Background

Providing appropriate immunizations is an important component of comprehensive HIV clinical care. Immunizing persons with HIV infection poses several challenges and concerns related to safety and efficacy.

Safety Concerns

Early in the HIV epidemic, several reports generated concern that vaccinations in persons with HIV infection could activate their cellular immune system and enhance HIV replication, thereby increasing HIV RNA levels and potentially accelerating the course of HIV disease.[1] These reports, however, involved persons with HIV infection who were not receiving potent antiretroviral therapy and investigators subsequently demonstrated that post-immunization increases in HIV RNA levels were transient and clinically insignificant. Further, in persons taking modern highly potent antiretroviral therapy, immunizations generally do not cause any detectable increases in plasma HIV RNA levels. Current guidelines recommend that immunizations should not be withheld in persons with HIV infection due to concerns of increases in HIV RNA levels.[2]

Risk of Live Vaccines in Persons with HIV Infection

Immunizations are generally safe in individuals with HIV infection, with the exception of live virus vaccines in patients with low CD4 counts. In patients with advanced immunosuppression, live vaccines can cause a potentially life-threatening disseminated infection with the live pathogen in the vaccine.

Challenges with Efficacy

Unfortunately, current or past advanced immunosuppression in persons with HIV infection is often associated with suboptimal responses to standard recommended vaccine doses; response to several vaccines appears to depend on current and nadir CD4 cell counts.[3,4,5,6] In general, responses to immunization are better when the vaccine is given as early as possible in the course of HIV infection or after immune reconstitution that has resulted from antiretroviral therapy.

Recommendations by Organizations

The Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for routine immunizations of adults, including specific recommendations for adults with HIV infection.[7,8] In addition, the Infectious Disease Society of America (IDSA) has issued a Clinical Practice Guideline for the Vaccination of the Immunocompromised Host.[9] Unfortunately, some
differences exist in the recommendations provided by the different organizations, which creates a challenge for clinicians. This topic aims to serve as a general immunization overview for clinicians who provide direct care to persons with HIV infection.
Pneumococcal Vaccine

Background

Risk of Pneumococcal Disease in Persons with HIV Infection

In the general population, *Streptococcus pneumoniae* causes significant disease, including bacteremia, meningitis, and pneumonia, and is responsible for approximately 4,000 deaths each year in the United States. In the early years of the HIV epidemic, the risk of invasive pneumococcal disease in persons with HIV infection was approximately 20 times higher than in adults without high-risk conditions.\[10\] Subsequently, the incidence of invasive pneumococcal disease has decreased in persons with HIV infection, likely due to (1) the widespread use of potent antiretroviral therapy that resulted in improved immune function and improved humoral responses to pneumococcal antigens during clinical infections and (2) population herd protection against invasive strains of *S. pneumoniae* following the widespread use of conjugate pneumococcal vaccines in children since 2000.\[11,12,13,14,15\] A study that examined the risk of invasive pneumococcal disease in persons with HIV during 1996-2011 at a large integrated healthcare system in the United States reported that in recent years the risk of invasive pneumococcal disease was sevenfold higher in adults with HIV infection compared with adults without HIV infection.\[16\]

Efficacy of Pneumococcal Immunization in Persons with HIV Infection

There are limited clinical trial data that address the efficacy and durability of pneumococcal vaccination in patients with HIV infection, but retrospective studies indicate the 23-valent pneumococcal polysaccharide vaccine (PPSV23) has modest clinical benefit, if any, in reducing rates of pneumococcal infections in persons with HIV infection. In addition, the immunologic response to PPSV23 is impaired in persons with CD4 counts below 200 cells/mm\(^3\) when compared with persons who have CD4 counts above this threshold, and optimal response to the polysaccharide vaccine likely occurs in persons with a CD4 count above 500 cells/mm\(^3\).\[14,17\] Based on the lack of convincing data with PPSV23, significant interest emerged in using the conjugate pneumococcal vaccine, in combination with a polysaccharide vaccine. Further interest was generated after investigators demonstrated enhanced antibody responses to pneumococcal polysaccharide vaccine after initial immunization with conjugate pneumococcal vaccine.\[18\] There are no published clinical efficacy data for PCV13 in adults with HIV infection, but a randomized control trial using two doses of PCV7 given 1 month apart in 496 adults (88% with HIV infection) in Malawi demonstrated a vaccine efficacy of 74% in preventing invasive pneumococcal disease; this study included a large number of patients with a CD4 count less than 200 cells/mm\(^3\).\[19\] No data exist regarding the efficacy of the combined PCV13 plus PPSV23 vaccine regimen as recommended for persons with HIV infection.

Vaccines

Two different pneumococcal vaccines are available—the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23).\[10\] The PCV13 contains antigens from 13 common *S. pneumoniae* serotypes.\[20\] The PCV13 was approved by the United States Food and Drug Administration (FDA) in 2011 and it replaced the previously used 7-valent pneumococcal conjugate vaccine (PCV7). Of note, the PCV13 serotypes include all 7 serotypes in PCV7 (Figure 1).\[20\]

Recommendations

The ACIP recommendations for pneumococcal immunization in adults with HIV infection combine the use of PCV13 and PPSV23, with the exact schedule based on age and whether the individual has previously received pneumococcal vaccine (Figure 2).\[7,10\]
**General Approach**: In general, pneumococcal immunization should be given to all adults with HIV infection and the vaccine should ideally be given prior to CD4 decline and preferably after the patient has received suppressive antiretroviral therapy. For individuals who have already experienced advanced immunosuppression and have a CD4 count less than 200 cells/mm³, the PCV13 should be given without delay. The timing of when to initiate PPSV23 in patients with advanced immunosuppression; remains unclear. In this situation, many experts would defer PPSV23 component until the patient starts on antiretroviral therapy and has achieved virologic suppression; some experts would defer therapy until the CD4 count increases to greater than 200 cells/mm³. [21, 22]

**No Prior Pneumococcal Immunization**: Adults with HIV infection who have never received pneumococcal vaccine should first receive PCV13, followed by a dose of PPSV23 (at least 8 weeks later), and then followed by a second PPSV23 dose (at least 5 years after the first dose of PPSV23). If the person received their last PPSV23 prior to age 65, they should receive a third dose of PPSV23 after age 65 (at least 5 years after the last dose of PPSV23).

**Received One Prior Dose of PPSV23**: Adults with HIV infection who have already received one dose of PPSV23 (but no dose of PCV13) should receive one dose of PCV13 (at least 1 year after PPSV23). A second dose of PPSV23 should be administered (at least 5 years after the first dose of PPSV23 and at least 8 weeks after a dose of PCV13). If the individual has received the two doses of PPSV23 prior to age 65, they should receive a third dose after age 65 (at least 5 years after the prior dose of PPSV23).

**Received Two Prior Doses of PPSV23**: Adults with HIV infection who have already received two doses of PPSV23 (but no dose of PCV13) should receive one dose of PCV13 (at least 1 year after the last dose of PPSV23). If the individual has received the two doses of PPSV23 prior to age 65, they should receive a third dose after age 65 (at least 5 years after the prior dose of PPSV23 and at least 8 weeks after the PCV13 dose).

**Received Prior Dose of PPSV23 after Age 65**: Adults with HIV infection who have already received two doses of PPSV23 prior to age 65 and one dose after age 65 (but no dose of PCV13) should receive one dose of PCV13 (at least 1 year after the last dose of PPSV23).

**Persons 65 and Older**: All persons with HIV infection who have received PPSV23 prior to age 65 should receive one additional dose of PPSV23 at age 65, or later, but this must be given at least 5 years after the last dose of PPSV23 and at least 8 weeks after a dose of PCV13.
Tetanus, Diphtheria and Pertussis (Tdap) Vaccine

Background

Tetanus, diphtheria, and pertussis are vaccine-preventable bacterial diseases that can lead to serious complications. Tetanus (lockjaw) can potentially cause muscle paralysis and carries a 20% mortality rate. Diphtheria causes a thick coating to form in the posterior pharynx that can lead to breathing difficulty, and, in some instances, death. Pertussis (whooping cough) causes severe coughing spells that can lead to pneumonia, hypoxia, sleeping problems, and rarely death. Widespread childhood vaccination has markedly reduced the number of serious complications related to tetanus, diphtheria, and pertussis in the United States among all age groups. Although pertussis vaccine has reduced the incidence of pertussis compared with the pre-vaccine era, the number of reported cases of pertussis has increased since the 1980s, primarily due to lack of long-term immunity with the pertussis vaccine.\[23\] In recent years, the ACIP has recommended expanding the use of Tdap to improve community immunity against pertussis and reduce the burden of disease among the general population.\[24\] Most individuals with HIV infection mount adequate antibody responses to tetanus and diphtheria toxins, though it is a T-cell dependent vaccine and the titers are often lower among those with CD4 count less than 300 cells/mm\(^3\).\[4,25\]

Vaccines

Several tetanus and diphtheria toxoid vaccines (Td) are currently licensed by the FDA. In addition, two tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines are approved by the FDA: Boostrix (for persons aged 10 and older) and Adacel (for persons aged 11 to 64 years). Both the Tdap and Td vaccines contain inactivated bacteria and thus are unlikely to pose any risk to individuals with HIV infection. When the Tdap vaccine was initially licensed, concern existed regarding the safety of administering the Tdap vaccine within 5 years of the Td vaccine. Subsequently, studies reported that administering the Tdap to an individual who had recently received Td (21 days to 2 years) was safe, other than a mild local reaction.\[24\]

Recommendations

- **General Approach**: Individuals with HIV infection should receive immunization with Tdap and Td per the same schedule as those without HIV infection.\[7\] The timing and dosing of the Tdap and Td vaccination in persons with HIV infection is not altered based on CD4 count.
- **No Prior Tdap**: For adults with HIV who have not previously received Tdap, give a one-time dose of Tdap, followed by a Td booster every 10 years.\[7\] Adults who previously received Td but have not had a Tdap dose should receive the Tdap vaccine regardless of the interval since Td was last administered.
- **Tdap for Pregnant Women with HIV Infection**: Give Tdap during every pregnancy to prevent pertussis morbidity and mortality in infants. The dose of Tdap should be given preferably during gestational weeks 27–36 and it should be administered regardless of the pregnant woman's prior history of receiving Tdap.\[26\]
**Haemophilus influenzae type b (Hib) Vaccine**

**Background**

*Haemophilus influenzae* infection is more common in adults with HIV infection than in the general population, but the annual incidence remains relatively low at 41/100,000 adults with HIV infection.[27] Only about one-third of cases of invasive *H. influenzae* involve type b, which is the type in the currently licensed vaccines. Multiple identifiable subtypes of *H. influenzae* and other unidentifiable types (called nontypeable *H. influenzae*) can cause a wide range of clinical disease, including bacteremia, meningitis, pneumonia, epiglottitis, cellulitis, and infectious arthritis. Infants and children younger than five years of age, adults over the age of 65, and Native American and Alaskan Indian populations are all at higher risk of disease.[28] Certain medical conditions also predispose individuals to *H. influenzae* disease, such as HIV infection, sickle cell disease, asplenia, complement and antibody deficiency syndromes, and receipt of chemotherapy, radiation or hematopoietic stem cell transplant. The conjugate *H. influenzae* type b vaccine is safe and effective in all age groups.[29]

**Vaccines**

The currently licensed *Haemophilus influenzae* type b conjugate vaccines are *Hiberix*, *ActHIB*, and *PedvaxHIB*. Additional Hib conjugate vaccines are licensed in combination with other vaccines, including *Comvax* (Hib combined with hepatitis B vaccine), *Pentacel* (Hib combined with DTaP and inactivated polio virus), and *MenHibrix* (Hib combined with meningococcal vaccine).

**Recommendations**

- Due to the low incidence of *H. influenzae* type b infections among adults with HIV infection, *H. influenzae* type b immunization is not recommended for routine administration to adults with HIV infection.[21]
- Per the ACIP recommendations, one dose of Hib vaccine should be administered to adults with HIV infection only if they have an indication for the vaccine, namely sickle cell disease, leukemia, or anatomic or functional asplenia.[7]
Meningococcal Vaccine

Background

Meningococcal meningitis, which is caused by *Neisseria meningitidis*, can cause severe complications, including brain damage, hearing loss, and learning disabilities. Risk factors that can increase a person’s risk of acquiring meningitis include very young age (infants are at highest risk), community setting (college dormitory, military barracks), travel to endemic regions, and certain medical conditions including HIV. Available data from population studies suggest that persons with HIV infection have an increased risk of developing meningococcal disease, with the relative risk estimated at 5 to 13-fold higher than in persons without HIV infection; the risk in persons with HIV infection appears to be higher with low CD4 cell counts and high HIV RNA levels.[30] In addition, several local outbreaks of meningococcal meningitis have been reported in the United States involving gay and bisexual men.[31, 32, 33]. Unpublished CDC data from 62 cases of meningococcal disease in persons with HIV infection found that serogroup C was the most common isolate, followed next by serogroup Y (Figure 3).[30] As with other vaccines given to individuals with HIV infection, low CD4 count and HIV RNA above 10,000 copies/mL are associated with decreased meningococcal vaccine response rate.[34]

Vaccines

Two quadrivalent meningococcal conjugate vaccines (MenACWY) covering groups A,C, W-135, and Y are licensed and available for use in the United States: MenACWY-D and MenACWY-CRM.[30] MenACWY is preferred for use in adults aged 55 and younger as well as for adults aged 56 years and older who were either previously vaccinated with MenACWY and are recommended for revaccination, or in whom multiple doses are anticipated. Meningococcal polysaccharide vaccine (MPSV4) is preferred for adults 56 and older who have not received MenACWY previously and who require a single dose only (e.g. travelers). In addition, serogroup B meningococcal vaccines (MenB) are now available, including MenB-4C, given as a 2-dose series and MenB-FHbp given as a 3-dose series. Both of the MenB vaccines are approved for persons aged 10 to 25 who have increased risk for meningococcal disease.

Recommendations

The following summarizes new 2016 recommendations from the ACIP regarding administering conjugate meningococcal vaccine to persons with HIV infection.[30]

- **General Approach**: Routine administration of meningococcal conjugate vaccine (serogroups A, C, W, Y) is recommended for persons with HIV infection; if possible, the same product of the meningococcal vaccine should be used for all doses.

- **Dosing Recommendations**: For persons 2 years or older, the ACIP recommends giving 2 doses (8-12 weeks apart) of either MenACWY-D or MenACWY-CRM.

- **Booster Doses**: For persons who were at least 7 years of age when they received the primary vaccine series, follow-up booster doses should be given every 5 years beginning 5 years after the initial series.

- **Conjugate Meningococcal B Vaccine**: Routine administration of conjugate meningococcal B vaccine is not recommended for persons with HIV infection.
Influenza Vaccine

Background

Influenza viruses typically circulate widely in the United States annually from the late autumn through early spring. Influenza A and influenza B are the types of viruses that cause human epidemic disease. New variants emerge due to frequent antigenic change (e.g. antigenic drift) resulting from point mutations and recombination events that occur during viral replication; antigenic drift is the virologic basis for seasonal epidemics and necessitates adjustment of the vaccine components each year.[35] Larger antigenic change, termed antigenic shift, has the potential to cause a worldwide pandemic since there is no pre-existing immunity among humans to the novel virus in this situation. Annual influenza vaccination is the primary means of preventing influenza and its complications. Persons infected with HIV have a higher risk of influenza-associated morbidity and mortality compared to the general population.[36] Studies in individuals with HIV infection suggest a single dose of inactivated vaccine generates a good humoral immune response, which does not improve significantly with the second dose. In persons with HIV infection who have a low CD4 cell count, the influenza vaccine does not generate good immune responses.[4]

Vaccines

Adults with HIV infection, including pregnant women, can receive inactivated influenza vaccine (IIV). The inactivated influenza vaccine options now include trivalent (contains two strains of influenza A and one of influenza B) and quadrivalent vaccines (contains two strains of both influenza A and B). A recombinant influenza vaccine (RIV) that does not contain any egg protein is approved for adults aged 18 to 49. The live attenuated influenza vaccine, also known as the nasal spray flu vaccine, is not approved for use nor recommended for use in immunocompromised individuals, including patients with HIV infection, due to concern that attenuated virus could lead to actual infection and result in prolonged viral shedding.

Recommendations

The following summarizes the 2017 ACIP recommendations for administering influenza vaccine to persons with HIV infection.[7,8]

- **General Approach**: All persons with HIV infection should receive a single annual dose influenza vaccine.
- **Recommended Vaccines**: Recommended routine influenza vaccines for persons with HIV infection include inactivated influenza vaccine (trivalent or quadrivalent) or recombinant influenza vaccine (trivalent).
- **Contraindicated Vaccine**: The live attenuated influenza vaccine should not be administered to persons with HIV infection.
- **Persons with Egg Allergy**: The recombinant influenza vaccine, which does not use an egg-based culture system, is available and safe for persons with an egg allergy.
- **Persons Aged 65 and Older**: Adults with HIV infection aged 65 years or older can receive the standard-dose inactivated influenza vaccine, adjuvanted inactivated influenza vaccine, or high-dose inactivated influenza vaccine.
Hepatitis A Virus (HAV) Vaccine

Background

Hepatitis A is a viral infection transmitted through food, water, or objects contaminated with fecal matter. Hepatitis A is usually an acute, self-limiting condition that does not require treatment though it can rarely cause fulminant liver failure. Hepatitis A rates are the lowest they have been in 40 years, likely due to the widespread use of the hepatitis A vaccine since 1995. Hepatitis A vaccine has been found to be safe and generally effective in persons with HIV infection, though seroconversion rates may be diminished for individuals with lower CD4 cell counts. One randomized control study found seroconversion rates of 94% in patients with HIV infection compared to 100% in persons without HIV infection, though rates were only 87% in patients with CD4 counts less than 300 cells/mm$^3$.[37] Another randomized control trial reported a greater discrepancy in response rates: two-thirds of persons with HIV infection who had a CD4 count greater than 200 cells/mm$^3$ seroconverted after two doses of vaccine compared to only 9% of those with lower CD4 counts.[3]

Two retrospective analyses, however, reached conflicting conclusions about the relationship between CD4 count and hepatitis A vaccine response: one study found that female gender and CD4 cell count at the time of vaccine, but not CD4 nadir, predicted response to vaccine whereas another study concluded that a suppressed HIV viral load, but not CD4 cell count, correlated with immune response.[38,39]

Vaccines

Hepatitis A vaccine is an inactivated vaccine that can be given either as Havrix or Vaqta, or as part of a combination vaccine (Twinrix) that contains both inactivated hepatitis A and recombinant hepatitis B vaccine. Havrix contains 1,440 ELISA units (El.U) of hepatitis A antigen and Vaqta contains 50 units (U) of inactivated hepatitis A; Twinrix contains 720 El.U of hepatitis A antigen (half of the Havrix dose) combined with 20 mcg of hepatitis B antigen (the full Engerix-B dose). The two brands of hepatitis A are interchangeable.

Recommendations

The following summarizes the ACIP recommendations for administering hepatitis A vaccine to persons with HIV infection.[7,8]

- **General Approach:** Administer Hepatitis A vaccination to all persons with HIV infection at risk of encountering hepatitis A virus, including men who have sex with men, health care workers, hemophiliacs, persons who inject drugs, persons working in or traveling to parts of the world that have high or intermediate hepatitis A endemicity, and patients with chronic liver disease.[40] In addition, the ACIP recommendations now state that any person who seeks protection from hepatitis A infection may receive hepatitis A vaccine.[7]

- **Timing of Vaccine:** Persons with HIV infection should be vaccinated against hepatitis A prior to a decline in CD4 counts (and after virologic response to antiretroviral therapy) to improve the likelihood of an adequate response, but vaccination should not be delayed in individuals at risk for hepatitis A acquisition.[9] For patients with advanced immunosuppression, most experts recommend deferring the hepatitis A immunization until the CD4 count has increased to greater than 200 cells/mm$^3$ in response to highly effective antiretroviral therapy.

- **Recommended Dosing Schedule:** The recommended hepatitis A vaccine schedule is two doses at 0 and 6 to 12 months (Havrix) or 0 and 6 to 18 months (Vaqta). The combined hepatitis A-hepatitis B vaccine (Twinrix) can also be administer as a 3-dose series (0, 1, and 6 months).
Hepatitis B Virus (HBV) Vaccine

Background

Hepatitis B virus is transmitted through percutaneous and mucosal exposure to infected blood or body fluids. Chronic infection with HBV can cause cirrhosis, liver failure, hepatocellular cancer, and death. Individuals with HIV have an increased risk of acquiring hepatitis B infection due to shared routes of HIV and HBV transmission, including injection drug use and high-risk sexual activity. When compared with persons who have HBV monoinfection, those coinfected with HIV and HBV have an increased likelihood of establishing chronic HBV after initial infection, accelerated progression of liver disease, and significantly higher rates of liver-related mortality compared with HIV-uninfected individuals.\cite{41,42} In light of these risks, vaccination against hepatitis B is very important for persons with HIV infection. Unfortunately, hepatitis B vaccine response rates in adults with HIV infection are significantly lower than in persons without HIV infection, with response rates that range from 18 to 71% (compared to 60 to 80% in patients without HIV infection).\cite{43,44} The impaired vaccine response in persons with HIV infection has been associated with a recent or nadir CD4 count less than 200 cells/mm\(^3\), detectable HIV RNA levels, and coinfection with hepatitis C virus.\cite{6,43}

Attempts to improve hepatitis B vaccine response rates have included giving a double dose (40 mcg instead of 20 mcg), increased number of doses (four instead of three), and using intradermal rather than intramuscular dosing.\cite{45,46,47}

Vaccines

There are two FDA-approved hepatitis B recombinant vaccines (Recombivax-HB and Engerix-B). The Engerix-B vaccine contains the standard 20 mcg of hepatitis B whereas Recombivax-HB contains a double, 40 mcg of hepatitis B dose. A combined hepatitis A-hepatitis B (Twinrix) vaccine is also available, which contains a standard 20 mcg dose of hepatitis B and 720 EI.U of hepatitis A.

Recommendations

The recommendations for hepatitis B immunization in persons with HIV infection differs among several existing guidelines as outlined below.\cite{7,9,41}

- **General Approach**: All persons with HIV infection who do not have active HBV or evidence of immunity to HBV should be vaccinated with a hepatitis B vaccine.

- **Pre-Vaccine Screening**: Pre-vaccine screening should include HBsAg, anti-HBs, and anti-HBc. A positive HBsAg indicates active infection and no vaccine is indicated. If the patient has a positive anti-HBs and anti-HBc, the patient does not need immunization. In addition, if the anti-HBs alone is positive (with a titer greater than 10 IU/mL), the patient is considered immune and has no need for hepatitis B immunization.\cite{41} The approach to patients with isolated anti-HBc is addressed below.

- **Timing of Vaccine**: The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommends providing hepatitis B vaccine to non-immune individuals at entry into care and before CD4 count declines to less than 350 cells/mm\(^3\).\cite{41} In addition, the guidelines recommend that patients who initially present with a low CD4 count should receive hepatitis B vaccine without delay, since some patients with a low CD4 will respond to the vaccine.

- **Dose and Schedule**: Expert recommendations regarding the dose and schedule of hepatitis B vaccine administration in persons with HIV infection range from giving a standard vaccine dose on a three-vaccine dose schedule (0, 1, and 6 months) to double-dose vaccine strength on a three or four-dose schedule. Although low CD4 count and high HIV RNA levels are associated with poorer vaccine response, there are no specific guidelines as to timing of vaccination relative to CD4 count or HIV RNA status.
- **OI Guidelines Dosing Recommendation**: The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommend using either (1) standard doses of hepatitis B vaccine given at 0, 1, and 6 months, or (2) the combined hepatitis A and B vaccine given as a 3-dose series (0, 1, and 6 months) or a 4-dose series (0, 7, and 21 to 30 days, and 6 months).[41] These guidelines note that some experts recommend using double-dose hepatitis B vaccine either in a 3-dose or 4-dose series, but the strength of evidence is lower than for standard dosing.

- **ACIP Dosing Recommendation**: The 2017 ACIP guidelines do not give any specific hepatitis B dosing recommendations for persons with HIV infection.[7, 8]

- **IDSA Practice Guidelines**: The 2013 IDSA Practice Guidelines for Vaccination of the Immunocompromised Host recommends considering using a high-dose (40 mcg) vaccine for adults and adolescents with HIV infection, but these recommendations do not specify whether to use Recombivax-HB or Engerix-B.[9] The IDSA Practice Guidelines also state that a three-dose series of the combined hepatitis A-hepatitis B vaccine (Twinrix) can be used for primary vaccination of adults and adolescents with HIV infection; the combined vaccine uses the standard 20 mcg dose of hepatitis B.

- **Post-Vaccine Antibody Testing**: Given the decreased response rate to hepatitis B vaccine in the setting of HIV infection, persons with HIV infection should have testing for antibody to hepatitis B surface antigen (anti-HBs) 1 to 2 months after completing the final dose of the vaccine series, with a titer of at least 10 mIU/mL considered protective.[9, 41]

- **Repeat Immunization**: If a post-vaccination anti-HBs concentration of at least 10 mIU/mL is not attained, a second 3-dose series of hepatitis B vaccine using standard-dose or high-dose vaccine should be administered.[41] In this situation, most experts recommend using high-dose vaccine. An alternative given by the 2013 IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host is that one single additional dose of hepatitis B vaccine can be administered, after which anti-HBs is tested again to determine if the full second series is required.[9] If a person with HIV infection has not responded to a total of 6 doses of hepatitis B virus vaccine, they are unlikely to respond to further doses. The opportunistic infections guidelines note that if the patient has a low CD4 count and fails to respond to the vaccine series, some experts would defer re-immunization until the patient has a sustained increase in CD4 count in response to antiretroviral therapy.

- **Isolated Core Antibody**: The optimal approach for patients with HIV infection with isolated anti-HBc (“isolated core antibody”) is unclear since this pattern may signify a false positive result, exposure in the distant past with waning anti-HBs, or occult HBV infection. The opportunistic infections guidelines recommend checking an HBV DNA and if negative administering a complete hepatitis B vaccine series to those with isolated hepatitis B core antibody.[41]


Measles, Mumps and Rubella (MMR) Vaccine

Background

Measles, mumps, and rubella are highly contagious viruses that can cause a wide range of clinical disease, including congenital syndromes. Since the introduction of the measles, mumps and rubella (MMR) vaccine, the incidence of these viral diseases has decreased by 99%.[48] Nevertheless, despite excellent MMR vaccine coverage in the United States, sporadic outbreaks continue to occur. Measles can cause significant morbidity and mortality in healthy individuals, and the impact is even greater in immunosuppressed patients, with one case report citing 40% mortality in patients with HIV infection.[48] Studies suggest that most individuals living with HIV in the United States have adequate antibody titers to measles although data from an ongoing observational cohort of United States Department of Defense beneficiaries found a seroprevalence of measles immunity of only 67%.[49] Adults born before 1957 are considered immune to measles and mumps. Based on limited available data, the immunologic responses to the MMR vaccine among individuals with HIV infection is modest at best, and the protection of the vaccine in these persons is not well established; MMR does not appear to have any significant detrimental impact on either CD4 count or HIV RNA levels.[49]

Vaccine

The measles, mumps, and rubella (MMR) vaccine is a live vaccine and thus it poses significant risk to severely immunocompromised individuals. There have been case reports of fatal pneumonitis in patients with advanced immunosuppression who received the vaccine.[50] Two MMR vaccines are FDA-approved: the trivalent M-M-R II and the quadrivalent ProQuad, which also contains varicella virus vaccine.

Recommendations

The following summarizes the ACIP recommendations for administering MMR to persons with HIV infection.[7,8]

- **General Approach:** For persons with HIV infection who do not have immunity to measles, the ACIP recommends giving one dose of MMR vaccine if the individual has no HIV-related symptoms and has a CD4 cell count greater than 200 cells/mm$^3$.
- **Additional Dosing of MMR:** A second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for individuals who (1) are students in a post-secondary institution, (2) work in a health care facility, or (3) plan to travel internationally.
- **Quadrivalent MMR-Varicella Vaccine:** The quadrivalent MMR-varicella vaccine is not recommended in persons with HIV infection.[9]
- **Contraindications:** The MMR vaccine and MMR-varicella vaccines are contraindicated in persons with HIV infection who have a CD4 count less than 200 cells/mm$^3$. In addition, MMR vaccine is contraindicated during pregnancy, and pregnancy should be avoided for 28 days after vaccination to minimize the theoretical risk of congenital rubella syndrome. Women without evidence of rubella immunity and a CD4 count of at least 200 cells/mm$^3$ should receive MMR vaccination upon completion or termination of pregnancy and before discharge from the health facility.
Varicella Vaccine

Background

Varicella-zoster virus (VZV), or the chickenpox virus, is a highly contagious virus that causes rash, fever, and potentially severe, disseminated disease in persons with weakened immune systems. Prior to the introduction of the varicella vaccine and the incorporation of this vaccine into the routine childhood immunization schedule, chickenpox was very common in the United States general population, causing over 4 million infections each year. Primary varicella zoster virus infection is uncommon in adults with HIV infection since most have acquired immunity through childhood infection.[51]

Vaccine

The varicella vaccine is a live attenuated vaccine that poses significant risk to persons with HIV infection who have advanced immunosuppression. The duration of protection from varicella vaccine is not known. In addition to providing protection against primary varicella infection, the varicella vaccine has also been shown in studies to reduce the risk of herpes zoster (when compared with wild-type infection).[52]

Recommendations

The following summarizes the ACIP recommendations for administering varicella vaccine to adults with HIV infection.[7,8]

- **General Approach:** Adults with HIV infection and no evidence of immunity to VZV and a CD4 count of 200 cells/mm$^3$ or greater should receive varicella vaccine. The vaccine does not need to be given to those born in the United States before 1980, or to those with VZV immunity.
- **Dosing Recommendation:** Two doses of varicella vaccine should be given 4 to 8 weeks apart.
- **Contraindications:** Varicella vaccine is contraindicated in persons with HIV infection who have a CD4 count less than 200 cells/mm$^3$. In addition, the quadrivalent measles, mumps, rubella, and varicella vaccine is not recommended for individuals with HIV infection. The zoster vaccine should not be used interchangeably with the varicella vaccine, since the zoster vaccine has a much higher titer of live, attenuated VZV.
Zoster Vaccine

Background

Although primary varicella-zoster virus infection is unusual in persons with HIV infection, the incidence of zoster among adults with HIV is 15-fold higher than among age-matched immunocompetent adults, and the risk is highest in patients with a CD4 count less than 200 cells/mm$^3$.[51] Individuals with HIV infection have additional increased risk in the first 4 months after starting effective antiretroviral therapy, likely as a result of immune reconstitution.[53] Following the widespread use of potent antiretroviral therapy, the incidence rate of zoster has markedly decreased compared with early years of the HIV epidemic.[54] Zoster is typically limited to a painful, dermatomal vesicular rash but can result in severe and complicated disease in adults with HIV infection, especially those with a low CD4 count.[55] The goal of using zoster vaccine in patients with HIV infection is twofold: prevent zoster and reduce the severity of zoster if it does occur.

Zoster Vaccines

Live Attenuated Herpes Zoster Vaccine

The live attenuated zoster vaccine is a live-virus vaccine with 14-fold higher titers of varicella virus compared to the varicella vaccine. It is currently licensed in the United States for the prevention of shingles in adults over age 50 and recommended by ACIP for adults over age 60.[7] This vaccine requires just one dose. Preliminary data indicated the live attenuated herpes zoster vaccine is safe and immunogenic in adults with HIV infection who have a CD4 count of at least 200 cells/mm$^3$, but this study remains unpublished.[56]

Herpes Zoster Subunit Vaccine

On October 20, 2017, the United States FDA approved the herpes zoster subunit vaccine, a recombinant adjuvanted vaccine, for persons 50 years of age and older. The new herpes zoster subunit vaccine contains recombinant glycoprotein E antigen subunit combined with the AS01B adjuvant; this vaccine does not contain live varicella-zoster virus (Figure 4).[57] The herpes zoster subunit vaccine has shown an efficacy of greater than 95% in preventing herpes zoster in phase 3 trials that enrolled immunocompetent older adults.[58,59,60] In addition, in a phase 1/2a trial, this same zoster subunit vaccine was administered to persons with HIV infection and it was safe and immunogenic.[61] The dosing schedule for the herpes zoster subunit vaccine is 2 doses, with the first dose at month 0, followed by a second dose administered anytime between 2 and 6 months later. The subunit vaccine offers a major advantage over the current live attenuated zoster vaccine since it does not carry any risk of causing varicella-zoster infection, regardless of the severity of the patient's immunosuppression. Accordingly, there are no contraindications for use of the herpes zoster subunit vaccine in persons with HIV infection.

Recommendations

Live Attenuated Zoster Vaccine in Persons with HIV Infection

The guidance for use of the live attenuated zoster vaccine in persons with HIV infection have consistent recommended against giving live attenuated zoster vaccine in patients with a CD4 count below 200 cells/mm$^3$ (due to the risk of developing disseminated varicella-zoster virus infection in an individual lacking immunity to varicella). For persons with HIV and a CD4 cell counts greater than 200 cells/mm$^3$, the recommendations have not been consistent across different organizations, primarily due to the lack of data. The following summarizes various recommendations from different societies regarding the use of live attenuated zoster vaccine in persons with HIV infection.

- ACIP: In the 2017 ACIP recommendations, herpes zoster vaccine is contraindicated in
patients with a CD4 count below 200 cells/mm$^3$; no recommendation is given for or against administering zoster vaccine in patients with HIV infection who have a CD4 count of 200 cells/mm$^3$ or greater.[7,8]

- **Opportunistic Infections Guidelines**: The 2014 Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adolescents and Adults: zoster vaccine is not addressed other than referring to the recommendation given by ACIP.[51]

- **HIVMA/IDSA Primary Care Guidelines**: The 2013 HIV Medical Association (HIVMA) and Infectious Disease Society of America (IDSA) Primary Care Guidelines for Persons Infected with HIV recommend against routinely administering zoster vaccine in persons with HIV infection as safety and efficacy is not known, but recommend considering giving to persons with HIV infection who are older than 60 and have a CD4 count greater than 200 cells/mm$^3$.[62]

**Herpes Zoster Subunit Vaccine In Persons with HIV Infection**

There are no formal recommendations yet for the use of the herpes zoster subunit vaccine in persons with HIV infection. Since this vaccine does not contain live varicella-zoster virus, it is unlikely that any guideline will consider this vaccine as contraindicated for persons with HIV infection, including those with advanced immunosuppression. It remains to be seen if immune response to the herpes zoster subunit vaccine in persons with HIV will vary significantly based on degree of immunosuppression. For the general population, the ACIP committee recently has issued the following recommendations.

- The herpes zoster subunit vaccine is preferred over the live attenuated zoster vaccine for adults 50 years of age and older.
- The herpes zoster subunit vaccine can be used in persons who have already received the live attenuated zoster vaccine. Details regarding the minimum acceptable interval between giving the herpes zoster subunit vaccine to a person who previously received the live attenuated zoster vaccine have not been released to the public.
Human Papilloma Virus (HPV) Vaccine

Background

Individuals with HIV infection have a high burden of HPV-associated disease: genital warts are more common and more difficult to treat in persons with HIV infection, abnormal cervical cytology is nearly 11 times more common in women with HIV infection compared with the general female population, and incidence studies estimate a 30-fold increased risk of anal cancer among persons with HIV infection.[62,63,64] Among individuals with HIV infection, the incidence of anal cancer among men and the incidence of cervical cancer among women have not declined in recent years, despite the presence of widespread antiretroviral therapy, suggesting that reversing HIV-induced immunosuppression is not enough to overcome the long latency of the carcinogenic effects of HPV.[64,65] Prophylactic vaccination against oncogenic subtypes of HPV has offered a new prevention strategy. Vaccination is both safe and effective in persons with HIV infection, with seroconversion rates of 95% in men age 18 and older who received the quadrivalent vaccine, and seroconversion rates of 92.3 to 100% among women with HIV infection aged 16 to 23 who received the quadrivalent vaccine.[66,67] The vaccines are most effective when given prior to an individual’s sexual debut before exposure to HPV, though even if one strain has already been acquired, the vaccine could still prevent against other strains. Unfortunately, most adults with HIV infection have not received HPV vaccine and most are older than the age recommended for use of these vaccines. Being on suppressive antiretroviral therapy may improve vaccine response.[66]

Vaccines

Three HPV vaccines have been approved by the United States FDA: bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV).[68] In the United States, the 9vHPV vaccine is the only HPV vaccine currently manufactured. The 9v vaccine includes the same 4 serotypes included in 4vHPV (6, 11, 16, and 18) and 5 additional cancer-causing HPV types (31, 33, 45, 52, and 58).[68] The HPV types 16, 18 account for approximately 66% of cases of cervical cancer, HPV types 6 and 11 account for approximately 90% of genital warts, and serotype 31, 33, 45, 52, and 58 combined account for approximately 15% of cervical cancers and 10% of invasive HPV-associated cancers.[68] The HPV vaccines are prepared from recombinant noninfectious virus-like particles and are considered safe for immunocompromised individuals since they do not pose any risk of transmitting infection (Figure 5). The 9-valent vaccine is FDA-approved for use in females and males for ages 9 through 26.

Recommendations

- **General Approach:** The ACIP recommends HPV vaccine routinely for females and males with HIV infection through age 26. The vaccine is recommended to start in children at age 11, but can be initiated at any time through age 26. Administering the HPV vaccine is based on the patient's age and not on past sexual history, HPV or Pap smear testing, or history of genital warts.
- **Dosing Recommendation:** For persons with HIV infection, the ACIP recommends that HPV vaccination should be given in a 3-dose series (given at 0, 1-2 and 6 months) at 11 or 12 years of age, and for those 13 to 26 years of age if not previously vaccinated.[68] A 2-dose schedule is now recommended for healthy boys and girls aged 9 to 14 years, but this 2-dose series should not be used in persons with HIV infection.[69]
- **Recommendation for Adults Older than 26:** There are no recommendations for the use of the HPV vaccine in women or men older than age 26.
- **HPV Vaccine in Pregnancy:** The ACIP recommends against administering HPV vaccine to pregnant women, but pregnancy testing is not needed prior to vaccination.[68] If a woman is found to be pregnant after vaccination, no intervention is needed; if a woman has started the vaccine series and becomes pregnant, the remainder of the 3-dose series should be delayed until completion of pregnancy. The largest HPV vaccine pregnancy registry to date shows no
adverse signals and at this time, pregnancy registries for the bivalent and quadrivalent vaccines have been closed. [68, 70] In addition, recent data with HPV4 suggest that HPV vaccine is safe if given during pregnancy.

• **Use as Therapeutic Vaccine:** The HPV vaccine is not recommended for therapeutic purposes in patients with HPV-related abnormal cervical or anal cytology.
Travel Vaccines

Background

An estimated 8% of travelers to the resource-limited regions of the world require treatment during travel, and major disease risks include vaccine-preventable illnesses.[71] Vaccines related to travel are generally not part of the initial evaluation process of persons with HIV infection, and newly diagnosed, treatment-naïve patients with CD4 counts less than 200 cells/mm$^3$ should delay travel until CD4 counts have been reconstituted with antiretroviral therapy in order to avoid immune reconstitution illness while traveling.[71] Many persons with HIV infection will eventually travel to regions of the world that require multiple preventive vaccinations, such as typhoid fever, cholera, yellow fever virus, Japanese encephalitis virus, and rabies virus. Recommendations for appropriate travel-related vaccines can be very complex and depend on numerous factors, including the immune status of the person with HIV-infection, the specific region of travel, and the types of exposure likely to occur in that region.[72]

Recommendations

All persons with HIV infection who are planning international travel should undergo an evaluation by a medical provider who has expertise in travel-related issues, and this travel evaluation should occur well in advance of the travel date to allow time for all appropriate immunizations to be given. The CDC provides an online resource for general information regarding HIV and travel.[72, 73]
Contraindicated Vaccines

Background

In general, caution should be exerted when administering any live virus vaccine to any immunocompromised individual, including persons with HIV infection. Certain live vaccines—Bacillus Calmette Guérin (BCG), vaccinia (smallpox), typhoid (21a) and live intranasal influenza—are contraindicated for all persons with HIV infection, regardless of CD4 cell count. In many resource-poor settings, BCG continues to be routinely administered to the general population in an effort to reduce the risk of tuberculosis infection. Unfortunately, persons with HIV infection who receive BCG as part of a general population vaccine program are at risk for subsequently developing disseminated vaccine-related tuberculosis, even years after receiving the vaccine.[74] The CDC recommends against the use of BCG for persons with HIV infection. Vaccinia immunization confers protection against smallpox and is still recommended for lab or healthcare workers who come into contact with the virus or attenuated strains through cultures or contact with infected animals or contaminated materials. Due to case reports of severe smallpox infection in persons with HIV infection after exposure to smallpox vaccine, the ACIP recommends against smallpox vaccination in persons with HIV infection in all non-emergency situations.[75]

Recommendations

The 2013 IDSA Practice Guideline for Vaccination of the Immunocompromised Host recommends the following regarding use of live vaccines for adults and adolescents with HIV infection:

- Live influenza vaccine is contraindicated, at any CD4 cell count.
- Quadrivalent measles, mumps, rubella and varicella vaccine is contraindicated regardless of CD4 count.
- Measles, mumps and rubella (MMR) and varicella vaccines are contraindicated with a CD4 count less than 200 cells/mm\(^3\), but indicated for a non-immune individual with a CD4 count of 200 cells/mm\(^3\) or greater.
- Zoster vaccine should not be used in highly immunocompromised patients. The recommendation for zoster vaccine in persons with HIV infection who have low-level immunosuppression is not clear: the online expanded version of the IDSA guideline lists zoster as contraindicated for individuals with HIV infection who have either high-level or low-level immunosuppression, but the shorter print article does not address zoster vaccine in persons with low-level immunosuppression. The ACIP also gives no recommendation for or against administering zoster vaccine in persons with HIV infection who have low-level immunosuppression.[76]
Summary Points

- Immune responses to vaccinations among persons with HIV infection are better when the vaccines are given as early as possible in the course of HIV infection or after immune reconstitution has occurred as a result of antiretroviral therapy.
- Vaccination is generally safe in persons with HIV infection, with the exception that live virus vaccines in patients with low CD4 counts can cause serious infectious complications.
- Adults with HIV infection should receive immunizations according to the CDC/ACIP schedule for the following inactivated vaccines: influenza; conjugate *H. influenzae* type b (Hib); tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap); tetanus toxoid, reduced diphtheria toxoid (Td); hepatitis B; hepatitis A; and 9-valent HPV in non-pregnant females and males ages 11 to 26.
- Pneumococcal vaccine-naïve persons should receive both the conjugate 13-valent (PCV13) and the 23-valent polysaccharide pneumococcal vaccine (PPSV23), and the recommended sequence and spacing of these vaccines depends on whether the patient has previously received any doses of polysaccharide pneumococcal vaccine.
- When giving the hepatitis B vaccine to adults with HIV infection, consideration should be given to using high dose (40 mcg) vaccine and/or using a four-dose schedule instead of the standard three-dose schedule. Post-vaccination antibody titers should be checked 1 to 2 months after completion of the primary hepatitis B vaccine series.
- Three doses of 9vHPV should be administered to all males and females though 26 years of age. The vaccine should ideally be given at age 11 or 12, but can be given as early as 9 years of age.
- All adults with HIV infection should receive two doses of conjugate meningococcal vaccine and booster doses are recommended every 5 years thereafter.
- MMR and varicella vaccines are indicated for asymptomatic persons with HIV infection who have a CD4 count greater than 200 cells/mm$^3$ if they lack immunity to these vaccine-preventable illnesses.
- Zoster vaccine should be avoided in patients with CD4 counts below 200 cells/mm$^3$ due to the risk of developing disseminated varicella-zoster virus infection; there is no consensus on whether the zoster vaccine should be used in persons with HIV infection who have CD4 counts above 200 cells/mm$^3$.
- Persons with HIV infection who plan to travel outside of the United States should undergo an evaluation by a medical provider who has expertise in travel-related issues well in advance of planned travel.
- Expert consultation is advised for management of immunizations in children with HIV infection.
Citations


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• Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Figure: Immunization schedule for HIV-infected adults. November 6, 2013. [AIDSinfo] -


Figures

Figure 1 Serotypes in the Pneumococcal Conjugate Vaccine 13 (PCV13)


Serotypes in PCV-7

4  6B  9V  14  18C  19F  23F

New Serotypes

1  3  5  6A  7F  19A

PCV-13 Serotypes
Figure 2 Recommendations for Pneumococcal Immunization in Adults with HIV Infection

Note green rectangles indicate administer PCV13 and dark blue rectangles indicate administer PPSV23. Light blue rectangles indicate prior receipt of PPSV23.

Figure 3 *Neisseria meningitidis* Isolates in Persons with HIV—United States, 1995-2014

Figure 4 Herpes Zoster Vaccines

Illustration by David H. Spach, MD

Varicella-Zoster Virus

Live Attenuated Zoster Vaccine
Zostavax

Herpes Zoster Subunit Vaccine
Shingrix
Figure 5 Production of Human Papillomavirus Subunit Vaccine

Conceptual rendition of production of human papillomavirus vaccine. The vaccine process involves recombinant synthesis of major capsid L1 proteins that self-assemble as a shell of 72 pentameric capsomeres to form viral-like particles (VLPs). The assembled pseudovirus is very similar to the native human papillomavirus and is highly immunogenic.

Illustration by David H. Spach, MD