression to cirrhosis and HBV-related complications.[2,45] Further, chronic HBV is associated with poorer HIV outcomes, with a nearly twofold higher risk of AIDS/death.[46] Hence, all HIV-infected persons without evidence of HBV immunity should be vaccinated.

Prevaccination serologic testing should be obtained including hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and antibody to hepatitis B surface antigen (anti-HBs).[7] The specific tests vary by guidelines,[6,7] but obtaining all three tests provides the most complete picture of HBV status. The presence of anti-HBs alone at levels of ≥ 10 mIU/mL is consistent with seroprotection from prior vaccination, and no further vaccines are required.[7] For those without protective levels of anti-HBs, vaccination against HBV with either Recombivax (Merck) at one dose of 40 mcg/mL on a three-dose schedule of 0, 1, and 6 months *or* Engerix (GlaxoSmithKline) using two doses simultaneously of 20 mcg/mL on a four-dose schedule of 0, 1, 2, and 6 months. Guidelines have increasingly recommended the use of the higher dose of HBV vaccine (40 mcg/mL) among immunosuppressed patients, including those with HIV.[8,15] Twinrix (which contains both HAV and HBV vaccines) can be utilized, but this vaccine only contains 20 mcg/mL of the HBV vaccine.

In general, accelerated vaccine schedules are not currently recommended among HIV patients as data are limited and the durability of vaccine responses may be compromised.[47] A unique challenge of HBV immunization is the requirement for three shots over a 6-month period. If the series is interrupted, it can simply be resumed where it left off. The institution of specific vaccine clinics and electronic (including text) reminders may be useful for ensuring series completion.[48]

Protective HBV vaccine responses among HIV-infected compared with HIV-uninfected persons are dissimilar, with rates of 18–68% and 60–95%, respectively.[49–52] Patients vaccinated prior to HIV infection have seroprotective responses similar to uninfected persons,[53] suggesting that the completion of the vaccine series prior to HIV infection is optimal. Given the lower seroconversion rates among HIV patients, higher doses of the vaccine (40 vs. 20 mcg/mL) have been advocated. For example, a study among 210 HIV-infected persons, randomized to a standard dose (20 mcg/mL) or double dose (40 mcg/mL) of recombinant hepatitis B vaccine found a seroconversion rates of 34% vs. 47%, respectively ($p = 0.07$).[54] Interestingly, higher seroconversion rates in the higher dose group were found among patients with CD4 counts ≥ 350 cells/mm^3, but not among those with CD4 counts < 350 cells/mm^3. In another study, the percentage of responders was 82% in the group receiving 40 mcg/mL (using a four-vaccine series) and 65% in the 20 mcg/mL group (using a three-vaccine series), although the number of

TABLE 1. VACCINE RECOMMENDATIONS FOR HIV-INFECTED ADULTS[a]

Vaccine	*Recommendations*	*Comments*
Inactivated (not live) vaccines		
Influenza, inactivated (IIV)	Yes, all HIV-infected adults	■ Administer a single dose (0.5 mL IM) of inactivated influenza vaccine annually ■ Live attenuated influenza vaccine (LAIV) is contraindicated in HIV-infected patients
Pneumococcal PCV-13 PPV23	Yes, all HIV-infected adults who have not received vaccination	■ One dose of PCV13 (Prevnar-13®, 0.5 mL IM), followed by: -For patients with CD4 count ≥200 cells/mm^3: PPV23 (0.5 mL IM) given at least 8 weeks after receiving PCV13 -For patients with CD4 count <200 cells/mm^3: PPV23 can be offered at least 8 weeks after receiving PCV13 *or* can await increase of CD4 count to >200 cells/mm^3 on CART ■ For individuals who have previously received PPV23: -One dose of PCV13 (Prevnar-13®) should be given at least 1 year after the last receipt of PPV23 ■ Re-vaccination with PPV23: -A single dose of PPV23 is recommended for individuals 19–64 years old if ≥5 years have e1apsed since the first dose of PPV23 -Another dose should be given for individuals 65 years or older, if at least 5 years have elapsed since previous PPV23 dose
Hepatitis B virus (HBV)	Patients without immunity to HBV (i.e., anti-HBs <10 mIU/mL) For patients with isolated anti-HBc, check HBV DNA, and if negative, administer vaccine series	■ Administer hepatitis B vaccine IM with Recombivax® at one dose of 40 mcg/mL on a three-dose schedule of 0, 1, and 6 months *or* Engerix® using two doses simultaneously of 20 mcg/mL on a four-dose schedule of 0, 1, 2, and 6 months ■ Combined hepatitis A and hepatitis B vaccine (Twinrix®) can be used for those susceptible to both viral infections. Utilized as 1 mL IM as a three-dose (0, 1, and 6 months) *or* four-dose series (days 0, 7, 21 to 30, and 12 months). Of note, the Twinrix® vaccine only contains 20 mcg/mL of the HBV vaccine ■ Anti-HBs should be obtained 1 month after completion of the vaccine series; an anti-HBs <10 mIU/mL is considered as a nonresponse ■ For vaccine non-responders: -Revaccinate with a second vaccine series -For patients with low CD4 count at the time of first vaccination series, consider delaying revaccination until after a sustained increase in CD4 count with CART -Recommend revaccinating using 40 mcg/mL doses of the vaccine
Hepatitis A virus (HAV)	HAV-susceptible patients with risk factors such as chronic liver disease, illicit drug users, or MSM. In addition, vaccinate prior to travel to an endemic area May consider vaccinating all HIV-infected persons	■ Administer a two-dose series of Havrix® (0, 6–12 months) or Vaqta® (0, 6–18 months) using 1.0 mL IM ■ For patients susceptible to both HAV and HBV infections, may use the combined HAV and HBV vaccine (Twinrix®) as described above
Tetanus toxoid, diphtheria, pertussis (Td/Tdap)	Yes, if 10 years have elapsed since last booster, or if the patient meets guidelines for pertussis vaccination such as pregnancy, close contact with infants, and working as a healthcare provider (Tdap)	■ Administer 0.5 mL IM every 10 years; substitute Tdap on single occurrence if not previously vaccinated with Tdap

(*continued*)

TABLE 1. (CONTINUED)

Vaccine	*Recommendations*	*Comments*
Human papillomavirus (HPV)	Yes (11–26 years)	*For females:* ■ HPV recombinant vaccine quadrivalent Gardasil® (Types 6, 11, 16, 18) at 0.5 mL IM at 0, 1–2, and 6 months, *or* ■ HPV recombinant vaccine bivalent Cervarix® (Types 16, 18) at 0.5 mL IM at 0, 1–2, and 6 months ■ Avoid during pregnancy *For males:* ■ HPV recombinant vaccine quadrivalent Gardasil® (Types 6, 11, 16, 18) at 0.5 mL IM at 0, 1–2, and 6 months
Meningococcal	Yes, with risk factors per the guidelines	■ Administer two doses (0.5 mL IM) of the meningococcal conjugate vaccine (MCV4), with the second dose given ≥8 weeks after the first dose. Conjugate vaccine preferred over the polysaccharide vaccine
Live vaccines		
Varicella	Consider among non-immune patients (VZV IgG seronegative) who have a CD4 count ≥200 cells/mm^3	■ Pre-vaccination testing advised to verify non-immune status ■ Primary varicella vaccination (Varivax®), two doses (0.5 mL SQ) administered 3 months apart
Zoster	Consider among those ≥60 years of age with known varicella immunity, and who are clinically stable with a CD4 count ≥200 cells/mm^3	■ Vaccine (Zostavax®) can be considered, but few data among HIV-infected persons ■ Administer a single dose of 0.65 mL SQ ■ A single study in HIV adults utilized two doses separated by 6 weeks,[94] but more data are needed regarding the preferred dosing schedule
MMR	Non-immune patients who have a CD4 count ≥200 cells/mm^3	■ Pre-vaccination testing advised to verify non-immune status ■ Administer single dose of 0.5 mL SQ

[a]Adapted from published guidelines.[6–8,15]

Anti-HBs, antibody to hepatitis B surface antigen; CART, combination antiretroviral therapy; HAV, hepatitis A virus; HBV, hepatitis B virus; HIV; human immunodeficiency virus; HPV, human papillomavirus; IIV, inactivated influenza vaccine; IM, intramuscular; LAIV, live attenuated influenza vaccine; MCV, meningococcal conjugate vaccine; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; SQ, subcutaneous; Td, tetanus toxoid and reduced diphtheria toxoid; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; VZV, varicella zoster virus.

vaccines varied by group.[55] Finally, a recent meta-analysis that included five clinical studies ($n = 883$ HIV patients, most of whom were vaccine naïve) found a significant increase in response rates using the higher dose vaccine (OR 1.96, 95% CI, 1.47–2.61).[56]

Hepatitis B vaccination should occur shortly after HIV diagnosis and should not be delayed since the development of protective levels of anti-HBs can occur at all CD4 counts and viral loads.[4] Since it is known that vaccine responses are lower in HIV-infected versus HIV-uninfected adults,[50–52] post-vaccination testing is critically important. Post-vaccination testing (i.e., anti-HBs level) should be obtained 1–2 months after the last vaccine in the series. If the anti-HB antibody is < 10 mIU/mL, then a second three-shot series (preferably using the higher dose at 40 mcg/mL) is administered. Responses rates to the second vaccine series vary, but have been reported as 51–77%.[57,58] Since vaccine response rates are correlated with the immunocompetence of the host, some experts suggest delaying the second vaccine series among initial non-responders until receipt of CART and a higher CD4 count. Response rates to vaccination have been estimated as 30–50% and 60–70% among not receiving and receiving CART, respectively.[59] The importance of CART for HBV vaccine responses was illustrated in a study that compared those on HAART with CD4 counts ≥ 350 cells/mm^3 with patients not on HAART with CD4 counts ≥ 350 cells/mm^3, and found that the latter had a significantly reduced odds of developing a vaccine response (OR 0.47).[59] Among those who receive a second vaccine series, a post-vaccination level should again be measured 1–2 months after the series; among those who still do not have an anti-HBs ≥ 10 mIU/mL, the benefit of additional doses is unclear and generally not recommended. Such patients should be advised that they may remain at risk for HBV infection and counselled on appropriate precautions. Other strategies to improve vaccine responses, including additional doses of vaccine and adjuvants, have been proposed although are not currently recommended due to insufficient data.[7]

Some patients have an isolated anti-HBc on prevaccination testing (HBsAg negative and anti-HBs negative). This pattern represents one of three distinct possibilities: (1) a false positive core test; (2) a resolved infection with waning of the titers for anti-HBs over time; and (3) chronic HBV infection with a nondetectable HBsAg. The latter group may have chronic inactive infection (HBV DNA is undetectable) or 'occult' infection (HBV DNA is detectable). Among those with an isolated anti-HBc, testing for HBV DNA is recommended and if negative, the HBV vaccine series should be administered.[15] Studies have shown that most HIV patients with an isolated anti-HBc have low anamnestic responses, suggesting that vaccination is appropriate. For example, a study of 69 HIV patients found that the overall anamnestic rate was only 16%.[60] If the antibody to hepatitis B e antigen (anti-HBe) was also positive, patients were more likely to have an anamnestic response (43%), however, the majority still required vaccination.[60] In summary, most HIV patients with an isolated anti-HBc are HBV DNA negative and not immune to HBV infection.[60,61] and should be vaccinated with the complete vaccine series.[7] Some have suggested that if an anamnestic response is uncertain, one dose of vaccine could be administered and the HBsAb response checked in 2–4 weeks,[50] however, a full vaccine series is currently recommended by the guidelines. Further studies regarding the use of three doses vs. one dose in anti-HBc positive and anti-HBs negative patients are needed.

Finally, the durability of the immune responses after HBV vaccination and the significance of seroreversion remain important questions. In the general population, a study among children found that 20 years after vaccination, 64% had anti-HBs ≥ 10 mIU/mL and among those will low antibody levels, anamnestic responses to vaccination were observed in 97%.[62] While this study confirmed the long-term immunogenicity of the HBV vaccine among immunocomptent hosts, few data exist among HIV-infected persons. One study among HIV-infected adults showed that only 10/17 (59%) maintained an antibody level ≥ 10 mIU/mL after 1 year of follow-up; however, data on anamnestic responses were not provided.[57] In a study of patients receiving CART, only 18/270 seroreverted during the 5-year follow-up period, suggesting that antiretroviral therapy may be important strategy for maintaining durable vaccine responses, but further studies are needed.[63]

Hepatitis A virus

Many HIV-infected adults are at particular risk for HAV infections.[64,65] The hepatitis A vaccine became available in 1996, and guidelines recommend for its use among HIV patients with specific risk factors including a history of drug (both injection and non-injection) use, men who have sex with men (MSM), and liver disease including chronic HBV or hepatitis C virus infection.[8] In addition, those traveling to countries endemic for the disease should be vaccinated. Recent HIV guidelines have also recommended that vaccination be considered for all nonimmune HIV patients regardless of risk factors.[15]

Prevaccination screening is cost effective when the prevalence of anti-HAV is > 30% (e.g., in the general population among persons > 40 years of age). Antibody testing, and subsequent vaccination among non-immune patients, should be performed at the time of HIV diagnosis. The vaccine is given as a two-dose series of Havrix (0, 6–12 months) or Vaqta (0, 6–18 months). Trinrix, which contains both HAV and HBV, can be utilized with doses at 0, 1, and 6 months *or* 0, 7, 21–30 days, and 12 months.

Most HIV-infected adults develop antibody responses to HAV vaccination with seroconversion rates of 68–96%,[66,67] with seroresponses varying by CD4 counts. For example, in a study of early-diagnosed HIV patients, those with a CD4 cell count ≥ 300 cells/mm^3 had a seroconversion rate of 100% versus 87% among those with a CD4 count of < 300 cells/mm^3.[66] One study examined three versus two shots with seroconversion rates (defined as an anti-HAV antibody ≥ 20 mIU/mL) of 83% and 69%, respectively ($p = 0.13$);[68] however, guidelines continue to recommend the two-shot vaccine series. After completion of the vaccine series, the antibody response (total or IgG anti-HAV) should be assessed 1 month later, and if negative, patients should be revaccinated, preferably after the CD4 count is ≥ 200 cells/mm^3.[7]

Regarding the durability of HAV vaccine responses, one study showed that 85% of HIV-infected adults maintained a seropositive response 6–10 years after a two-dose vaccine series.[69] To date, there are no specific guidelines regarding monitoring anti-HAV over time or for revaccination with the HAV vaccine among HIV-infected adults.

Tetanus, diphtheria, and pertussis

Vaccination recommendations for tetanus, diphtheria, and pertussis mirror those for the general population. HIV-infected persons should receive booster doses of tetanus-diphtheria (Td) every 10 years. A single dose of Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Boostrix or Adacel) should replace the next dose of Td if the patient has not previously been vaccinated.

Compared with HIV-uninfected adults, studies have shown similar response rates to tetanus vaccination, but lower responses to diphtheria among HIV-infected persons (protective antibodies 83–100% and 61–73%, respectively), which vary by CD4 counts.[70] No current data specifically exist regarding the Tdap vaccine among HIV-infected adults, but responses are likely similar for the tetanus and diphtheria components. Data regarding immune responses after pertussis vaccination among HIV-infected adults are needed.

A study among HIV-infected children found that response rates after tetanus vaccination waned quickly,[71] bringing into question whether the current guidelines recommending Td boosters every 10 years among HIV patients are adequate. Until further data are available, assuring that Td immunizations are administered at least every 10 years is advised.

Human papillomavirus (HPV)

HIV patients have an elevated risk of HPV infections, and the subsequent development of HPV-related cancers (e.g., cervical, anal).[72,73] HPV vaccines were introduced in 2009 and are currently recommended for HIV-infected persons aged 9–26 years. There are two available vaccines: Gardasil which contains four serotypes (HPV 6, 11, 16, and 18) and Cervarix with two HPV serotypes (HPV 16 and 18). The former vaccine is preferred since it is FDA-approved among both men and women, and provides protection against genital warts. Three doses of the HPV vaccine are administered at 0, 1–2, and 6 months, and the series can simply be continued if an interruption occur.[8] The vaccine is not live so it can be administered to patients with any CD4 count, but is generally avoided during pregnancy, largely due to the lack of safety data.

The optimal timing of HPV vaccination is prior to sexual debut. Among HIV-infected persons with prior high-risk sexual exposures, its effectiveness may be reduced. There are few data among HIV-infected individuals aged 13–26 years regarding prior exposures to the HPV vaccine types to determine the proportion that may benefit from vaccination. A recent cross-sectional study in HIV-infected men and women (median age of 47 years) found that 73% were infected with at least one HPV vaccine type: HPV 16: 64%; HPV 6: 39%; HPV 18: 31%; and HPV 11: 8%.[74] Since rates of concurrent HPV infections vary by age, gender, sexual history, and geographic region, more data especially among HIV-infected adolescents and young adults are needed.

Current guidelines do not recommend for testing for HPV DNA or serologic screening before vaccination. Further, a history of genital warts, abnormal cytology, or positive HPV DNA test result is not a contraindication for vaccination since prior abnormalities may be due to other HPV types not contained in the vaccine.[8] Finally, routine screening for HPV-related diseases should continue despite vaccination since the vaccine does not cover all HPV types that cause cervical and anal cancers.

In the general population, HPV vaccination has a $>95\%$ efficacy in preventing cervical abnormalities and genital warts, but data are currently lacking among HIV-infected persons. Immunogenicity and safety studies among HIV-infected persons are becoming available in select populations. A study of HIV-positive adolescents found seroconversion occurred in $>96\%$ of vaccine recipients, with geometric mean titers of 27–262 times greater than the seropositivity cutoff value, but still lower than among age-similar historical controls.[75] In a study of adult HIV-infected men, seroconversion rates of $>95\%$ were found for each of the four HPV types,[76] while a recent study in young women showed seroconversion rates of 92–100%, depending on the receipt of CART.[77] Persons with HIV RNA levels $>10{,}000$ copies/mL and/or CD4 counts <200 cells/mm^3 had poorer seroconversion rates.[78]

Meningococcal

Available meningococcal vaccines include polysaccharide (Menomune) and conjugate (Menactra and Menveo) types for the protection against serogroups A, C, Y, and W-135. Approved vaccines in the US do not currently include serotype B. HIV-infected persons with one or more of the following risk factors are recommended to receive meningococcal vaccination: (1) first-year college students up through 21 years who are living in residence halls and have not received a dose on or after their 16th birthday; (2) those with asplenia or persistent complement component deficiencies; (3) those travelling or living in hyperendemic or epidemic areas (e.g., sub-Saharan Africa, pilgrimage to Mecca); and (4) those working as microbiologists handling *Neisseria meningitidis* or as military recruits.[8] HIV-infected adolescents should also be vaccinated with two doses of the vaccine, with the first dose given at 11–12 years of age and a booster at age 16 years. Based on the current ACIP guidelines,[8] HIV infection alone is not currently an indication for vaccination.

Recently there has been discussion regarding the potential value of meningococcal vaccination among other ''at-risk'' HIV-infected persons including MSM and/or those with high-risk sexual behaviors. Though scattered cases of invasive meningococcal disease among HIV-infected men have appeared since early in the epidemic,[79] a recent outbreak of invasive meningococcal disease among MSM living in New York City has caused concern.[80] A follow-on epidemiologic study estimated the risk of invasive disease among HIV-infected persons residing in NYC as 10-fold higher compared with the overall general population, with the greatest risk among those with CD4 counts <200 cells/mm^3.[81] While at the present time vaccination is not recommended for all HIV-infected adults, vaccination should be considered per local public health department guidance, among patients requesting vaccination, and in outbreak settings.

The preferred vaccine among HIV-infected persons is two doses of the meningococcal conjugate vaccine, with the second dose given ≥ 8 weeks after the first dose. A booster vaccine is recommended every 5 years if the risk factor persists. Follow-up testing for immune response is not currently recommended or widely available.

Data among HIV-positive youth have shown poorer responses among HIV-infected versus HIV-uninfected persons

(81% with one or dwo doses in HIV-infected vs. 100% with one dose in HIV-uninfected).[82] In another study among young HIV patients, lower immune responses were also noted (seroconversion to A: 68%; C: 52%; Y: 73%; and W-135: 63%), with poorer response rates among those with more advanced HIV disease.[83] Regarding the number of doses, a study found that two doses (versus one) significantly improved response rates among those with CD4% $\geq 15\%$, but that those with a low CD4% ($< 15\%$) had poor responses in both groups.[84] The second dose of meningococcal vaccine may be especially important for inducing adequate responses to all four serogroups (e.g., C).[85]

These studies demonstrate the importance of the vaccinating early in the course of HIV infection, and the importance of the second vaccine in the series. These data also suggest the possible need for alternative dosing strategies for ensuring adequate protection among HIV-infected persons, especially among those with low CD4 counts. Further studies are needed, including information on the meningococcal vaccine's clinical efficacy, durability, and vaccine responses among older patients.

Live Vaccines

Live vaccinations are generally contraindicated among HIV patients. For some live vaccines, evidence for the potential proliferation of vaccine-related viruses in the host exists (e.g., varicella vaccination in a severely compromised host),[86] while for other vaccines the risk is largely theoretical (e.g., LAIV). In general, the use of the inactivated form of the vaccine (vs. live) should be utilized when available (e.g., influenza, polio, and typhoid). Evidence-based exceptions to the use of live vaccines should be noted, as certain vaccines (e.g., MMR, varicella, yellow fever, and zoster) may be considered if the level of immunosuppression is low (CD4 count ≥ 200 cells/mm^3).[6]

Varicella

HIV patients have a higher incidence of varicella zoster virus (VZV) infections and related deaths.[87,88] The varicella vaccine (Varivax), which became available in 1995, is not currently licensed for use in HIV-infected persons. However, this vaccine may be considered among clinically stable patients with a CD4 count ≥ 200 cells/mm^3 who are without evidence of varicella immunity (i.e., lack of prior vaccination, serologic evidence of immunity, and clinician or laboratory diagnosed varicella or zoster).[8] The vaccine should be avoided in patients with more severe immunosuppression (e.g., CD4 counts < 200 cells/mm^3) as disseminated vaccine-related infection has been described.[86]

Most HIV-infected adults have evidence of prior infection or immunity, with one study showing that 95% were immune.[89] Hence, a varicella IgG antibody level should be obtained before vaccine administration to ensure that the patient is seronegative and requires vaccination. The varicella vaccine is administered as a two-dose series, with doses separated by ≥ 3 months.[7] Anti-herpetic medications should be discontinued during the period of -1 to $+14$ days of vaccination, since these medications can potentially inhibit post-vaccination immune responses.

There are currently no clinical data on varicella vaccination among HIV-infected adolescents or adults. However, studies in children have shown good immunogenicity (similar to antibodies levels post-natural infection), and have demonstrated preventive efficacy against both varicella and zoster.[90–92]

Zoster

Similar to the varicella vaccine, the zoster vaccine (Zostavax), which became available in 2006, is not specifically licensed for use in immunosuppressed patients. However, HIV-infected persons are at particular risk for VZV reactivation, with one study estimating the incidence of shingles as 3.2 cases per 100 person-years.[88]

The zoster vaccine may be considered among HIV-infected adults with known varicella immunity (i.e., a history of varicella or zoster, or VZV positive without history of varicella vaccination) who are ≥ 60 years of age and have clinically stable HIV infection with a CD4 count of ≥ 200 cells/mm^3.[6] Among patients with no history of varicella/zoster and a negative VZV IgG level, providers can consider varicella (Varivax) vaccination reviewed above.

In the general population, Zostavax has been shown to reduce the incidence of shingles, the severity of disease, and the occurrence of post-herpetic neuralgia.[93] Data evaluating the vaccine among HIV-infected patients is limited. A study of 286 HIV-infected adults found that two doses of Zostavax (administered 6 weeks apart) was safe among HIV patients who had CD4 counts of ≥ 200 cells/mm^3 and undetectable HIV viral loads. The study also found that patients with higher CD4 counts had more robust antibody titers.[94] More data on the ideal dosing schedule, safety, and efficacy of this live vaccine among HIV-infected persons are needed.

Measles–Mumps–Rubella

Cases of measles, mumps, and rubella continue to sporadically occur in the US.[95–97] highlighting the importance of vaccination against these infectious agents. Further, measles can be a life-threatening infection among immunocompromised persons, including those with HIV.[98]

Most HIV-infected adults are immune against measles ($\sim 95\%$),[99,100] hence prior to vaccination, antibody testing should occur. The MMR vaccine can be administered among HIV patients who lack immunity and who have a CD4 count ≥ 200 cells/mm^3.[101,102] Adverse complications, such as measles pneumonitis, have been described in patients with lower CD4 counts hence vaccination should be avoided in this group.[103,104]

Responses rates to vaccination vary by the patient's immune status.[101] In one small study, only 2 of 6 (33%) patients had a durable positive antibody response at 1 year, but this data was from the pre-CART era.[99] During the CART era, a cross-sectional study of 26 HIV-infected patients (most receiving CART with a mean CD4 count of 496 cells/mm^3) and 22 controls found that vaccine responses were not statistically different at 3 months (81% vs. 86%, respectively). At 1 year post-vaccination, a higher proportion of HIV-infected adults had lost measles antibodies; however, cellular responses were similar.[102]

Revaccination among those without an adequate response to initial vaccination has been shown to be effective in children on CART; however, there are currently no data among HIV-infected adults.[105,106] Further, no data exist regarding vaccine responses to the mumps and rubella components of

the MMR vaccine among HIV-infected adults; however, vaccination can be considered among non-immune patients who are at risk and who have adequate CD4 counts (≥ 200 cells/mm^3).

Travel-Related Vaccines

HIV-infected travelers may be at increased risk of complications from infectious diseases acquired at their destination.[107] HAV and influenza are the two most commonly acquired infections during travel, and vaccination should be considered based on the individual's itinerary. Vaccinations for travelers should be guided by resources including those available from the Centers from Disease Control and Prevention.[108]

Polio

A single lifetime polio booster is recommended among adults at risk for exposure. The inactivated form of the polio vaccine should be utilized for HIV patients travelling to an endemic area. The oral polio vaccine (OPV), which is a live vaccine, is contraindicated.[109]

Studies regarding polio responses among HIV-infected persons are limited, but one study found a 78–100% response rate, with the best responses among those with a CD4 ≥ 300 cells/mm^3.[70] Responses to polio vaccination may be blunted among patients not receiving CART, and vaccine failures have been described with low CD4 counts (e.g., < 200 cells/mm^3).[110] There is no current recommendations regarding post-vaccination testing, and the duration of protection is currently unknown among HIV-infected persons.

Yellow fever

Yellow fever is endemic to specific areas of South America and Africa. HIV-infected persons should ideally avoid travelling to yellow fever endemic locations. Among those who cannot alter their itineraries and who will be exposed to a substantial risk of infection, vaccine can be considered among those with asymptomatic HIV infection and a CD4 count ≥ 200 cells/mm^3. Close attention to the itinerary is suggested to ensure that vaccination is needed.[107]

Regarding immune responses to yellow fever vaccination, HIV patients have lower vaccine response rates compared to HIV-uninfected persons, with studies showing that 83–100% develop neutralizing antibody.[111–114] Evaluation of >200 HIV patients meeting vaccine guidelines found no adverse events among recipients; however, studies could not detect infrequent adverse events.[111] Adverse events have been described among HIV patients with low CD4 counts, including a case of post-vaccination myeloencephalitis.[115] No cases of viscerotropic disease in HIV patients have been described to date.[107] Options among HIV-infected travelers with low CD4 counts (e.g., < 200 cells/mm^3) include cancelling travel to the endemic location, or obtaining a waiver and adhering to strict mosquito avoidance, although this is not ideal.

Typhoid

HIV-infected adults who require typhoid vaccination should receive the parenteral inactivated capsular polysaccharide vaccine (Typhim Vi, Pasteur Merieux), rather than the oral live vaccine. Lower post-vaccination responses to typhoid vaccination have been described among HIV patients and have been correlated with low CD4 counts.[116] Similar to other travel-related infections, HIV-infected patients should be counselled that vaccination may not offer complete protection and be advised regarding additional preventive measures (e.g., avoidance of potentially contaminated food and water).

Other travel-related vaccines

HIV patients may require additional vaccinations prior to travel, including rabies and Japanese encephalitis virus (JEV) vaccines. There are few specific data regarding these vaccines among HIV patients. Guidance of the use of these vaccines should follow standard travel guidelines.[108]

Timing of Vaccination

The ideal timing of vaccinations among HIV-infected individuals remains uncertain, particularly among those who will soon initiate CART, since immune reconstitution typically improves vaccine responses.[48,57,59,67,112] The dangers of delaying vaccination include the risk of infection and the potential missed opportunity for vaccination due to lost follow-up.[117] In general, the administration of vaccines should occur at the initial HIV visit, or shortly thereafter in cases in which pre-vaccination testing is needed. For vaccines such as influenza, pneumococcal (with the conjugate vaccine), and hepatitis (A and B), administration should not be delayed since HIV-infected patients (even those with CD4 counts < 200 cells/mm^3) can develop adequate post-vaccination responses.[4,7]

If responses are not adequate after the initial vaccination, revaccination after CART initiation and a sustained increase in CD4 count can be considered, especially for HAV and HBV vaccines.[7] Several studies have found that higher CD4 counts,[48,57,67,112] suppressed HIV viral loads,[32,48,112,118] and receipt of effective CART[48,59] predict better response rates. Among early-diagnosed HIV patients, vaccines should be immediately administered since this group has near normal immune responses.[10]

Vaccine Recommendations for Household Members

In addition to vaccination of HIV-infected adults, household members should be vaccinated based on current guidelines[8] as this may reduce exposure to infectious agents providing a ''circle of protection''.[6] For example, annual influenza vaccination of household members is advised with either IIV or LAIV.[6,8] All inactivated vaccines can be safely administered to household members. Live vaccinations including MMR, varicella, and zoster can also be given to household contacts who meet criteria for vaccination.[8] If skin lesions develop after varicella or zoster vaccination, lesions should be covered and the HIV patient should avoid contact with the household member until the lesions resolve.[6] Travel vaccines among household members are generally considered safe, including oral typhoid and yellow fever vaccinations; OPV should be avoided since the polio virus can be spread via stool and could lead to vaccine-associated paralytic poliomyelitis.[109]

Future Directions

Although vaccines are available to protect HIV-infected adults against several infectious diseases, questions remain about the clinical efficacy and durability of immune

responses, and whether HIV patients require alternate dosing or booster schedules. More data on the optimal timing of vaccination are also needed, including whether to wait until after CART initiation and if so, the optimal timing after CART. In addition, among those vaccinated before the receipt of CART, data are needed whether revaccination should occur and for which vaccines.

Conclusions

Vaccinations are a sometimes overlooked, but critical, component of the care of HIV-infected adults. HIV providers must ensure vaccine coverage among their patients, with vaccinations ideally administered shortly after early HIV diagnosis and before loss of immune responsiveness. Patients with severe immune degradation (e.g., CD4 <200 cells/mm^3) are at the highest risk for vaccine-preventable diseases, but unfortunately have the poorest responses to vaccinations. Whether to vaccinate patients with low CD4 counts at presentation or wait for some degree of immune restoration after starting CART remains an important question. More immunogenic vaccines are needed, as well as studies to define the optimal timing for vaccination among those with advanced disease.

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Address correspondence to:
Dr. Nancy Crum-Cianflone
Naval Medical Center San Diego
34800 Bob Wilson Drive, Ste. 5
San Diego, CA 92134-1005

E-mail: nancy32red@yahoo.com